Chapter

A Clinical Overview of Hospital-Acquired Legionella Pneumonia: Prevention Is the Key?

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Abstract

Legionella pneumophila is a Gram-negative bacteria that cause community-acquired pneumonia in very common circumstances. Although it is rare to develop hospital-acquired pneumonia due to *Legionella pneumophila*, there are cases where the infection appears during its presence in the hospital environment or because of the existence of Legionella outbreaks. It is important to mention that the colonization of this organism is mostly found in some hospital water supplies. The prevention of the spreading of this nosocomial pathogen is crucial for the hospital setting by identification of the bacteria. Using surveillance and control of infection, as well as maintaining beneficial isolation of those patients with the disease, could prevent the dissemination of this rare infection among hospitalized patients that are highly vulnerable. The treatment should be effective and according to the standard of care guidelines. The initiation of empiric antibiotic therapy is critical once the pathogen is suspected to be the etiology of pneumonia.

Keywords: legionella pneumonia, hospital, hospital-acquired, prevention, clinic, epidemiology, pneumonia, management

1. Introduction

Legionnaires' disease is a severe type of pneumonia. It is typically acquired by inhalation of contaminated water containing the *Legionella pneumophila* gram-negative bacteria. The severe pneumonia occurs most frequently in susceptible patients (i.e., former or current smokers, chronic diseased patients, immunosuppressed patients and those >50 years of age) [1]. The most commonly transmission of contaminated water is from showerheads, some medical equipment (i.e., respiratory devices), cooling towers, hot tubs, hydrotherapy equipment's and/or decorative water fountains [2]. Several countries have different recommended strategies for the prevention of *Legionella pneumophila* dissemination. They measure dangerous concentrations and they use water sampling frequency with activation of alerts of the *L. pneumophila* levels. These strategies always depend on local regulations and the geographic variations. Although, the regulations have some differences, all of them include three principles: (1) the supervision of critical spots (which are locations in a hot water installation where water stays, and makes the *L. pneumophila* in a suitable growth temperature range for some

time), (2) avoiding water stagnation in specific parts of the system and the prevention of the proliferation and (3) requirement of a sufficiently high temperature to prevent the growth and spread of *L. pneumophila*. The European Working Group for Legionella Infections recommends that the total volume of the storage tank needs to be heated to 60°C for at least an hour a day, depending on the risk of spreading [3]. In the United Kingdom, the Department of Health recommends maintaining hot water temperatures at a temperature lever >55°C and cold water <20°C to prevent the proliferation of *L. pneumophila* in the water systems. Also, when cooper and silver ionization is introduced to a new building in conjunction with appropriately managed water, there is a better control in the dissemination of the bacteria [4]. It is important to mention that Legionella prevention should start with the correct design and construction of the water networks. During facilities renovations or a construction of a new one, the pipe runs should be as short as practical [5]. Usually, the evaluation of water systems for Legionella is until after the disease has been identified and confirmed. Thus, it is recommended a practical approach of periodic testing for Legionella, along with proper water treatment to avoid large-scale outbreaks [6]. In addition of water management in all health care facilities, it is crucial to have better methods for detecting Legionella in the water systems and in some of the clinical specimens to enhance the preventive strategies and the clinical diagnosis. In the United States, the CDC developed a toolkit to for all Medicare-certified healthcare facilities to assist in the water management in order to reduce the growth and transmission of the bacteria [7].

One of the preventive methods is to run cultures and other diagnostic methods to assess the rate of spreading of the gram-negative bacteria. According to a study made in Pittsburgh, Pennsylvania, water cultures are more significantly more sensitive than collected swab cultures in detecting *Legionella pneumophila*. This study was done due to an outbreak of nosocomial Legionnaires' disease among 22 veterans in the Veterans Affairs Pittsburgh Healthcare System [8]. The reality is that testing for atypical pathogens in patients is poorly standardized in a realistic scenario, especially in low-income countries where some guidelines are needed for the implementation of a suitable diagnosis. One of the major implications of this approach is the wide heterogeneity across continents and countries [9].

The risk management in hospitals of *Legionella pneumophila* seems to be underrepresented in the literature. A literature review done by Leiblein, et al., stated that further research in the field of risk management and prevention of Legionella in the water systems must be perform [10].

