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Emerging Epidemics of Cutaneous Leishmaniasis in Iran: Operational Aspects, Management and Implemented Control Approaches

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ABSTRACT

Cutaneous leishmaniasis (CL) in Iran could be considered as an emerging disease that is rapidly increasing and expanding its traditional geographical range to new foci. Sixteen registered emerging epidemics have occurred since 1998 in different provinces. Various risk factors, including agricultural development, earthquake, movement to endemic areas, construction of buildings near colonies of rodents, sleeping outside, cross-border movements, and poor sanitation, play crucial roles in the expansion of the disease. The mentioned risk factors can lead to the gradual or sudden emergence of new CL epidemics, and long-lasting endemic foci can also erupt into epidemics. This paper reviews the emerging epidemics published between 1998 and 2019 in Iran with particular emphasis on the operational aspects of control and related risk factors caused by anthroponotic CL (ACL) and zoonotic CL (ZCL). The competent surveillance system should be extended to all high-risk areas to facilitate controlling the emerging epidemics of ACL and ZCL in the affected areas.

INTRODUCTION

Leishmaniasis remains a significant health problem with growing serious health impacts, more frequently in the Eastern Mediterranean Region (EMR), Indian Subcontinent, Latin America, and Africa [1]. Leishmaniasis is neglected mainly in tropical countries and constitutes the ninth-largest disease burden in terms of global morbidity and mortality among infectious diseases [2].

The disease occurs in 98 countries and three territories on four continents [3], where approximately 12 million people are affected, over one billion people are currently at risk and 1-2 million new cases occur annually [4]. Cutaneous leishmaniasis (CL) is the most common form of the disease, representing 75% of the total cases in which more than 90% of the cases are from Afghanistan, Iran, Iraq, Syria, Algeria, Saudi Arabia, Peru and Brazil [5]. CL is mostly unreported and concentrated in remote rural areas or urban slums [2].

Over the past decades, global data indicated emergence of new CL foci in different countries, *i.e.*, Bolivia [6], Pakistan [7], Afghanistan [8], Morocco [9], Israel [10], Brazil [11], Libya [12], Sri Lanka [13], Europe [14] and Iran [15]. Various risk factors including environmental modifications due to urbanization and natural disasters, lack of competent vector and reservoir control strategies, population displacements, drug resistance, poor sanitation, and human behaviors play essential roles in expansion of the disease [1,5,16-19]. The mentioned risk factors can converge to gradual or sudden emergence of epidemics and long-lasting endemic foci can also erupt into epidemics [11].

National reports by the Ministry of Health and Medical Education (MOHME) in Iran have shown an average incidence rate of 20 and 40 cases per 100,000 people [15,20]. In Iran, this disease occurs in 17 of 31 provinces. In recent years, official reports indicate an average of 15,000-20,000 cases per year. Although CL is among the notifiable diseases, the real incidence is underestimated as many people with CL in the endemic areas, particularly in remote ones, do not usually refer to physicians. This portion varies with the area, indicating an underreporting of the actual burden of the disease.

This review focuses on the published works between 1998 and 2019 on anthroponotic cutaneous leishmaniasis (ACL) and zoonotic cutaneous leishmaniasis (ZCL), the two

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primary manifestations of the disease in Iran, and the adopted control measures.

Here, we discuss various aspects of the emerging epidemics of CL in Iran. We also reviewed the practical aspects of control approaches, and implementation of preventive measures including environmental management, chemical control strategies, vector, and reservoir incrimination and control approaches, personal protective measures, detection (passive and/or active) and identification of cases, treatment and referral of CL patients to higher provincial levels. Our literature review indicated no previous report on the topic. Therefore, to our knowledge, this work was the first comprehensive review of the CL emerging epidemics which explores the operational aspects of CL in Iran.

