Chapter 2

Transmission to Humans

Miroslava Avila-García, Javier Mancilla,
Enrique Segura-Cervantes and
Norma Galindo-Sevilla

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1. Introduction

Tissue parasites such as *Leishmania* are transmitted from host to host through a vector species, and transmission can be from human to vector to animal or vice versa (zoonotic transmission), which occurs in rural and periurban environments or from human to vector to human (anthroponotic transmission), which occurs in urban environments. *Lutzomyia* and *Phlebotomus* species have long been known as the primary transmitters of leishmaniasis. However, in recent decades, evidence has been building for the existence of alternative transmission pathways. These pathways involve direct contact with infected tissues, such as may be encountered during surgical/therapeutic procedures, biological/reproductive activities, certain work-related practices and by unsafe drug use, all of which are reviewed below.

2. Transmission forms

2.1. The life cycle of *Leishmania* spp.: the vector transmission

Leishmania spp. is a parasite with a dimorphic life cycle that is controlled by the passage from vector to host [1]. As such, the parasite has developed novel adaptations to survive within the vector [2]. The vector phase of the life cycle begins when the vector ingests blood containing the parasites. Following ingestion, the parasites eventually reach the midgut, where they are held for approximately 4 hours in the peritrophic matrix. There, the amastigote cells differentiate into small, motile cells with short flagella, a form known as the procyclic promastigote. Next, *Leishmania* initiates the first stage of the vector life cycle, which occurs over the following 24-48 hours. The body of the parasite elongates in the next 72 hours to form the nectomonad

promastigote, and the microorganism then breaks down the peritrophic matrix to reach the midgut lumen and migrate into the thoracic region of the vector. Once there, the promastigotes differentiate into leptomonad promastigotes by decreasing in size and changing the location of their flagella, which is followed by a second replication cycle during days 5-7. This process produces a massive infection in the anterior portion of the midgut, where the parasites differentiate into metacyclic promastigotes within the stomodeal valve, ensuring a large number of parasites for the purpose of infection. To protect the metacyclic promastigotes, the leptomonads also differentiate into gel-producing promastigotes, which surround the leptomonad and metacyclic promastigotes. The latter cell type is considered to be the infective form of the parasite because it possesses an elongated flagellum, which allows for motility and resistance to complement-mediated lysis. When metacyclic promastigotes differentiate into haptomonad promastigotes, they form parasitic rings that plug the stomodeal valve, eventually leading to its degeneration. Finally, this process allows the parasites to pass into the proboscis [2], where they can inoculate the host during feeding of the vector.

Upon entering the host, the parasite first encounters a host immune reaction following activation of the complement system. With respect to this process, four distinct activation pathways have been identified: the classical pathway, the alternative pathway, the lectin pathway and the extrinsic pathway [3]. In humans, the parasite can evade the immune response by inhibiting complement-mediated lysis, which occurs within the phagolysosomes of macrophages. This protective effect is conferred by the membrane protease gp63, or leishmanolysin, which inhibits attacks against the parasite cell membrane by adhering to complement components [4]. Promastigote-stage parasites differentiate into small, round cells 3-5 μm in size that lack flagella, known as amastigotes. This form can be readily observed within host cells by microscopy, where they are referred to as Leishman-Donovan [5] bodies. Finally, when multiplication of the parasites exceeds the holding capacity of the phagocytic cell, cell lysis occurs, releasing the parasites to infect new cells.

By some conservative estimates, a vector might release between 1-1000 metacyclic promastigotes into the host during feeding [6-7]. However, other estimates based on molecular biology techniques indicate that a vector might release as many as 600 to 100,000 metacyclic promastigotes during a feeding period and that this number varies as function of feeding time. In addition, it is known that large numbers of parasites actually increase vector feeding time, as the parasites physically obstruct proper functioning of the proboscis [8]. Therefore, based on these findings, between 100 and 100,000 metacyclic parasites are commonly used to inoculate the footpads or pinnae of animals in *in vivo* models of infection [8-10].