2. Epidemiology

All Legionnaires' disease cases are reported to the Centers for Disease Control and Prevention (CDC). In 2015, a national surveillance data confirmed a total of 2809 Legionnaires' disease cases. Those cases were reported to the CDC from 21 jurisdictions, including 85 definite (3%) and 21 (17%) possible health-care associated cases. This last high rate marks the importance of case prevention among health institutions and the implementation of effective water maintenance programs, as well as a proper case identification. The most frequent health-care facility associated with this disease was a long-term care facility, with 80% of the definite cases [11]. In the United States, the reported cases of Legionnaires' disease have increased nearly 4.5 times since the year 2000. It could be related to the increased susceptibility of the population, the access to new diagnostic methods or a combination of both [12]. One of the main causes of transmission is closely related to professions where there is nebulization with water, mainly among workers with

long term exposure. The outbreaks tend to be seasonally, especially in the hottest months of the year (May–August) [13].

Although, it is historically associated with healthcare institutions, it is important to mention that some retirement homes are also at risk of dissemination of the disease. The healthcare-associated cases represent a proportion of cases in elderly patients (>60 years of age). Drinking contaminated water can contribute to outbreaks. De Filippis, et al., collected hot water and biofilm samples from showerheads of retirement homes. Then they were tested by culture method. It resulted in 140 hot water and biofilm samples collected, with Legionella found in 36.8% of the samples. The results suggested that the colonization of these retirement homes is occasional, but further studies were suggested [14].

Although there are limited data available, the incidence reported is around 10–15 cases detected per million population. From them, 75–80% are >50 years and 60–70% are male with underlying chronic diseases [15].

Nevertheless, the prevention of Legionella still remains a critical issue, even in healthcare facilities where monochloramine disinfection has been introduced. It is documented that monochloramine has a better impact that free chlorine alone on Legionella control [16].

Although, this makes that continuous treatments with low monochloramine doses induced a viable but non-culturable state of Legionella. A study made by Casini, et al., obtained water and biofilm samples and isolated Legionella with the use of standard procedures. It emphasized the importance of keeping an appropriate and uninterrupted monochloramine dosage to ensure the control of *L. pneumophila* colonization in water supplies for hospitals [17].

Another chemical disinfection method used in water systems is the chlorine dioxide. It is reported that the duration of the effective protection of chlorine dioxide is reliable and could support the process in the framework of risk management activities in hospitals. This was documented by Vincenti, et al., where the duration of chlorine dioxide method in eradicating Legionella was analyzed in a large hospital in Rome. The observation was made from samples takes between 2011 and 2018. It concluded that Legionella was never detected at 4 years of follow-up [18].

3. Pathophysiology

Legionella pneumophila can be found in biofilm formations, as a single microbe in freshwater and manmade devices such as, shower heads, air conditioning systems, cooling towers and water fountains. This intracellular pathogen is the causative agent of a severe form of pneumonia known as legionnaires' disease [19]. Once transmission to the human lung is established through inhaled infectious aerosols, *L. pneumophila* is engulfed by the macrophage where it replicates, causes inflammation and consequently pneumonia [20]. Jäger et al., showed, through human lung tissue explants that *Legionella pneumophila* damage to lung is characterized by "destruction of its connective tissue, proteinaceous exudate and delamination of alveoli", [21] thus the physical symptoms.

L. pneumophila obtains shelter from harsh environmental conditions by forming an advantageous relationship with unicellular protozoa. Besides shelter it provides nutrients for survival and infectivity. Once *L. pneumophila* utilizes all the protozoa's nutrients, it exits the host as bacterium capable of thriving within monocytes and macrophages in case of inhalation through the infected particles. Once inhaled, the bacteria reach the alveoli, enter alveolar macrophage through coiling phagocytosis or normal phagocytosis, and cause legionnaires' disease. Previous studies have shown that this is thanks to genes that encode for effector proteins with eukaryotic

characteristics that are injected through the legionella containing vacuole. This is known as molecular mimicry [19, 22]. Cazalet et al., found 30 genes of *L. pneumophila* that encoded for proteins with high resemblance to eukaryotic proteins and another 32 genes involved in protein-protein interactions within eukaryotic domains [23].

