International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 890-895 www.ijprajournal.com ISSN: 2249-7781

"Review on Pharmacovigilance of Levofloxacin on Legionnaires Disease"

Piyush .K. Rodge
(Final Year B.Pharmacy)
Department of Pharmacovigilance,
Faculty of Pharmacy.
Mahavir Institute of Pharmacy, Varvandi,Nashik, India

Submitted: 10-01-2023 Accepted: 21-01-2023

ABSTRACT :-

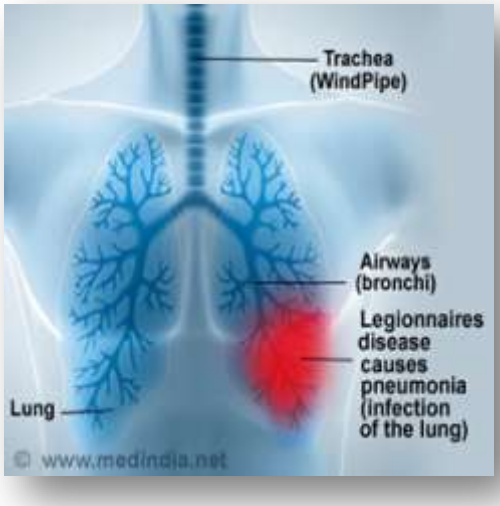
Legionnaires disease is one of the type of pneumonic illness. Major risk factors include immunodeficiency, smoking, alcoholism and chronic obstructive pulmonary disease among others. The causative agents of Legionella are freshwater bacteria which may present any where like swimming pool, tanks, lakes, etc. Many antibiotics are used to treat this and Levofloxacin is one of the antibiotic which is mostly use for Legionnaires disease. Administering of levofloxacin in large amount may cause many side effects and common adverse effect may seen according to patient health but sometimeserious adverse effect may cause death also but by taking levofloxacin no death recorded yet.

KEYWORDS :-Legionnaires disease, pneumonia, Levofloxacin, Adverse effect, USA.

I. INTRODUCTION :-

Legionnaires first founded in American legion in 1976. Then Joseph McDade, CDC (Centre of Disease Control) scientist who discovered the cause of Legionnaires' disease. This is mostly found in United states of America and in European countries. It is spread through aerosolized water particle. It is respiratory disease instigated by the Legionella species. Especially it is caused by gram negative bacteria name as "Legionella pneumophila". This disease is a type of pneumonia. It is mainly affected to our lungs. Legionella pneumophila is found in large bodies of water including natural water sources such as rivers, lakes and reservoirs, but usually in low numbers. They may also be found in purpose-built water systems such as cooling towers, evaporative condensers, hot and cold water systems.

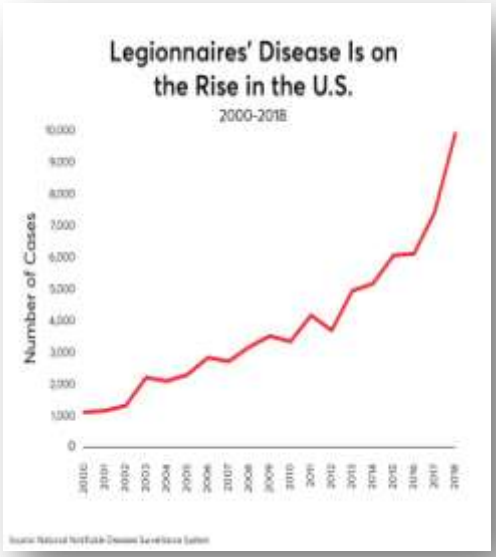
The length of time between exposure and symptom onset is two to ten days but may be up to twenty. No vaccine is available yet. Prevention depends on good maintenance of water system. Treatment of Legionnaires' disease is done with the help of antibiotics.



"Legionnaires" disease is very serious, but most of people survive. Survival rate about 1 out of every 10 people who gets sick with Legionnaires' disease will die due to complications from their illness. For those who get "Legionnaires" disease during a stay in a healthcare facilityabout 1 out of every 4 will die.

GRAPHICAL REPRESENTATION OF INCREASINGLEGIONNAIRES IN UNITED STATES:-

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 890-895 www.ijprajournal.com ISSN: 2249-7781



The number of cases reported to CDC (Centre of Disease Control) has been on the rise since 2000. Health departments reported nearly 10,000 cases of Legionnaires disease in the United States in 2018. However, because Legionnaires disease is likely underdiagnosed, this number may underestimate the true incidence. A recent study estimated that the true number of Legionnaires disease cases may be 1.8–2.7 times higher than what is reported. More illness is usually found in the summer and early fall, but it can happen any time of year.

It is unclear whether this increase represents artifact (due to increased awareness and testing), increased susceptibility of the population, increased Legionella in the environment.