2.2. Organ transplants, blood transfusions and hemodialysis

Therapeutic advances in a wide variety of medical fields have dramatically improved overall quality of life and life expectancy in modern societies. This has partly been achieved through the development of techniques such as organ transplantation, hemodialysis, and blood transfusion, which are particularly useful for the treatment of chronic disease. However, the transmission of infectious diseases during such procedures must account for and avoided. Furthermore, human migration can easily transport diseases transmitted by vectors from

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endemic locations to non-endemic locations, as often happens with protozoan parasites of the blood, such as *Leishmania* [11-12], *Trypanosoma* and *Plasmodium* [3].

During organ transplantations, there are several possible ways in which microorganisms such as *Leishmania* can be transmitted, including reactivation of dormant parasites in the recipient following treatment with immunosuppressants, infection by parasites derived from the donor, transmission of parasites through blood transfusions during the surgical procedure and *de novo* transmission [11-12]. *Leishmania* infections have been observed in individuals who have undergone kidney [13-16] and liver [17-18] transplants, as well as in patients that have undergone heart [17, 19-23], lung [24], pancreas [25], stem cell [26-27] and bone-marrow transplants, although these are less common. Overall, the number of leishmaniasis cases resulting from organ transplants is estimated to be fewer than 100 in total [11, 13-16], which were mainly associated with kidney transplants. A primary risk factor for transmission is whether the donor had lived in an area where leishmaniasis was endemic. However, this subject is not commonly addressed during screening processes, and relevant laboratory tests are not usually carried out on organ donors [28]. Therefore, it is important to generate and review epidemiological data concerning leishmaniasis, as the number of infected individuals who are asymptomatic could be even greater than the number of those showing clinical symptoms [17]. There have also been reports of organ donors who were asymptomatic before surgery but who died of leishmaniasis several months after the transplantation procedure. Furthermore, there has been at least one case in which an organ recipient developed leishmaniasis symptoms two years after the transplantation procedure [29]. In cases where individuals show symptoms approximately one month after transplantation, transmission is generally considered to be due to the reactivation of dormant parasites within the recipient [30]. On the other hand, in cases where leishmaniasis symptoms are observed approximately 18 months after receiving a new organ, transmission is generally considered to be due to the *de novo* acquisition of parasites [11-12, 16]. In either case, the suggested course of treatments to favour transplant survival includes corticosteroids [24], immunosuppressants [13-14], or monoclonal antibodies [11], which favor the development of leishmaniasis.

Infrequent or atypical symptoms can cause delayed diagnosis of leishmaniasis. The primary clinical signs and symptoms related to *Leishmania* infections due to organ transplantation are fever, splenomegaly, hepatomegaly, leukopenia and hypoalbuminemia [14, 31-32]. Unfortunately, the therapeutic responses to such cases are often insufficient to save the patient's life, which can be ascribed to late diagnoses, particularly severe infections and other health complications [13] due to prolonged immunosuppressive regimens [16, 24].

Blood volume loss or deficiencies in specific blood components are indicators that a transfusion of blood or blood-derivatives from a donor to a recipient may be necessary. Blood transfusions are frequently performed during or after surgical interventions, and in the case of leishmaniasis patients with a history of organ transplantation and blood transfusion, the disease is generally considered to be a complication of the transplantation process [15, 32-33]. In patients without such a background, infections are generally considered to have occurred through the transfusion of blood or blood-derived products. The first case of *Leishmania* transmission via a blood transfer was documented in China in 1948, when two girls were given 20 mL of blood

intramuscularly to stimulate passive immunity against measles and rubella. The blood came from their mother, who was hospitalized days later with symptoms suggestive of visceral leishmaniasis; this diagnosis was made one month after her being hospitalized. Therefore, due to the medical history of the mother, the girls were monitored over the subsequent months. Both girls developed leishmaniasis 9-10 months after the blood transfer [34]. Although this case was not due to blood transfusion *per se*, it is the first documented case in which the use of blood components for therapeutic purposes resulted in the contraction of leishmaniasis.