3.1 Strategy

Legionella's life cycle consists of two main phases. In order to survive against harsh environmental conditions, legionella enters a "reversible dormant state", known as the viable but not culturable state (VBNCS) [24] When environmental conditions improve, like in the case of phagocytosis by *Acanthamoeba castellanii*, the bacterium represses its virulent traits and goes into its exponential phase, in which it replicates within the protozoa [6]. This process of replication takes round 15 hours to complete [25]. Once lack of nutrients and environmental stress strikes, *L. pneumophila* coordinates its differentiation to the mature intracellular form (MIF) and the stationary phase form (SPFs), both with virulent traits characterized by high motility and cytotoxicity and proceeds to lyse the cell and infect cells in proximity. Although studies are lacking on the mechanisms by which the host cell is lysed by the bacterium [24, 25]. SPFs present flagella, loose outer membrane, and a well-defined inner membrane, while MIFs typically appear as stubby rods with complex envelope, both being able to colonize alveolar macrophages [24]. Legionella accomplishes this physiologic and morphologic change by the coordination of LetA/LetS and sigma factors RpoS and FiA [26]. When there is low availability of amino acids, RelA, a ribosomal enzyme, synthetizes alarmone ppGpp (guanosine pentaphosphate) with subsequent activation of sigma factor RpoS and LetA/S. LetA/S work in conjugate to induce the expression of CsrB homologues which are RNAs that can sequester CsrA. CsrA expression represses the flagellar sigma factor fliA, which translates into a non-motile pathogen, with reduced virulence [27]. Studies have shown that through legionella's exponential phase, the bacterium increases its resistance against heat, and antibiotics [24].

3.2 Legionella and the host cell

The key mechanism for *L. pneumophila* inert ability to survive against the harsh intracellular environment is its secretory system. *Legionella pneumophila* uses a type IVB secretion system (T4BSS) encoded by the delayed in organ trafficking/intracellular multiplication gene [28]. The T4BSS is involved in endocytic and secretory pathways as well as ubiquitination, host lipid metabolic exploit and cell death prevention by enabling the formation of the vacuole in which the bacterium resides for multiplication [29]. When a phagosome is formed, it matures, acidifies, and fuses with the lysosome. The phagolysosome can digest the contained organism through different bactericidal peptides, reactive oxygen species (ROS) and hydrolytic enzymes. Once the pH of the phagolysosome achieves certain acidity, these hydrolytic enzymes get activated leading to the destruction of the pathogen [28]. The acidification is accomplished by a proton pump ran by ATP hydrolysis called the vacuolar-ATPase (v-ATPase). This v-ATPase is made up by the trans-membrane domain V_0, and the cytosolic V_1 domain, which translocate H^+ across the lipid bilayer and hydrolyzes ATP used for proton translocation respectively [30]. Prior research suggests that *Legionella pneumophila* secretes SidK, an effector protein that halts acidification of the phagolysosome by interaction with v-ATPase in early stages of infection. Zhao et al. showed that Binding of Sidk to the v-ATPase decreased its affinity, although only by 40% of v-ATPase activity, suggesting the presence of other effector proteins [30].

A key element on the formation of the LCV is the ability to disrupt vesicle trafficking between the ER and the Golgi apparatus. This interception of vesicle is what gives the LCV the ability to expand for replication and its ER-like properties [31].

Multiple studies show that *L. pneumophila* can accomplish this by targeting Rab1, a member of the Ras superfamily GTPases. Rab proteins are essential to the secretory pathway, and these proteins are localized in specific intracellular membranes, mainly ER and Golgi [32]. Control over inactive GDP-bound and active GTP bound GTPases are controlled by Guanine nucleotide exchange factors (GEFs) and GTPase-activating proteins (GAPs). This is where the DrrA/Sidm effector protein plays its role. Due to its high affinity for GDP-bound Rab1, DrrA/Sidm acts as a GEF, exposing its master molecular switch allowing for the recruitment of vesicles [33]. Furthermore, previous studies have suggested that the N-terminal region of DrrA is involved in AMPylation reaction that is essential for the localization and maintaining of Rab1 in the LCV by avoiding Rab1 deactivation by GAFs [34]. These reactions are reversed through SiD and Lem3 effector proteins respectively. Further modification of Rab1 is accomplished by SidE, SdeA, SdeB, and SdeC effector proteins through a complex ubiquitination process.