Emerging epidemics. CL falls into the category of emerging diseases, which includes those that either have recently appeared in populations, or are of a rapid increase in incidence or expanding their geographic range to new foci [21]. CL appears to be an emerging disease in most parts of Iran, north-east Afghanistan [8], and north-west Pakistan [7]. In Iran, epidemiological data indicate a considerable rise in CL in many provinces defined as emerging foci (Table 1]. The majority of the recent epidemics have stricken central provinces of Qom [22,23] and Isfahan [24] down to the south [23], southeast [25-31] and central [24] of the country (Fig. 1]. Outbreaks and epidemics are characteristics of both ACL and ZCL, which are caused *by Leishmania tropica* and *Leishmania major*, respectively.

In Iran, *L. tropica* causes ACL, which is transmitted by *Phlebotomus sergenti*, a sandfly that lives equally well in the vicinity of human habitation or far from people, and the human (*Homo sapiens*) is the reservoir host [11]. This species tends to live in towns and villages inside the affected human populations, mainly in the emerging epidemic foci of the two neighboring provinces of Iran (Fig. 1]; Kerman [32-34] and Yazd [35]. The causative agent of ZCL, *L. major*, is transmitted by the sandfly, *Phlebotomus papatasi*. This species has an extensive distribution range in semi-arid landscapes, and it is frequently synanthropic (living in close association with the human) but also lives far from human habitation. The distribution range of this species is broader than that of *Ph. sergenti*, which is limited by the presence of suitable reservoir hosts [36-38]. It feeds on a wide variety of hosts, including mammals particularly gerbils and humans [39-43].

Emerging outbreaks of both ACL and ZCL are often associated with migration and the introduction of susceptible individuals into endemic areas where anthroponotic or enzootic transmission cycle is established. Seasonal labor movements may also spread the disease, with the return of migrants to endemic areas, as appears to have occurred in several foci in Kerman [25,29,31,35,44], Yazd [35] and Sistan and Baluchistan [45], Fars [46] and Isfahan [24] provinces.

Cross-border movement is also a significant risk factor [1,5,45]. Many new-comers from endemic areas of Pakistan and Afghanistan cross-border and arrive in different provinces of the country. Such infected migrant carriers are believed to be the primary source of outbreaks in some parts of Iran. Other contributory factors favoring transmission of CL included primitive housing conditions and low standards of hygiene, which increase the risk of transmission in urban and peri-urban areas. For instance, construction of buildings near rodent colonies [22,24], organic remnants, piles of bricks, and stones constitute potential breeding and resting sites for sand flies [24]. Generally, CL is a disease of poverty that is more prevalent among low-income groups and those with limited access to health care facilities [11].

Control strategies. In most instances, no single effective measure is available to reduce transmission, and commonly a combination of various approaches is more effective. Control measures can be implemented in the case of epidemics, but they need to be based on previous experience which is adapted to local conditions. In all instances, the following measures should be undertaken immediately [36].

Assigning a health clinic. The first step to control an emerging epidemic of CL is to establish a specific health clinic. This clinic can be used as a headquarter for various activities involved in the course of the control program. In the southeastern Iranian district of Bam and the surrounding cities, the emerging epidemics of CL occurred in several foci, after the massive earthquake in 2003 [18,25-27,29-31,44,47]. Most of the control activities including personnel training, face-to-face health education, diagnosis and identification of CL cases, treatment of patients, active and passive case-finding, implementation of vector control measures, modification of the physical environment, and referral of non-healing cases to specialists or assigned clinics, were initiated.

Detecting and identifying cases. The initial lesion starts as an erythematous papule (Fig. 2A) and then develops to a painless nodule (Fig. 2B), which may produce a nodule and pruritus. The papule or nodule may heal without developing into an ulcer or other clinical forms. The nodules usually ulcerate in a volcanic or satellite form; elongated lesions tend to align along skin creases or evolve to one of the several clinical forms of the disease (Fig. 2A-I). Various clinical presentations might develope due to the generation of strain or species specificity of the causative agent and also specific types of immune responses to *Leishmania* infection [26,48,49]. The lesions may heal spontaneously and leave small scars or produce a large scar (Fig. 2J).