In general, the causative agents of visceral leishmaniasis belong to the *donovani* complex of species, although there have also been reports of visceralization in species more typically related to the mucocutaneous and cutaneous clinical presentations of the disease. These types of clinical presentations have primarily been observed in individuals with compromised immune systems, such as HIV-positive patients. However, there has been a single reported case of a patient with these characteristics who also had a history of kidney transplantation and blood transfusions. Furthermore, there was no history of vector exposure as the patient was not living in an endemic region. The infection hypothesis was ruled out by searching for signs of *Leishmania* in the blood by PCR and by searching for *Leishmania*-specific antibodies in the donor and in the recipient of the second kidney. The patient's death was caused by complications due to the presence of *T. cruzi*, *S. aureus* and *L. mexicana*. Although the patient's transfusion donors could not be evaluated, based on analysis of other possible transmission pathways, it was concluded that the most likely pathway of infection was through blood transfusion [35].

Among other notable cases of secondary leishmaniasis due to blood products and transfusions, there was the case of a patient with an autoimmune disease, idiopathic thrombocytopenic purpura. The patient was transfused with concentrated platelets on multiple occasions over the 2-3 year period prior to the development of leishmaniasis, a diagnosis that was confirmed by bone marrow aspiration [36].

Another case involved an infant who received a blood transfusion within 7 days of birth due to integument pallor with a subsequent diagnosis of myelofibrosis. The blood donor was a relative who died three months after the donation, after developing hepatosplenomegaly, pyrexia and a fever of unknown origin; the diagnosis was made *postmortem* after the detection of Leishman-Donovan bodies. The infant began to show abdominal distension, fever and integument pallor one month after the transfusion. At 5 months of age, visceral leishmaniasis was diagnosed from a spleen aspirate that scored positive for Leishman-Donovan bodies. Leishmaniasis treatment was initiated without improvement, and two months later, the infant was rehospitalized with anemia, respiratory distress, hepatomegaly and splenomegaly. A liver biopsy revealed changes consistent with steatohepatitis with necrotic foci and lipid granulomas. Furthermore, the biopsy was positive for anti-*Leishmania* antibodies (rK-39), whereas the infant's family members were negative for these antibodies. Due to a severe anemic syndrome, the infant was given a blood transfusion. Despite treatment with antimonials, the infant showed no improvement and indeed worsened with the development of septicemia caused by *Staphylococcus*, *Klebsiella* and *Pseudomonas*. A change of drugs to Amphotericin B only deteriorated the infant's health further, and it died one month after admission [37].

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In a case involving an elderly patient, a 77-year-old woman with a history of chronic atrial fibrillation, hypertension and chronic kidney disease with hemodialysis treatment underwent surgery due to cholecystitis, during which time she received two units of blood. A month and a half later, she presented with fever, diaphoresis and chills during a hemodialysis session and over the next 24 hours; she also showed occasional diarrhea and weight loss. These symptoms did not improve despite treatment with antibiotics. In the intensive care unit following hemodialysis, the patient showed thrombocytopenia and hypotension with good ventricular systolic function, requiring volume recovery and vasopressor therapy; hydrocortisone was also included in the treatment. A bone marrow aspirate confirmed the presence of intracellular amastigotes and numerous extracellular promastigotes, although these were not observed in the peripheral blood. Treatment with Amphotericin B increased her platelet numbers, although hemodynamic deterioration continued until the patient's death. Cultures begun previous to death showed the presence of *Acinetobacter baumannii*, a bacterium that is resistant to multiple types of antibiotics. During a *postmortem* examination, the presence of *Leishmania* parasites in the bile was tested for due to prior gastrointestinal symptoms. The transmission of *Leishmania* through the blood was confirmed when one of her donors (to the source of the units transfused during the cholecystectomy) tested positive for *Leishmania*-specific antibodies [38].