L. pneumophila avoids host cell death to allow for replication by upregulation BCL-2 and blocking the activity of BNIP3 and BCL-Rambo. The only implicated factor in inhibition of BNIP3 and BCL-Rambo in past research studies had been only SidF. A recent study suggests that there is still unexplored territory pertaining to avoidance of host cell apoptosis. Speir et al. showed with mutant strains of legionella lacking SidF, that there was not any significant increase in the rate of cell death, suggesting presence of other effector proteins [35].

Past studies have shown that the LCV exploits the hosts lipid metabolism to generate a vacuole with Golgi apparatus characteristics to facilitate the hijacking of vesicles trafficked between the ER and the Golgi apparatus. The LCV acquires a composition like that of the Golgi apparatus by enriching the LCV with PtdIns4p a phosphoinositide through the T4BSS and SidF, LepB, AR1f, LecE, LpdA effector proteins. SidF in conjunction with host 5-phosphatase OCRL1 reduces PtdINs(3,4) P2 into PtdIns4P, while LpdA synthesizes phosphatic acid and LecE activates this phosphatidic acid to produce diacylglycerol, which lead to the recruitment of host Kinase D proteins with consequent recruitment of PI4IIIKB and production of PtdIns4P [35].

4. Diagnosis

4.1 Urine antigen "the rapid test"

Urinary antigen test can be used to detect Legionella. This method requires monoclonal antibodies that recognize lipopolysaccharide antigens from *Legionella pneumophila* serogroup 1 in a urine sample. Results can be available in the next few minutes, giving it an advantage for rapid diagnosis. Sensitivity ranges from 69 to 100%, and specificity ranges from 99 to 100%. One main disadvantage from this test is that it overlooks the detection from other serogroups and species of Legionella. This can be related that about 8% of patients infected with Legionella fail to excrete urine antigens [36–38].

4.2 Microbiological culture "the gold standard"

Isolation by culture continues as the gold standard for Legionella disease. It is superior to identify all of the known species and serotypes of Legionella. Sensitivity

can get up to 81% and specificity range from 99%. A variety of samples from the lower respiratory tract can be used for culturing, the most commonly use is sputum. Although in these patients the disease is developed as an atypical infection, the majority of them produce little or no sputum at all. Other acceptable specimens used are fluid from bronchial aspiration, bronchial alveolar lavage, and pleural fluid. The less used are lung tissue taken from a biopsy. The most successful and selective isolation media used for Legionella is the buffered charcoal yeast extract agar, also known as BYCE agar. A positive growth is available within 3–5 days, although when it co-exists background flora, will require addition treatment to reduce it, this can delay result up to 2 weeks [39].

Environmental isolation can be also obtained by culture test but requires a various preparation techniques to decrease the presence of environmental flora from samples, as well as different media. [37, 40]

4.3 Direct fluorescent antibody "the confirmatory technique"

The using of this test helps to confirm a suspected overgrowth of Legionella in a culture. After 3 days of incubation, a direct fluorescent antibody applies to the specimen staining the viability to growth. Sensitivity for L. pneumophila serogroup-1 ranges up to 70% and specificity is 99%. Quick results can be possible to obtain, but requires expert techniques [41–43].

5. Treatment

For *Legionella pneumophila*, a high-level of suspicion and prompt initiation of adequate antimicrobial therapy is critical to improve clinical outcomes. Failure to administer proper antimicrobial therapies at an early stage of the infection has been associated with higher mortality rates [44]. The correct choice of antibiotic depends not only in its in vitro bactericidal or bacteriostatic activity, but also in its ability to penetrate the cell membrane of host tissue. This is because Legionella resides within host tissue cells. The preferred families of antibiotic are the fluoroquinolones (levofloxacin and moxifloxacin) and the macrolides (azithromycin) [45, 46].

The situations suggesting pneumonia by Legionella are: Gram stains of respiratory samples revealing many polymorphonuclear leukocytes with few or no organisms, hyponatremia, pneumonia with prominent extrapulmonary manifestations (diarrhea, confusion, etc.), failure to respond to administration of beta-lactams, aminoglycoside antibiotics, or both and recent traveling [46–48]. When treating *Legionella pneumophila*, the first choice of antibiotics should be macrolides or quinolones. Quinolones are more active than macrolides. Sometimes may be preferred in other patients whom drug interactions could be a problem. For example, in immunocompromised patients the potential for interaction with medications like cyclosporine or protease inhibitors is documented to be in a less with quinolones than with macrolides.