SURVIVAL OF LEGIONELLA ACCORDING TO THE TEMPERATURE :-

Water Temperature	Effect
Above 158°F (70°C)	Legionella dies almost instantly
Between 140 and 158°F (60 and 70°C)	90 percent destroyed in 2 min
Between 122 and 140°F (50 and 60°C)	90 percent destroyed between 80 to 124 min
Between 118 and 122°F (48 and 50°C)	Can survive but do not multiply
Between 90 and 108°F (32 and 42°C)	Ideal growth range
Between 77 and 113°F (25 and 45°C)	Growth range
Below 68°F (20°C)	Dormant, can survive below freezing

Legionella will die immediately at temperatures of 158 Fahrenheit (70 degrees celsius), but you need not keep your water in this range forever. In fact, at only 122 Fahrenheit (50 degrees celsius), most Legionella bacteria will die over a few hours. Raise the temperature again just a few degrees, and the bacteria will die within minutes. According to temperature is given in table above the survival of Legionella is depend.

SYMPTOMS :-

The length of time between exposure to the bacteria and the appearance of symptoms is generally 2–10 days, but can more rarely extend to as long as 20 days. For the general population, among those exposed, between 0.1 and 5.0% develop the disease, while among those in hospital, between 0.4 and 14% develop the disease.

Those with Legionnaires' disease usually have fever, chills, and a cough, which may be dry or may produce sputum. Almost all experience fever, while around half have cough with sputum, and one-third cough up blood or bloody sputum. Some also have muscle aches, headache, tiredness, loss of appetite, loss of coordination, chest pain, or diarrhea and vomiting. Up to half of those with Legionnaires disease have gastrointestinal symptoms, and almost half have neurological symptoms, including confusion and impairedcognition. "Relative Bradycardia" may also be present, which is low to normal heart rate despite the presence of a fever.

Laboratory tests may show that kidney functions, liver functions, and electrolyte levels are abnormal, which may include low sodium in blood. Chest X-rays often show pneumonia

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 890-895 www.ijprajournal.com ISSN: 2249-7781

with consolidation in the bottom portion of both lungs. Distinguishing Legionnaires' disease from other types of pneumoniaby symptoms or radiologic findings alone is difficult; other tests are required for definitive diagnosis.

People with Pontiac fever, a much milder illness caused by the same bacterium, experience fever and muscle aches without pneumonia. They generally recover in 2–5 days without treatment. For Pontiac fever, the time between exposure and symptoms is generally a few hours to two days.

CAUSES OF LEGIONNAIRES DISEASE :-

There are many causes which through the legionnaires may cause like from hot tubs and whirlpools, cooling towers in air, hot water tank heater but mild hot water, through decorative fountain which are found in gardens, through swimming pools. Sometimes it may cause through drinking water also.

Smoking and Drinking alcohol may increase the chances to cause Legionnaires. It decrease our immunity power and due to smoking our lungs get damage and it may increase the chances to face Legionnaires.

TREATMENT FOR LEGIONNAIRES :-

Most effective antibiotic include most macrolides, tetracycline, ketolides and quinolones. There are three major classes of antibiotics that are highly active in vitro against Legionella bacteria. Fluoroquinolones (eg. Levofloxacin, Moxifloxacin), Macrolides (eg. Erythromycin, Azithromycin) and Tetracyclines (eg. Doxycycline).

Legionella multiply within the cell, so any effective treatment must have excellent intracellular penetration. The antibiotics used most frequently have been levofloxacin, doxycycline and azithromycin.

Macrolides (Azithromycin) are used in all age groups, while Tetracyclines (Doxycycline) are prescribed for children above the age of 12 and Quinolones (Levofloxacin) above the age of 18. Rifampicin can be used in combination with a quinolone or macrolide. Whether Rifampicin is an effective antibiotic to take for treatment is uncertain. Tetracyclines and erythromycin led to improved outcomes compared to other antibiotics in the original American Legion outbreak. These antibiotics are effective because they have excellent intracellular penetration in Legionella-infected cells. The recommended treatment is 5–10 days of Levofloxacin or 3–5 days of Azithromycin, but in people who are immunocompromised, have severe disease, or other pre-existing health conditions, longer antibiotic use may be necessary. During outbreaks, prophylactic antibiotics have been used to prevent Legionnaires' disease in high-risk individuals who have possibly been exposed.

The mortality at the original American Legion convention in 1976 was high (29 deaths in

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 890-895 www.ijprajournal.com ISSN: 2249-7781

182 infected individuals) because the antibiotics used (including penicillins, cephalosporin, and aminoglycosides) had poor intracellular penetration. Mortality has plunged to less than 5% if therapy is started quickly. Delay in giving the appropriate antibiotic leads to higher mortality.