Seven U.S. military groups assigned to Operation Desert Storm in the 1990s developed atypical clinical presentations of *L. donovani* infection that were suggestive of Kala-azar. The symptoms included stiffness, nonproductive cough, diffuse abdominal tenderness, diarrhea, nausea, headache, myalgia, and arthralgia without organomegaly. One of the patients was asymptomatic, whereas two had diseases that compromised their immune systems: renal carcinoma and HIV. The diagnoses were performed using an immunofluorescent antibody test (IFAT). In all cases, the onset of symptoms occurred 1-14 months after their time in Saudi Arabia, and none showed lesions that may have aided in the diagnosis of leishmaniasis [39]. These clinical cases led U.S. authorities to recommend that all candidates who had visited the Persian Gulf be rejected as blood donors. This situation was further complicated by the fact that the conditions under which the *Leishmania* parasite might survive in blood products in bank bloods were unknown. As a result, *in vitro* assays were performed on parasites isolated from the soldiers. The *Leishmania* parasites that were isolated from the individuals participating in Operation Desert Storm included *L. tropica*, *L. major* and *L. donovani*. These parasites were maintained in log-phase culture and used to inoculate donated blood samples, which were then stored at 4ºC for 35 days or at 24ºC for 5 days. It was observed that in whole-blood units stored under these common blood-bank conditions, *L. tropica* intracellular parasites within monocytes could survive up to 30 days at 4ºC and up to 5 days at 24ºC, in contrast to promastigotes in stationary phase or free amastigotes that does not. With respect to fresh frozen plasma, it was observed that intracellular parasites could survive inside monocytes for 25 days at 4ºC and for at least 5 days in the platelet fraction at 24ºC. For erythrocyte fractions frozen with glycerol, survival time of the parasite was 35 days at 4ºC [40]. It is clear that *Leishmania* shows low-temperature resistance, highlighting the very real possibility of parasite transmission from infected individuals, either in the preclinical or asymptomatic phase, to immunocompromised individuals via blood products.

Transmission of *Leishmania* via blood transfusions has been demonstrated in domestic animals [41] and model organisms, and these typically present symptoms following treatment with either infected human blood or blood from experimentally infected animals [40, 42-43]. For example, blood transfusions can be carried out in rodents by transferring 0.1-1.0 mL blood via tail-vein [40] or intracardiac injection [43]. In a study involving hamsters, all groups that received infected blood showed symptoms between 90-120 days following transfusion [43]. It was found that 22.1% of the transfused hamsters scored positive for *Leishmania* by PCR analysis, and 14.75% remained positive when the test was performed again after 12 months. All of the monocyte cultures were negative. Furthermore, it was demonstrated that 29.5% of the transfused hamsters tested positive by at least one of the techniques, with PCR being the most sensitive assay [44].

There have also been various clinical studies carried out on individuals attending blood banks in which the presence of the parasite was assessed for using techniques such as ELISA (enzyme-linked immunosorbent assay) [45], IFAT [46], Western blotting, culturing and PCR [44-45]. ELISA experiments showed that 2.4% of the individuals had *Leishmania*-specific antibodies, whereas 3.5% scored positive by Western blotting analysis; both tests showed a seroprevalence of 7.6%.

Furthermore, questioning may be insufficient to exclude donors that have visited endemic areas within the last 12 months or that have had clinical diagnoses of leishmaniasis, as recommended by the WHO publication *Blood donor selection: guidelines on assessing donor suitability for blood donation*. Therefore, there is a clear need to develop laboratory techniques to identify this microorganism in blood or derivatives, and indeed, several studies have been carried out to detect the presence of *Leishmania*-specific antibodies in healthy individuals who have donated blood.

In cutaneous species, such as those belonging to the *L. mexicana* complex, it is unknown whether the parasite can be transmitted through blood in humans under the same conditions as the visceral species. However, as was previously mentioned, it should be noted that there are cases of HIV patients that have developed visceral leishmaniasis when infected with cutaneous species [35].

