REVIEW ARTICLE

Review and A Brief Report on the Health Perspective, Causative Agents, Vectors, and Reservoirs of Visceral Leishmaniasis in Iran

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Abstract

Background: Visceral leishmaniasis (VL) is still widespread in tropical and subtropical regions worldwide. The vector of the disease is a sandfly, when infected with *Leishmania* parasite, can transmit the parasite from humans to other vertebrates. As knowledge about causative agents, vectors, and reservoirs of VL in Iran is necessary to control the disease, the present review study has focused on the disease elimination status from a health perspective in the country.

Methods: In a recent review, various databases, such as Web of Science, PubMed, Scopus, Cochrane Library, Science Direct, Google Scholar, MEDLIB, Irandoc, Magiran, and SID were searched using the keywords "visceral leishmaniasis", "VL", "kala-azar", "causative agent", "parasite", "vector", "reservoir", and "Iran", and the retrieved data were extracted and reviewed independently during 2001-2019.

Results: 475 published studies were recorded about VL in Iran from 2001 to 2021. 68 articles were later excluded from the study due to duplication after the initial review. *Leishmania infantum* and *L. tropica* were the causative agents, and dogs and humans were the reservoirs. The most common vectors were *Phlebotomus major*, *P. kandelakii*, *P. keshishiani*, *P. alexandri*, *P. perfiliewi*, and *P. tobbi* in different country regions.

Conclusion: The prospect of eliminating VL in Iran is inadequate. Based on the findings, *L. infantum* and *L. tropica* were the causative agents, and humans and the Caninae subfamily were the VL reservoirs in the country. These findings can be added to the literature when health policymakers target preventive measures for VL in Iran.

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Keywords: Disease reservoirs, Iran, Leishmaniasis, Vector-borne diseases

Introduction

Leishmaniasis is a group of parasitic infectious diseases endemic in most parts of the world, especially in tropical and subtropical regions.[1] Various species of *Leishmania* parasite are the causative agent of the disease,[2] and sand flies (different species of *Phlebotomus*) are the vector, leading to the transmission of the illness to healthy people via biting.[3] Global reservoirs of the disease are reported to be humans, dogs, and rodents. They can be seen in clinical cutaneous, visceral leishmaniasis (VL) or Kala-Azar, and mucocutaneous forms with incubation periods from 3 to 8 months.[4] *Leishmania donovani* and *L. infantum* are often the causative agents of the disease in different regions of the world.[5]

Clinical manifestations of the disease include

self-limiting cutaneous, indurating mucocutaneous, and fatal visceral forms.[6] VL is still a dangerous type of leishmaniasis and can be life-threatening.[7] VL is often asymptomatic and later becomes symptomatic in some cases.[8] In endemic areas, the disease is often asymptomatic, occurring acutely in children and chronically in adults.[9] The disease causes various symptoms and complications, such as fever, weakness, anemia, fatigue, and enlargement of the liver and spleen, causing death if left untreated.[10-12]

If not diagnosed and treated on time, the disease can lead to mortality in 98% of cases, especially in infants.[13] Therefore, timely diagnosis and treatment of the disease are vital.[11] Over the past few decades, more than 2,000 cases of VL have been reported from 31 Iranian provinces with an annual average of 200-300 cases. In a 16-year study, the infection rate was about 23 cases per year in only one province where this disease was endemic (Fars province, southern Iran).[14]

There are various approaches to reduce infection and control the disease, such as controlling disease-carrying insects and reservoirs, treating the patients, and preventing healthy people from being infected. One or more of these measures are singly or simultaneously applied in some regions of the world based on their conditions, availability of facilities, and effectiveness of the method to control the disease. Controlling vectors and killing or treating reservoirs are the most effective approaches to control and prevent the disease.[15, 16] Because the infection will not be transmitted without an infected reservoir and disease-carrying insects that may bite healthy people, interrupting these transmission chain points would have a significant effect on the disease control.[17, 18]

To adopt a proper approach, it is necessary to identify the disease's reservoirs, vectors, and disease characteristics in each region. Various studies conducted on reservoirs and vectors of VL have reported humans and animals, such as rodents, dogs, wild canines, and some other animals as the common reservoirs, and sand flies as the vectors of the disease.[9, 19] However, the diversity of reservoirs is different in various country regions that have changed over time. If a reservoir is not infected at the beginning of the disease in a region, it will be infected later due to an increase in its incidence.[20] Accordingly, the authors aimed to review the health perspective, the causative agents, vectors, and reservoirs of VL in Iran.