Azithromycin is the drug of choice for children with suspected or confirmed Legionella disease. Erythromycin is not often used now even though it is highly effective, but its use has been related with considerable side effects (i.e., gastrointestinal and ototoxicity), especially when used intravenously. Azithromycin has been shown to be the more active macrolide against *Legionella pneumophila* followed in order of activity by erythromycin, roxithromycin, dirithromycin, and clarithromycin [44, 47, 49]. Azithromycin is the safest macrolide. The advantage is due to its good intracellular penetration, bactericidal activity, proven clinical efficacy, short duration of treatment and good safety profile. Furthermore, the

15-membered lactone ring of Azithromycin does not interact with cytochrome P450 (CYP) 3A4 isoenzymes (i.e., cyclosporine). Unlike the other types of macrolides, this reduces the potential for drug interactions. The initial course should be intravenously administered. After a good clinical response is detected, it can be switched to the oral route. In patients with severe disease or unresponsive to monotherapy, the addition of rifampin is recommended [45, 50]. The recommended Azithromycin dose is 500 mg IV/PO q24h for 5 days. Alternatives are: Clarithromycin 500 mg IV/PO q12h for 10 days and Erythromycin 1 g IV q6h or 500 mg PO q6h [47].

Quinolones have all been shown to inhibit the intracellular growth of *L. pneumophila*. The most potent inhibitors of intracellular multiplication, in order of decreasing activity, were levofloxacin, ciprofloxacin, and ofloxacin [45]. Levofloxacin stops multiplication of bacteria by preventing the reproduction and repair of their genetic material (DNA) and it appears to be associated with a more rapid resolution of symptoms, a shorter time to clinical stability and consequently shorter length of hospital stay then the macrolides. Levofloxacin, either 500 mg PO/IV qd for 10 days or 750 mg PO/IV qd for 5 days, can cure most of the patients and is becoming the antibiotic of choice for Legionella disease [45, 49, 51].

Other alternatives include Doxycycline 100 mg PO/IV q12-24h for 7–21 days or sulfamethoxazole/trimethoprim DS 800 mg/160 mg 1–2 tabs PO q12h or 20 mg/kg/day IV q6-12h for 7–10 days [47, 49]. Rifampicin is very active against extracellular and intracellular Legionella spp. In the clinical setting, monotherapy is not recommended. In case Rifampicin resistance emerges, it has been reserved for adjunctive therapy in severe cases of Legionella infection. Another limitation of Rifampicin is the potent induction of cytochrome P450 enzyme system and the potential for drug interactions [45].

The usual duration of therapy for most antibiotics is 5–10 days. This is often adequate to completely treat patients with Legionella infection. Although, a duration of therapy up to 3 weeks may be considered in immunocompromised patients or in patients with severe disease or with other pre-existing health conditions (chronic heart, lung, liver or renal disease, diabetes mellitus, alcoholism, malignancies, and asplenia) [44]. Patients should be switched from intravenous to oral therapy when they are hemodynamically stable and present a clinical improvement and, also, if they are able to ingest medications and have a normally functioning gastrointestinal tract. Before discontinuation of therapy the patients should be afebrile for 48–72 hours and should be have at least one criteria for clinical stability (Temperature ≤ 37.80°C, heart rate ≤ 100 beats/minutes, respiratory rate ≤ 24 breaths/minutes, systolic blood pressure ≥ 90 mm Hg, arterial oxygen saturation ≥ 90% or pO_2 ≥ 60 mm Hg on room air, normal mental status and ability to maintain oral intake). Patients should be discharged home as soon as they are clinically stable, and they have no other medical problem. Additionally it is important to have a safe environment for continuity of care. The inpatient observation while receiving oral therapy is not required [44, 51, 52].