In individuals with chronic kidney disease, hemodialysis is a therapy that can greatly improve patient prognosis and prolong and improve their quality of life. However, like many other therapeutic procedures, hemodialysis can have adverse effects, including bacteremia and sepsis due to poor aseptic techniques during treatment [47]. Indeed, it has been documented that if proper care is not taken to sterilize hemodialysis equipment, including the cleaning and replacement of disposable parts, there is high risk of acquiring infectious/contagious diseases [47], including parasitic infections. Unlike with the situation with *Toxoplasma*, [48] *Leishmania* has not been directly linked to hemodialysis patients, although large assays for *Leishmania*-specific antibodies have been performed [49-50] that found the parasite in 9-25% of patients in endemic areas [50]. Despite the fact that no studies directly link *Leishmania* infection to hemodialysis treatment, perhaps because most patients with kidney disease who are treated with hemodialysis also have a clinical history of immunosuppressive blood treatment, organ transplantation and multiple blood transfusions [38, 50-51]. All of these conditions increase

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the possibility of acquiring leishmaniasis and negatively affect patient health, making the analysis of causal factors difficult.

2.3. Sexual transmission

2.3.1. Leishmaniasis in sexual organs in humans

Cases of leishmaniasis of the sexual organs have been reported, manifesting as lesions on the genitals, and such cases have been reported in both humans [52-56] and in animals [57-58]. Three possible mechanisms for the development of leishmaniasis of the sexual organs and genitals have been suggested: (1) local infection derived from a wider systemic infection; (2) infection due to exposure of the genitals to a vector in an endemic area; and (3) infection due to direct contact of the genitals with an ulcerated lesion during intercourse [59].

By questioning patients, such cases of genital leishmaniasis in humans could not always be directly linked to either intercourse [52-53] or to sleeping naked in endemic areas [55]. However, in cases where the lesions were observed on the vulvar regions [53], direct vector-mediated infection can be ruled out, leaving open the possibility for localized infection of systemic origin or from intercourse with a previously infected individual.

It should be noted that genital ulcers can have numerous causes, and thorough diagnoses should be conducted in all cases to avoid confusion with other diseases, such as squamous cell carcinoma or primary syphilis [55]. Likewise, the presence of other types of infectious microorganisms should also be ruled out [59].

2.3.2. Leishmaniasis in sexual organs in animals

Among animals, domestic dogs are considered to be the main reservoir of *Leishmania*, and this parasite has been detected in canine sexual organs as well [57-58]. In females, the absence of exposed genitals and internal sex organs suggests that infections are either systemic in origin or sexually transmitted, which is especially true in non-endemic areas [60-61].

It has been observed that when *L. chagasi* infects sexual organs (e.g., the testis, epididymis and prostate) and genitals (e.g., the glans and foreskin), it can induce an inflammatory response. In addition, macrophages infested with parasites accompanied by neutrophils in the foreskin have also been observed in dogs. In one study involving dog semen, the presence of the parasite was detected by PCR in 8 out of 22 samples analyzed [57], a finding which suggests the possibility of sexual infection between animals. Indeed, when 12 serologically negative females were mated to males that tested serologically positive for *L. chagasi*, 165 days after mating, 3 out of the 12 females were serologically positive and 6 out of the 12 females scored positive by PCR [62]. Although the external genitals and the vulva are the most commonly affected areas in symptomatic and asymptomatic females, females that scored positive for *Leishmania* by PCR also showed effects in at least one other region of the reproductive system. Histological changes included perifollicular lymphocytic infiltration with intracellular parasites as well as inflammatory infiltration in the vulvar dermis [58]. Other trials have been carried out in which male and female dogs infected with *Leishmania* were mated to observe vertical transmission.

However, it remains unclear whether sexual transmission plays an important role in vertical transmission [63].

2.4. Congenital transmission

2.4.1. Congenital leishmaniasis in humans

Vertical transmission is defined as the congenital transmission of a pathogenic microorganism, condition, or characteristic from one generation to the next via the placenta, hematogenous, the birth canal, or nursing at the maternal breast [64]. Vertical transmission has been demonstrated for visceral leishmaniasis caused by *L. donovani* and *L. infantum.* The first case of vertical transmission in leishmaniasis was reported in 1926 in a pregnant woman who began to show symptoms suggestive of leishmaniasis during her first trimester. The treatment for visceral leishmaniasis was administered upon the exclusion of malaria and typhoid fever as differential diagnoses by laboratory results. Upon treatment, the symptoms disappeared, and the pregnancy continued to term. The birth took place without complications via the vaginal canal, and the neonate was of normal weight. However, both mother and neonate exhibited a general state of deterioration immediately postpartum. Visceral leishmaniasis was not suspected, and the symptoms were fever, diarrhea, and abdominal pain. Due to the state of the mother, nursing did not occur. The child was tracked during its first year and presented with anemia and splenomegaly. A biopsy of the spleen revealed the presence of Leishman-Donovan bodies [65], indicating that vertical transmission of leishmaniasis had occurred.