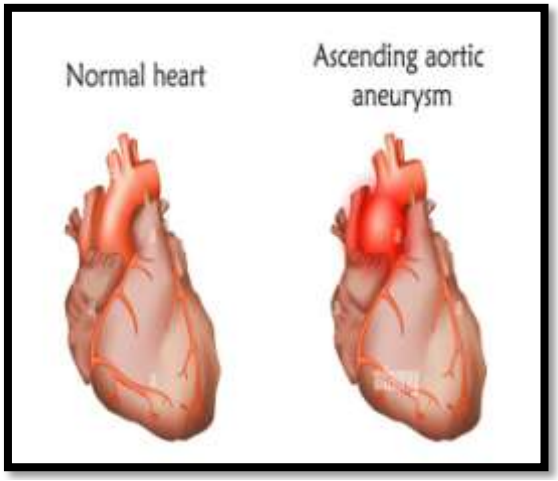
The sooner therapy is started, the less likely the chance of developing serious complications. In many cases, treatment requires hospitalization. The minimum duration of therapy is 5 days for patients. Patients with mild infection generally require 5 to 7 days of therapy. Patients with severe infection or chronic comorbidities generally require 7 to 10 days of therapy. Parenteral therapy is advised initially as the patient may not tolerate antibiotics given by mouth because of potential gastrointestinal symptoms.

ANTIBIOTICS WHICH ARE USED AND THERE DOSES:-

- Levofloxacin 750 mg, one tablet for seven to ten days.
- Rifampin 300 to 600mg orally or intravenously every 12 hours.
- Azithromycin, one followed by 500 mg one tablet once a day for seven to 10 days.
- Erythromycin 1000mg intravenously every 6 hours, 500mg orally every 6 hours.
- Doxycycline 100mg orally or intravenously every 12 hours

LEVOFLOXACINONLEGIONNAIRES:-

Our suggestions is that Levofloxacin is a safe and effective treatment for Legionella pneumonia. Levofloxacin appears to be more effective than clarithromycin in treating severe cases of Legionnaires Disease. Although fluoroquinolones possess excellent in vitro activity against Legionella, few large-scale clinical trials have examined their efficacy in the treatment of Legionnaires disease. Levaquin is a brand name of Levofloxacin. Levofloxacin was more active than Erythromycin and as active as Ofloxacin or Ciprofloxacin in this disease.Administering this drug may lead to the higher risk in patient above 60 year of age. Administering this drug may lead to the higher risk in patient above 60 year of age. Some peoples may report Abdominal Pain Dizziness, Gases and difficulty in sleeping. One of the rare adverse effect is given in below image is representing the damage to the Aorta.



Aneurysm is a swelling or ballooning in the wall of the artery. Aortic aneurysm is a balloon-like bulge in the aorta, the large artery that carries blood from the heart through the chest and torso. Aortic aneurysms can dissect or rupture: The force of blood pumping can split the layers of the artery wall, allowing blood to leak in between them.

In Clinical trials studies, the Data from first six clinical trials encompassing 1997 total patients have been analysed to determine the efficacy of Levofloxacin (500 mg or 750 mg) in treating patients with community-acquired pneumonia due to Legionella.

Of the 1997 total patients with CAP from the clinical trials, 75 patients had infection with a Legionella species. Demographics showed a large portion of these patients were < 55 years of age and non-smokers. More than 90% of mild-to-moderate and severe cases of Legionella infection resolved clinically at the posttherapy visit, 2 to 14 days after treatment termination. No deaths were reported for

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 890-895 www.ijprajournal.com ISSN: 2249-7781

any patient with Legionnaires disease treated with Levofloxacin during the studies.

Levofloxacin was efficacious at both 500 mg for 7 to 14 days and 750 mg for 5 days. Legionnaires disease is not associated only with smokers, the elderly, and the immunosuppressed, but also has the potential to affect a broader demographic range of the general population than previously thought.

Fluoroquinolone development over the past 15 years has not been without problems. Various agents—notably, temafloxacin, trovafloxacin, and grepafloxacin—have been withdrawn or suspended due to serious.Adverse drug reactions (ADRs) common to all types of fluoroquinolone therapy can be summarized as class effects, subdivided into common and rare class reactions and potentially serious idiosyncratic reactions, as follows. Common-class ADRs include effects on the central nervous system (CNS) and the gastrointestinal (GI) system, and on the skin. These effects occur at varying rates relevant to individual agents but are rarely serious. Rare-class ADRs include phototoxicity, QTc (heart rate–corrected QT) prolongation and associated cardiac arrhythmias, tendonitis, and, rarely, target organ damage. According to this data Clinical trials on Levofloxacin are studied.