Methods

The present study reviewed causative agents, reservoirs, and vectors of VL in Iran performed based on PRISMA guidelines for systematic review studies.[21] Two researchers independently performed all stages of the research, including the search, articles selection, articles quality assessment, and data extraction.

Searching the Articles

In an initial search, the authors extracted all Persian and English articles published from the beginning of 2001 to the end of 2021 during a search in scientific databases, including Web of Science, PubMed, Scopus, Science Direct, Google Scholar, IranDoc, Magiran, SID, and some others databses All articles were searched for medical subject headings (Mesh), and the keywords "visceral leishmaniasis", "VL", "kala-azar", "vector", "parasite", "causative agent", "reservoir", and "Iran", using "AND" and "OR" operators.

Inclusion and Exclusion Criteria

The authors included all published Persian and English language articles based on previously mentioned medical subject headings in this review. They excluded articles on cutaneous and mucocutaneous leishmaniasis, low-quality articles lacking the causative agent, vectors, reservoirs of the disease, undetermined study place, review studies, meta-analysis, and case reports or case series.

Quality Assessment of Articles

The quality assessment of articles was performed using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist,[22] which consists of 22 sections that are scored based on the importance of each section. The checklist's lowest and highest scores are 15 and 33, respectively. A score of 20 was considered acceptable in this study.[23]

Data Extraction

First, two researchers independently investigated the articles by reviewing the titles and abstracts and considering the inclusion and exclusion criteria. Then they reviewed the full texts of the papers and presented reasons when both researchers rejected an article. Next, the third person judged the articles in the case of any disagreement between them. Finally, data were extracted using a pre-prepared checklist, including the research location, research time, population of the study, and types of parasite, vectors, and reservoirs.

Selection of Study

The authors extracted 475 articles by searching databases. First, the articles were entered into Endnote software, and 76 articles were later excluded from the study due to duplication after the initial review. Moreover, after reviewing titles and abstracts, the authors excluded 287 irrelevant articles. They also excluded 80 articles that did not include information about disease reservoirs. Finally, 68 articles that met the inclusion criteria entered the systematic review process (Figure 1).