The epidemiological antecedents of leishmaniasis are crucial when pediatric patients or those of childbearing age develop symptoms suggestive of leishmaniasis. A mother who was diagnosed with *L. infantum* by ELISA had been on a farm when she was between 28 and 30 weeks pregnant. The child was born by elective caesarean at 38 weeks in a non-endemic zone in the Ukraine. At the age of eight months, the nursing child suddenly exhibited a fever, decreased appetite, weakness, pallor of the integuments, bruising, hepatosplenomegaly, tachypnea, and lymphadenopathy. An aspirate of the bone marrow revealed ovoid cells of 3-5 μm that were identified as Leishman-Donovan bodies [66].

In Germany, there have been two reported cases of leishmaniasis involving mothers who visited endemic zones prior to their pregnancies. The first case involved a 16-month-old pediatric patient with visceral leishmaniasis whose mother had traveled to endemic zones two years earlier [67]. The second case was a 15-month-old child with visceral leishmaniasis whose mother was on a farm in an endemic zone between 20 and 22 weeks of pregnancy [68].

Chronic visceral leishmaniasis has been linked to premature birth and materno-fetal deaths. [69] A histological analysis of the placenta and an aspirate of the lymphatic ganglion revealed the presence of thrombotic, vascular changes in the placenta of a fetus at five months of gestation in a mother that had been infected with leishmaniasis for two months [70]. Neonates carried to term from infected mothers have remained asymptomatic during the first weeks or months of life. However, Leishman bodies have ultimately been detected in the bone marrow, and anti-*Leishmania* antibodies have also been detected, corroborating the diagnosis of leishmaniasis [65, 69, 71].

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Leishmaniasis can be accompanied by concomitant infections by organisms from similar genera. During the second trimester, a pregnant patient was initially treated for leishmaniasis and showed improvement at 30 days. The baby was born vaginally at 36 weeks without complications and weighed 1,700 grams. He was readmitted three days later for deterioration due to probable malaria and tuberculosis, but he did not show improvement following treatment. Amastigotes were detected in an aspirate of the lymphatic ganglion of the mother. In addition, IgG antibodies were detected in the baby; these antibodies were attributed to passive transplacental transfer of parasite-specific antibodies from the mother to the fetus, negating the need for treatment. He was admitted once more at seven months old for symptoms suggestive of *Plasmodium falciparum,* and he did not show improvement upon treatment. A bone marrow aspirate revealed *Leishmania*. However, despite treatment, the infant died. An autopsy revealed that the presence of abundant *Leishmania* parasites in the kidneys, spleen, thymus, bone marrow, liver, and lungs and *Candida* spp. in the respiratory tract [70].

Individuals, whether mother or offspring, in endemic zones can be infected for months or years prior to the onset of symptoms. For example, a woman visited an endemic zone and became pregnant two years later. She did not experience any symptoms during her pregnancy or postpartum while in the non-endemic zone nor was there evidence of the existence of the vector in the geographic area. While the mother remained asymptomatic, the infant exhibited symptoms of possible visceral leishmaniasis, which was confirmed by various laboratory tests [67].

There is evidence that cutaneous leishmaniasis is associated with perinatal health problems, as has been observed in Brazil, where women with *L. braziliensis*-mediated cutaneous leishmaniasis developed vegetative or atypical lesions at the 18th week of pregnancy. Of these patients, 10% delivered prematurely and the fetus died in another 10% of the cases. A biopsy of one of the fetuses revealed intense inflammatory exudates predominated by neutrophils, and parasites were detected by electrophoresis [72].