II. CONCLUSION:-

Legionella infection can occur in both immunocompetent and immunocompromised patients, certain risk factors in the immunocompromised are associated with an increased incidence. T cell and cell mediated immunity play a key role in body's defense against the bacteria.

Levofloxacin are used as antibiotics, rather than some more antibiotics are used to treat. More use of Levofloxacin may cause many Adverse Effect (ADR) rarely it may cause serious adverse effect like death of the person in minor condition but more than 90% people get treated. Levofloxacin offers a combination of documented efficacy and tolerability, and provides an important option for the treatment of bacterial infections, including CAP (Community-Acquired Pneumonia) and AECB (Acute Exacerbations of Chronic Bronchitis) compared with standard agents used in the management of lower respiratory tract infections.

In study Levofloxacin was found to be highly effective against Legionella infections, leading to clinical success in more than 90% of patients. It should be noted that, while not all patients with Legionnaires disease in these six studies fulfilled the criteria for cure, not a single patient died during the course of hospitalization and/or treatment. Levofloxacin treatment was as successful in patients with severe to moderate Legionella infection.

REFERENCES

[1]. Deepika Slawek, Diana Altshuler, Yanina Dubrovskaya and Eddie Louie. Tigecycline as a Second-Line Agent for Legionnaires' Disease in Severely Ill Patients

[2]. https://my.clevelandclinic.org/health/diseases/17750-legionnaires-disease#:~:text=Legionnaires'%20disease%20is%20very%20serious,to%2080%25%20of%20the%20time

[3]. Outbreaks Associated with Treated Recreational Water - United States, 2000–2014Michele C. Hlavsa, MPH1; Bryanna L. Cikesh, MPH1,2; Virginia A. Roberts, MSPH1; Amy M. Kahler, MS1; Marissa Vigar, MPH1,2; Elizabeth D. Hilborn, DVM3; Timothy J. Wade, PhD3; Dawn M. Roellig, PhD1; Jennifer L. Murphy, PhD1; Lihua Xiao, DVM, PhD1; Kirsten M. Yates, MPH1; Jasen M. Kunz, MPH4; Matthew J. Arduino, DrPH5; Sujan C. Reddy, MD5; Kathleen E. Fullerton, MPH1; Laura A. Cooley, MD6; Michael J. Beach, PhD1; Vincent R. Hill, PhD1; Jonathan S. Yoder, MPH1.

[4]. Aji Peter, Edwin Routledge, Present-day monitoring underestimates the risk of exposure to pathogenic bacteria from cold water storage tanks Institute of Environment, Health and Societies, Brunel University London, Uxbridge, Middlesex, UnitedKingdom, 2 Aqua Technologies Europe Ltd, Hounslow, Middlesex, United Kingdom.

[5]. https://www.intechopen.com/search?term=clinical%20research

[6]. Legionnaires Wikipedia - https://en.wikipedia.org/wiki/Legionnaires%27_disease

[7]. Legionella pneumonia cases over a five-year period: a descriptive, retrospective study of outcomes in a UK district hospital, Tom Wingfield, Sam Rowell, Alex Peel, Deeksha Puli, Achyut Guleri and Rashmi Sharma.

[8]. https://www.sciencedirect.com/science/article/abs/pii/S0012369216589879
[9]. Legionnaires diseaseCyngor sir YNYS MON ISLE OF ANGLESEY COUNTY COUNCIL
[10]. www.ynysmon.gov.uk , www.anglesey.gov.uk
[11]. Assessment of the Legionnaires' disease outbreak inFlint, Michigan, Sammy Zahrana,b, Shawn P. McElmurryc, Paul E. Kilgored, David Mushinskia, Jack Pressc, Nancy G. Lovee,Richard C. Sadlerf, and Michele S. Swansong,1.
[12]. https://www.towerwater.com/what-temperature-kills-legionella/
[13]. https://www.slideshare.net/PiyushRodge/clinical-trials-254842818?qid=cd95938b-58ff-4f0a-9570-353651b217e4&v=&b=&from_search=1
[14]. https://my.clevelandclinic.org/health/diseases/17750-legionnaires-disease#:~:text=Legionnaires'%20disease%20is%20very%20serious,to%2080%25%20of%20the%20time
[15]. National Library of Medicine (NIH) National Center for Biotechnology Informationhttps://www.ncbi.nlm.nih.gov/books/NBK7619/
[16]. National Library of Medicine (NIH) National Center for Biotechnology Informationhttps://www.ncbi.nlm.nih.gov/books/NBK430807/
[17]. National Library of Medicine (NIH) National Center for Biotechnology Informationhttps://www.ncbi.nlm.nih.gov/pmc/articles/PMC4053061/
[18]. Centers of Disease Control and Prevention (CDC)https://www.cdc.gov/legionella/fastfacts.html