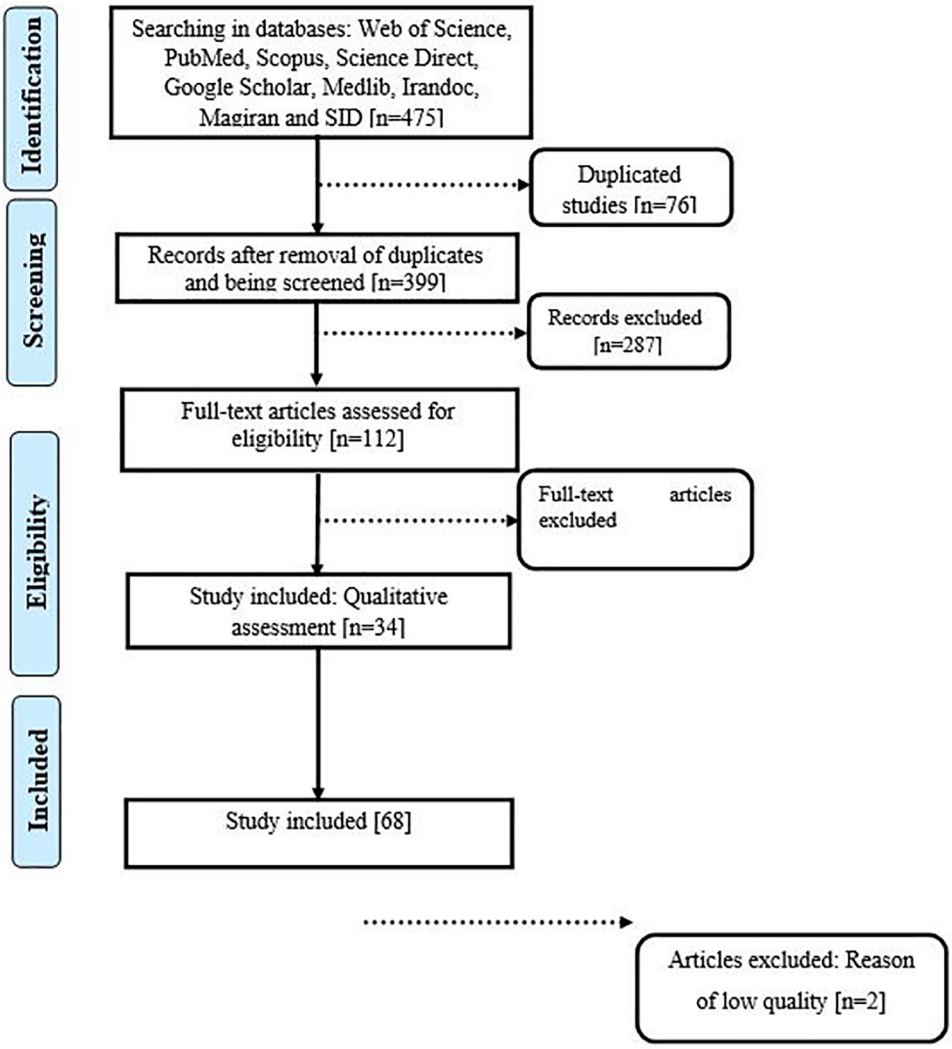

Figure 1: PRISMA flowchart for the systematic review.

Results

Causative Agents of VL in Iran

The present study was a systematic review of the causative agents, vectors, and reservoirs of VL in Iran. The findings indicated that *L. infantum* and *L. tropica* were the main causative agents of VL in the country. Various studies have investigated the type of parasite that causes VL, especially in regions of the country where the disease is endemic.[24-26] *L. infantum* was reported as the causative agent of VL in Bushehr,[27] Ardabil, Fars, East Azerbaijan, Azarshahr, Kerman, Chaharmahal and Bakhtiari, Tehran, and Khuzestan, respectively.[28-35] On the other hand, *L. infantum* and *L. tropica* were illustrated as the secondary causative agents of VL in two studies conducted by Hajjaran et al. (2013, 2014). They studied VL in different provinces of Iran.[36, 37] Moreover, Bamorovat, et al. (2015) demonstrated infection with *L. tropica* in stray dogs in the city and suburbs of Kerman as a well-known focus of Anthroponotic CL.[38] In a study by Mohebali et al. (2006) in Meshkinshahr, *L. infantum* and *L. tropica* were shown as the causative agents of VL.[39] Therefore, this study showed co-infection by *L. tropica* and *L. infantum* in Iran (Table 1, Figure 2).

Vectors of VL in Iran

As shown in Table 2, some species of *Phlebotomus* are the vector of *L. infantum* in different regions of Iran. In East Azerbaijan, *P. caucasicus* and *P. sergenti* were demonstrated as reservoirs of *L. infantum*.[39] In another study, infection of *P. kandelakii* with *L. infantum* was observed in East Azerbaijan.[40] Furthermore, *P. major* and *Sergentomyia sintoni* were found with natural promastigote infections of *L. infantum* in Shahreza, and *P. perfiliewi* as the VL vector in the northeast of Iran,[41-43] Azizi et al. (2006) revealed the presence of *P. alexandri* in Nurabad Mamasani in Fars province.[44] *P. major* and *P. tobbi* were also detected as VL vectors in Qom and Alborz provinces, respectively.[45, 46] In addition, *P. perfiliewi* and *P. kandelakii* were found in Ardabil and similar areas in northwestern Iran,[47, 48] Azizi et al. (2008) exhibited *P. major* in Fars province.[49] In other studies, *P. tobbi* and *P. perfiliewi*

Table 1: Characteristics of articles regarding Visceral Leishmaniasis entered into this systematic review