For parasitological diagnosis, skin scraping is obtained from the edge of the active lesion using a small scalpel and blade. A smear is prepared from the materials obtained, fixed, and stained by Giemsa or an equivalent stain and microscopically examined for detecting amastigotes [50]. Simultaneously, another specimen should be obtained for culture in simple biphasic media such as Novy-MacNeal-Nicolle (NNN) medium and then subculture in RPMI1640 for further characterization of the causative agent to strain or species level by molecular (PCR) or biochemical (isoenzyme electrophoresis) techniques and/or in some instances animal inoculation [11,50,51]. The availability of powerful new tools expands the power of laboratory-based surveillance and increases the feasibility of field applications. Identification of the causative agent is essential for treatment modality and

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strategy planning [36,52].

Treating the cases. The standard therapy for all clinical forms of leishmaniasis is pentavalent antimonial drugs, including meglumine antimoniate (Glucantime) and sodium stibogluconate (Pentostam), although the latter drug has currently no further use in the treatment of leishmaniasis [52]. Most of the clinical features are unresponsive to therapy and serve as the primary source for the transmission of the *Leishmania* agent [19,48,53-55].

In Iran, meglumine antimoniate is the drug of choice, which is given by systemic or intralesional injections, as recommended by WHO [62] and by the guidelines of the MOHME [15]. Glucantime is given to the patients free of charge by the governmental health clinics throughout the country. This drug is frequently used in combination with the second-line compounds or along with cryotherapy [15]. Unfortunately, this medication is of limited use due to prolonged treatment schedule, toxicity, parenteral administration and emergence of resistance [63,64]. For the treatment of non-healing forms of CL, such as lupoid leishmaniasis, a frequent sequel of ACL, a combination of Glucantime and allopurinol has been used with acceptable efficacy [65].

Personal protection measures. Individual protective measures in endemic and emerging epidemic foci include the application of repellents, such as diethyltoluamide (DEET), to skin or clothing to reduce man-vector contact. Bednets, screens, and curtains impregnated with insecticides such as permethrin or deltamethrin may provide proper protection [66-68]. Dressing of the lesions reduces the contacts between humans and the biological vector [15]. Data exhibited that implementation of impregnated bed nets and insecticide residual spraying (IRS) and long-lasting insecticide-treated nets (LLITNs) were highly effective in the control of the principal vectors against both ACL and ZCL in endemic areas of the country; although, they are not well accepted behaviorally [66,67,69,70].

Environmental management. Modification of the physical environment may have a dramatic effect on the relative abundance of vectors and levels of transmission. Actual or potential sand fly breeding sites, such as rubble and garbage piles, can be eliminated through community involvement in urban and peri-urban areas to help control the vector population. About 10 million tons of debris and raw bricks were removed after the 2003 Bam earthquake [71]. Climate change has not been well studied in Iran, although it plays an important role and might have substantial effects on the ecology and distribution of vectors and reservoir hosts. Global warming, rainfall, and humidity are expected to affect the epidemiology of CL by several mechanisms, which in turn could lead to massive movement and migration of people to CL endemic areas, where the transmission cycle is active [5,13,16].