6. Prevention

Even though *Legionella pneumophila* is a very uncommon etiology of nosocomial infection, the CDC recommends a high degree of suspicion when there are cases of nosocomial pneumonia with unknown etiology [53]. The presence of warm water is suitable for the growth of the bacteria (20–45°C). It is known that Legionella colonizes hot water distribution systems in 12–70% of hospitals in some geographic areas. For example, a study made in Hungary showed that Legionella was found in 90% of some surveyed hospitals that were >30 years old [54]. Also, it is

documented that Legionella can survive at higher temperatures (>60°C) but keeping a hot water at that range can cause third-degree burns in some patients (1 second of exposure to hot water in children, and 5 seconds of exposure to hot water in adults). It is important that hospital regulations focus on maintaining proper water temperatures [55].

The frequent monitoring of hospital water system is mandatory when there is Legionella pneumonia documented in a patient hospitalized, or even when there is suspicion of Legionella. Water sample cultures are the most prevalent method for ascertaining colonization of water. The interpretation of Legionella testing can vary from geographical area, but some facilities can act and start the management of Legionella contamination when the culture results show a level of detection of 1 CFU/mL [56].

A water management program is indispensable for Legionella prevention, and it should be implemented in every hospital since the incidence has been rising up in the United States. A survey developed in Minnesota in 2017, was applied in 137 acute-care, critical care, and long-term hospitals. Only 84 surveys were returned and 3 were incomplete and excluded from the analyses. From them, 27% of the hospitals had a pertinent water management program. The 7% of those facilities measured pH at which cold and hot water were stored. The temperature range of the hot water storage was reported to be 42–62°C. All of the hospitals were supplied by community drinking water sources. Less than 5 used secondary disinfection systems (i.e., reverse osmosis, ultraviolet light, or chlorine). Also, only 21% of the responding facilities have reported to regularly test the water for the presence of Legionella [57]. They concluded that significant water management should be put into practice to protect patients from nosocomial Legionella [58].

In some other countries like Italy and Australia have developed programs for control and preventive measure for legionellosis. In Northern Italy, the water systems are routinely tested for Legionella. A questionnaire was applied to 739 hospitals, and 178 were completed. It showed that 97% of the hospitals do routine tests for the presence of Legionella in water, and 62% detected a positive result. The most common control measure is disinfection of water systems, mostly with thermal shock and chlorine dioxide [59]. Also, the implementation of a water safety plan and disinfection with monochloramine prevented legionellosis in another hospital in Catania, Italy. The results after 3 years of application have proven to be highly effective in controlling the growth of Legionella and thus preventing nosocomial infections [60].

In Brisbane, Australia, they use genomic epidemiological methods to execute a rapid and effective water treatment to characterize and eradicate *L. pneumophila*. This was started to be used due to a background of two proven nosocomial cases of *L. pneumonia*. The trace of the whole genome sequence analysis was initiated from isolates of affected patients and a prospective isolated were collected from hospital water distribution systems. The aggressive intervention to resolve this included the closure of the hospital, scalding of the water system with 60°C for 10 minutes, and treatment with alkaline detergent and 10 mg/L free chlorine, as well as the installation of in-line chlorinator systems and intensive monitoring for the presence of LPSG1 in water specimens. The combinations of all these approaches proved to be a good support in the management of Legionella contamination [61].

7. Conclusions

Legionnaires' disease is a potential preventable disease. The access to clean water should be essential for all the hospital environments, though, *Legionella*

pneumophila is quite atypical. The implementation of certain methods like avoiding critical spots and the prevention of water stagnation will help to decrease the risk of proliferation of the gram-negative bacteria, as well as its growth and spreading throughout the healthcare facilities. Most hospital water systems are complex and different one from another, and this is a reason for maintenance of an adequate temperature, such as >60°C water temperature is recommended. Though, the prevention of damage to patients (third-degree burns) should be taken in consideration. This could be an alternative for prevention of the bacterial dissemination. The recalling in the pathophysiology of the bacteria will help us understand the natural history of the disease and thus comprehend our best choice for diagnosis and treatment. The diagnosis of patients with *Legionella pneumophila* is also quite important, and the microbiological culture should be used as a gold standard. The treatment needs to be initiated as soon as Legionella is suspected, and the patients should be placed in isolated rooms. Failure to starting the treatment will increase the risk of mortality among the patients. Further studies should be done to evaluate strategies of prevention of dissemination of the disease in all healthcare facilities, including the successful approaches that have been already performed in some other countries.

Conflict of interest

The authors have nothing to disclose.

Notes/Thanks/Other declarations

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