Reference	Year	Research place	Causative agent	Vector	Reservoir	Diagnosis method
[5]	2012	Kohgiluyeh and Boyer-Ahmad	*Leishmania infantum*	-	Dog	Direct agglutination test [DAT]
[27]	2001	Bushehr city	*L. infantum*	-	Human	DAT
[31]	2006	Northwest of Iran	*L. infantum*	-	Dog	DAT
[54]	2015	East Azerbaijan	*L. infantum*	-	Cat	NNN and BHI Agar
[31]	2006	Azarshahr	*L. infantum*	-	-	DAT
[9]	2021	Fars province	*L. infantum*	-	Dog	PCR and DAT
[33]	2017	Kerman city	*L. infantum*	-	Cat	ELISA and PCR
[30]	2010	Shiraz	*L. infantum*		Cat	PCR and isoenzyme
[32]	2012	Nurabad mamasani	*L. infantum*	-	Dog	PCR
[35]	2008	Fars province	*L. infantum*	-	Human and Dog	DAT and PCR
[36]	2013	Tehran	*L. tropica*	-	Dog	RAPD-PCR
[37]	2014	Iran	*L. tropica*	-	-	PCR-RFLP
[38]	2015	Kerman city	*L. tropica*	-	Dog	PCR
[39]	2006	Meshkinshahr	*L. tropica* and *L. infantum*	-	-	DAT
[40]	2004	East Azarbaijan	*L. infantum*	*Phlebotomus keshishiani*, *P. sergenti*	-	PCR
[41]	2013	East Azarbaijan	*L. infantum*	*P. kandelakii*	-	PCR
[42]	2008	Shahreza	*L. infantum*	*P. majo, P. sergenti*	-	PCR
[43]	2009	Northeast of Iran	*L. infantum*	*P. perfiliewi*	-	PCR
[44]	2006	Nurabad mamasani	*L. infantum*	*P. alexandri*	-	PCR
[45]	2007	Qom	*L. infantum*	*P. major*	-	DAT
[46]	2014	Alborz	*L. infantum*	*P. tobbi*	-	PCR
[47]	2014	Northwest of Iran	*L. infantum*	*P. perfiliewi*	-	PCR
[48]	2018	Ardabil	*L. infantum*	*P. kandelakii*	-	DAT
[49]	2008	Fars province	*L. infantum*	*P. major*	-	PCR
[50]	2012	Ardabil	*L. infantum*	*P. tobbi*	-	PCR
[51]	2009	Ardabil	*L. infantum*	*P. perfiliewi*	-	PCR and ELISA
[52]	2013	Fars province	*L. infantum*	*P. papatasi*	*Tatera indica*	PCR
[53]	2015	Ardabil, Fars	*L. infantum*	*P. kandelakii*, *P. major*, *P. alexandri*	-	DAT
[56]	2012	Kohgiluyeh and Boyer-Ahmad,	*L. infantum*	-	Dog	DAT
[57]	2004	Tehran, Meshkinshahr, Isfahan, Bushehr, East Azerbaijan	*L. infantum*	-	*Rhombomys opimus, Meriones libycus, T. indica*), And dogs	Random Amplified Polymorphic DNA [RAPD]
[58]	2011	Sarab county	*L. infantum*	-	Fox	ElISA and IFA

were remarked as VL vectors in Ardabil province and *P. papatasi* as the VL reservoir in Fars province.[50-52] Although VL had a variety of vectors in Iran, *P. kandelakii*, *P. major*, *P. alexandri*, *P. sergenti*, and *P. tobbi* were reported as the most common vectors of *L. infantum* in different regions of Iran (Table 2).[53]

Reservoirs of VL in Iran

We systematically recorded 32 studies on VL reservoirs as the canine and various rodents in Iran from 2001 to 2021. Canines were reported as the reservoir of VL in Kohgiluyeh and Boyer Ahmad, Tehran, Fars, and Khuzestan provinces.[9] Some studies confirmed the existence of *L. infantum* in cats in Fars, East Azerbaijan, and Kerman provinces[30, 33, 54] as well as the reservoirs of *L. infantum* in Fars province.[28, 31, 55] Furthermore, dogs were noted as VL reservoirs in Bushehr, Fars, and Kohgiluyeh and Boyer-Ahmad provinces, respectively.[5, 27, 34, 35, 37, 56] On the other hand, Rassi et al. (2013) illustrated *Tatera indica* as the reservoir of *L. infantum* in Fars province.[52] Mohebali et al. (2004) presented rats of *Meriones persicus* and *Mesocricetus auratus* as the reservoirs of *L. donovani* and *L. infantum* in Bushehr and Ardabil provinces, respectively.[57] In a study by Khanmohammadi et al. (2010) in Sarab County, *L. infantum* was observed in foxes.[58] According to the studies mentioned above, dogs and humans are, respectively, the most common reservoirs of *L. infantum* in Iran. *L. infantum* infection was also seen in foxes, cats, and rodents in some regions of Iran.[30-33] Table 3 shows the infection rate and reservoirs of VL in Iran (Table 3).