Table 1. Emerging epidemics of cutaneous leishmaniasis in Iran, 1998 to present

Region or district/province	Occurrence year	Main risk factor	Identification method	Cutaneous form	Reference
Orzoeihe/Kerman	1998	Agricultural development	ELISA, IFAT& mouse inoculation	ZCL	[27]
Ardestan/Isfahan	1998-1999	Construction of buildings (rapid urbanization)	Isoenzyme	ZCL	[24]
Ghanavat/Qom	1998-2001	Construction of buildings near colonies of rodents & movement to endemic areas	RAPD-PCR	ZCL	[22]
Yazd/Yazd	1999-2000	Human movement & high density of vector	RAPD-PCR	ACL	[35]
Ardakan/Yazd	2001	Construction of buildings near colonies of rodents, sleeping outside & agricultural development	RAPD-PCR	ZCL	[56]
Sabzevar/ Khorasan Razavi	2001-2002	Construction of buildings near colonies of rodents, poor sanitation& sleeping outside	RAPD-PCR	ZCL	[57]
Bam/Kerman	2008	Earthquake	Conventional PCR	ACL	[58]
Zarindasht/Fars	2003	Earthquake	Conventional PCR	ZCL	[59]
Shiraz/Fars	2003	Construction of buildings	Nested-PCR	ZCL	[46]
Mirjaveh/ Sistan&bluchestan	2005-2006	Cross-border movements	Conventional PCR & mouse inoculation	ZCL	[45]
Ghomrood&Ghavavat /Qom	2006-2011	Immigrants	ITS1-PCR	ZCL	[23]
Dehbakri Bam/Kerman	2008	Movement to ACL endemic areas	Conventional PCR	ACL	[31]
Mohammadabad Jiroft/Kerman	2008	Movement to ACL endemic areas	Nested-PCR	ACL	[44]
Bahraman/Rafsanjan, Kerman	2006-2010	Colonies of rodents, human habitations	Conventional PCR	ZCL	[60,61]
Nezamabad Bam/Kerman	2010	Movement to ACL endemic areas	Conventional PCR	ACL	[25]
Abdanan/Ilam	2015-2016	Multiple	RFLP-PCR	ZCL	[17]
Narmashir county/Kerman	2016	Population displacement	HRM-PCR	ACL	[18]

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Fig. 1. Geographical distribution of emerging epidemics of anthroponotic cutaneous leishmaniasis (ACL) and zoonotic cutaneous leishmaniasis (ZCL) in Iran, 1998-2019



Fig. 2. Representative of skin lesions observed in cutaneous leishmaniasis patients in epidemic foci of Iran [53]: (A) An erythematous papule, (B) a nodule, (C) lupoid leishmaniasis, (D) an erysipeloid, (E) sporotrichoid, (F) diffuse cutaneous lesions, (G) disseminated cutaneous leishmaniasis, (H) multiple cutaneous ulcers, (I) ulcerated lesions with lymph edema, (J) a vast scar.

A significant risk factor in Orzoeihe district in the western province of Kerman, southeast of Iran, was established with the new water wells and electric pumps, which created new irrigation schemes and cultivation of new crops. This new agricultural project provoked a sharp change in the reproduction patterns of the main reservoir, *i.e.*, the gerbils [26,27]. A large area was cultivated with cucumbers, melons, and various other grain crops, which provided an extraordinarily suitable source of food for gerbils and breeding of vector for ZCL. Consequently, there was a sudden increase in the population of rodents and vectors, followed by an epidemic of ZCL in rural residential areas [26-28].

Other contributing factors can also trigger and increase the rate of the CL epidemics and facilitate the broader and more rapid spread of infection. Following the earthquake in Bam, various occupational positions became available during the reconstruction of buildings. Economic conditions encouraged mass movement [25,29,31,44] from various provinces particularly Fars [46] and Qom [22,23] to the affected areas. Numerous susceptible labor forces, mostly from non-endemic areas within the province and from other provinces of the country, traveled to disastrous areas, where active foci of CL were present. Migration is a significant risk factor for ACL [13,72].

Incriminating vectors. A wide range of vectors continues to be incriminated in foci in different parts of the country [32,37,60]. However, the role of some vectors in the transmission of CL has not well been established. Among different species of phlebotomine sand flies, only *Ph.*

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sergenti and *Ph. papatasi* are incriminated as the principal biological vectors of ACL and ZCL, respectively [24,32,39-41,43,73,74].