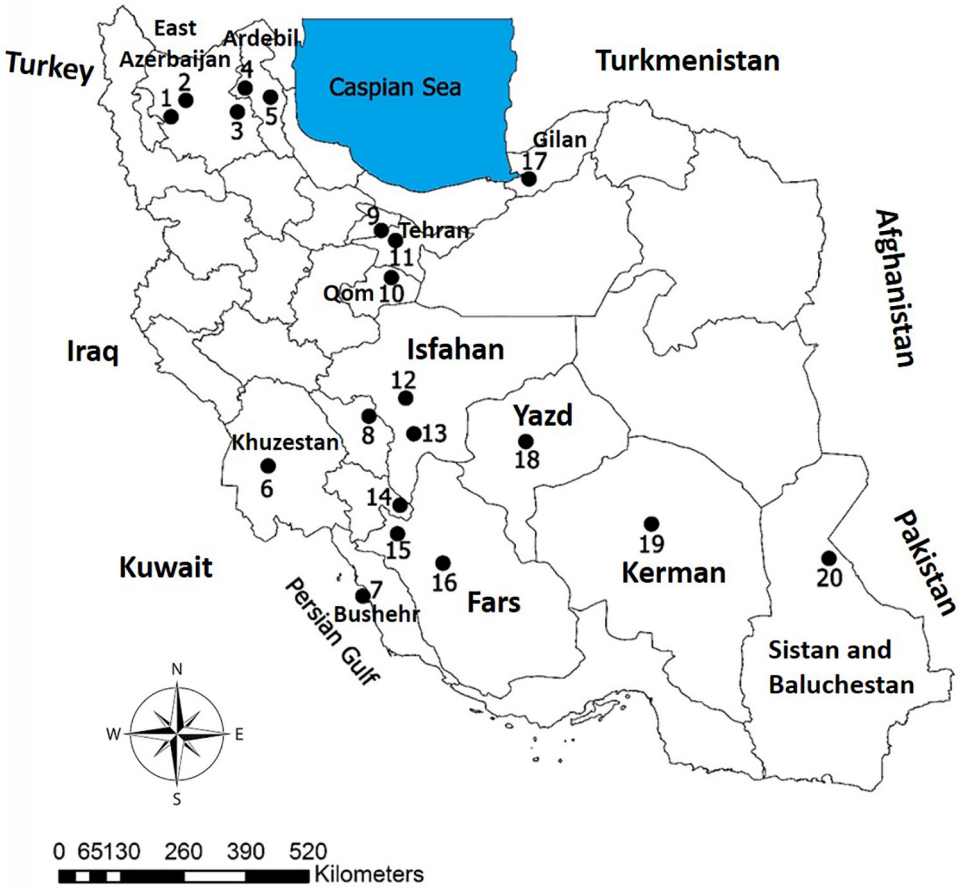

Figure 2: Various endemic regions of VL in different areas of Iran, while *L. infantum* was reported as the causative agent (1. Azarshahr, 2. Sarab, 3. Tabriz, 4. Meshkin Shahr, 5. Ardabil, 6. Ahvaz, 7. Bushehr, 8. Shahr-e Kord, 9. Karaj, 10. Qom, 11. Tehran, 12. Esfahan, 13. Shahreza, 14. Yasouj, 15. Nurabad, 16. Shiraz, 17. Gorgan, 18. Yazd, 19. Kerman, 20. Zahedan).

Table 2: Vectors of Visceral Leishmaniasis in Iran

Vector	Some important infection rates (%)	Reference
Ph. caucasicus	4.2	40
Ph. kandelakii	4.223	41
Ph. major	2	42
Ph. perfiliewi	14.3	43
Ph. alexanderi	17.34	44
Ph. tobbi	1.25	46
Ph. perfiliwi	6.16	47
Ph. major	8.3	49
Ph. tobbi	6.25	50
Ph. perfiliwi	1.47	51
Ph. papatasi	17.6	52

Table 3: Reservoirs of Visceral Leishmaniasis in Iran

Reservoir	Some important infection rates (%)	Reference
Dog	23.4	58
Rodent	13.7	57
Human and dog	93.3	56
Dog	88.24	55
Dog	46.7	9
Cat	6	54
Cat	10	30
Cat	19.29	68
Rodent (*Tatera indica*)	44	46
Rodent (*Nesokia indica*)	0.24	67

Table 4: The infection rate in reservoirs of Visceral Leishmaniasis in Iran based on serologic and molecular tests

PCR-positive		Seropositive/parasitology (%)		Reference
-		Dogs 21.6	Children 7	29
-		Cats 10		30
-		5.3		31
23		Dogs 5.5		32
16.7		Cats 6.7		33
30		-		34
North-western Fars	South-eastern Fars	North-western Fars	South-eastern Fars	35
16	8.5	1.9	1.3	
DAT	59.2	-		36
83.3		-		37
0.42		-		38
-		11		39
3.33		Dog 46.7		9
0.24		Rodent 39		67

Table 4 demonstrates the infection rates in reservoirs of VL based on serologic and molecular tests.

Discussion

Leishmaniasis occurs in three forms worldwide, including symptomatic (acute and chronic), asymptomatic (latent), and subclinical (mild symptoms).[5-7] Despite the wide variety of VL vectors for *L. infantum* and *L. tropica*, the main vectors were *P. sergenti*, *P. major*, *P. kandelakii*, and *P. tobbi, P. kandelakii* and *P. perfidious*, *P. major*, *P. keshishiani*, and *P. alexandri* in northwestern and southern regions of Iran.[59] In another study, *L. infantum* was the causative agent, and *P. kandelakii*, *P. perfiliewi*, *P. transcaucasicus*, *P. tobbi*, *P. major*, *P. keshishiani*, and *P. alexandri* were the vectors of VL in Iran.[6] In some review studies in Iran, *L. infantum* was demonstrated as the causative agent of VL, while *P. major*, *P. kandelakii*, *P. keshishiani*, *P. alexandri*, *P. perfiliewi*, and *P. tobbi* were the vectors.[60, 61]

Our findings also indicated that dogs and humans were the reservoirs of VL due to *L. infantum* and *L. tropica* in different regions of Iran. In addition, dogs, cats, and rodents were the animal reservoirs of *L. tropica*, and dogs were demonstrated as the most common reservoir.[61] On the other hand, domestic and wild dogs were implicated as the reservoirs of *L. tropica,* and the infection was seen randomly both in humans and rodents.[6, 59] In a meta-analysis conducted by Shokri et al. (2017), 16% of dogs were infected with *L. infantum* in Iran.[62] Doges and some other species of subfamily caninae, including foxes and jackals, were respectively reported as the main reservoirs of *L. infantum* in Iran.[11, 60] Indeed, dogs were the reservoir of *L. tropica*, but *L. tropica* reservoirs were first reported to be humans and then dogs in the country.[60, 63] In the current study, *P. sergenti* and *P. major* were the main vectors of *L. infantum* and *L. tropica*, and dogs, the Caninae subfamily, and humans were the reservoirs, while the dogs were the most important reservoir.

Conclusion

Given that vectors and reservoirs of VL play an important role in reducing the disease burden [64-66], special attention should be paid to domestic and wild dogs in endemic regions of VL. The spread of the disease to other vectors and species of *Phlebotomus* and new reservoirs, such as cats, Caninae subfamily (e.g., foxes and jackals), and rodents such as *Nesokia indica* [67], should also be taken into consideration because it can increase the distribution and prevalence of the disease in endemic regions and other areas.[68] Based on the findings of this review, first *L. infantum* and then *L. tropica* were the causative agents of VL in Iran. The vectors consisted of sandflies, including *P. sergenti*, *P. major*, *P. kandelakii*, and *P. tobbi*, and the main reservoirs were dogs, Canidae, and humans. It was shown that some species of rodents, which were not previously infected, and cats and foxes, could be the new reservoirs of VL in Iran.

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