Incriminating reservoir hosts. The reservoir hosts vary among foci and must be carefully determined before the adoption of control measures. Despite *Leishmania* spp. isolation from various species of gerbils, the role of these rodents in the maintenance of *L. major* requires more studies and elucidation. *Rhombomys opimus*, the great gerbil, is the primary reservoir host of *L. major* in the arid regions of central Iran [75-77]. However, *Tatera indica*, *Meriones libycus* and *Meriones hurrianae* are other important reservoir rodents in some foci [38,42,78].

While ZCL is confined to small rodents, the primary reservoir host in most provinces of Iran, and comprise approximately 80% of the total cases of human CL caused *to L. major*, ACL encompasses only 20% of the overall cases [15]. In Iran, ACL is induced by *L. tropica* which is largely limited to humans, but incidental cases of dogs have also been reported in some ACL foci. This fact represents that dogs may also be implicated in the life cycle of the parasite and play a secondary role in transmission of the *L. tropica* infection [79-83].

Control of ACL. Control of ACL is mainly limited to early diagnosis and prompt treatment of patients through an effective surveillance system which requires a dedicated active and passive case-detection [30,36]. At present, no vaccine is available [68,84,85], and the use of first-line drugs, *i.e.*, the pentavalent antimonials, is limited due to toxicity, low efficacy, cost, and the emergence of drug resistance [52,63,64]. In the Old World, leishmaniasis recidivans (lupoid leishmaniasis), is usually caused by *L. tropica* and become destructive and disfiguring over the years [47,49,65]. In foci of ACL, particularly in Bam lupoid lesions last for many years and patients might carry parasites throughout the long periods of several sessions of transmission cycles [47,62]. During Bam epidemics, insecticide spraying of houses, outdoor yards, and high-risk areas was repeatedly practiced to control *Ph. sergenti*; however, these methods were not adequately evaluated [29,31,86]. Application of large scale impregnated screens and curtains in high-risk areas of the city of Bam [68] have also shown significant short-term efficacies. The results also suggested that shrinkage in the human reservoir pool in response to the intervention might play a significant role in prolonging the preventive effect beyond the insecticidal life of impregnated materials in foci of ACL. Special attention should be paid to those with underlying diseases including diabetics, young children, opium addicted individuals, HIV coinfection and those with chronic diseases [19,87-89] who might be at higher risk of contracting severe infection, particularly during the transmission season.

Control of ZCL. Control of ZCL is very different from ACL since it occurs in an acute form with shorter duration time and often needs no treatment. In emerging epidemics, control efforts should be directed toward gerbils as the primary reservoir host and also *Ph. papatasi* as the primary biological vector. In the foci where *R. opimus* is the primary host, the inexpensive and remarkably effective approach [19,76,77] was using zinc phosphide [2.5%) as a rodenticide. *Rhombomys* is readily identifiable by its burrow system and distinctive morphology [61,75]. This control program has significantly reduced the incidence rate of ZCL when compared to the control group at the end of the first and second year of operation [77].

Malarial spraying impact. Malaria control programs, based on outdoor and indoor residual insecticide spraying, have introduced a side benefit for leishmaniasis control and decreased its incidence in endemic areas [90]. In many areas, the resurgence of leishmaniasis is believed to be due to the cessation of these campaigns.

CONCLISION

In Iran, CL appears as an emerging disease with a significant burden and serious public health impact. This disease is rapidly increasing and expanding its geographic range to new foci in most provinces of the country. Various risk factors played essential roles in increasing the CL cases, which consist of environmental modifications due to urbanization and disasters, population movements, lack of vector and reservoir control strategies, drug resistance, poor sanitation, human behaviors, and climate changes. Such changes can lead to the emergence of new CL epidemics. The effective surveillance system should be sustained and extended to all high-risk areas to control the emerging epidemics of ACL and ZCL in the affected areas. Experiences gained during emerging epidemics could be used as a model to develop control programs and also plan future control strategies, particularly in emerging foci, where a gradual or sudden eruption of the new cases of CL occurs.

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CONFLICT OF INTEREST

The authors declare that there is no issue related to this article to be conceived as a conflict of interest.

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