2.4.2. Congenital leishmaniasis in animals

In Brazil, a trial was performed with asymptomatic and symptomatic mixed-breed dogs that were infected with *L. donovani* and *L. infantum*. There were four dogs in each group, and the livers, spleens, lymph nodes, bone marrow, kidneys, and hearts of their offspring were analyzed by PCR for infection. The numbers of offspring obtained from symptomatic or asymptomatic mothers (26 vs. 27) were nearly identical. The placentas and the offspring were analyzed by PCR, and 13 of the 26 placentas and 9 of the 26 offspring of the symptomatic mothers were positive for the parasite, while 13 of the 27 placentas and 8 of the 27 offspring from the asymptomatic mothers were positive. Furthermore, it was noted that PCR was more sensitive for parasite detection in comparison to immunohistochemistry and hematoxylin and eosin staining [73]. Another study in Italy involved seven female dogs that had been diagnosed with leishmaniasis by serology, microscopy, and PCR. Two of the seven were treated with N-methylglucamine prior to pregnancy, and one of the seven was treated during pregnancy. The pups were examined between 3 and 30 days of age. The parasite was detected in 8 of the 31 pups in both groups, and only 2 of the 8 pups developed symptoms [74].

2.4.3. Experimental models of congenital transmission

In a murine model of visceral leishmaniasis, twenty 12-week -old female BALB/c mice were infected with *L. infantum*. They were mated 8 weeks later with healthy males, and the females were sacrificed at days 13 and 18 of gestation. The offspring were sectioned in half for PCR analysis. In 15 of the 20 pregnant mice, the parasite was detected by PCR in the spleen. In the offspring, 3 of the 88 placentas and 4 of the 88 pups tested positive for *Leishmania* by PCR [75]. In studies to determine vertical transmission of *Leishmania* in beagles, parasitemia was detected in the liver, spleen, and bone marrow of the offspring [63].

In experimental model in which hamsters were infected with 10^6 parasites/mL of *L. panamensis* during the first week of pregnancy, 24 of 93 (25.8%) of the offspring from infected mothers were PCR positive to *Leishmania*, 2 months after the birth [76]. Furthermore, mice infected with high inoculums of *L. mexicana* strain, known as cause of cutaneous leishmaniasis, showed that all female and their placentas were positive to PCR analysis, and revealed that the infection was present in 39 of 110 offspring of infected mothers, also fetal deaths and resorptions were observed [77]. Then is important to be aware to the fact that leishmaniasis could be transmitted transplacentally and causes fetal resorption, death, and reduction in offspring body weight.

2.5. Other factors related to substance abuse and work environment

2.5.1. Drug use

In cases of leishmaniasis infection due to fomites, such as sharp, contaminated objects, the most vulnerable population are illicit drug users. In a Spanish study of syringes used for recreational drug use, it was reported that 32-52% of the syringes were contaminated by *Leishmania*, as determined by PCR. Moreover, 3 different genotypes were identified in multiple samples, confirming that the individuals had shared syringes. Therefore, programs that limit the sharing of needles should decrease the infection rate among vulnerable individuals [78-79].

2.5.2. Work environment transmission

As described above, *Leishmania* spp. can be transmitted through fluids such as blood and by contact with animals or even contaminated objects. In all cases, there must be an entry route, which is usually a wound. In staffs dedicated to clinical, diagnostic or medical research, it is not uncommon to find reported cases of *Leishmania* infection, although many such likely go unrecognized [80]. Infections due to accidental exposure can be affected by a variety of factors, including kinematics (e.g., the path and characteristics of exposure and the amount of inoculum), parasite characteristics (e.g., pathogenicity, virulence, viability and infective dose) and host characteristics (e.g., immune status, barrier status and actions following the accident) [80]. However, the possibility of infection due to vector exposure in an endemic region should not be ruled out when performing questioning [81]. The first case of work-related leishmaniasis was reported in 1930, and to date, there have been 12 reported cases of *Leishmania* infection due to accidents at work; these have included 6 different *Leishmania* species, with *L. donovani* being implicated in half of the affected individuals. In these cases, the incubation period ranged

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from 3 weeks to 8 months after the accident. Although the United States is not considered to be an endemic region, it has had more than half of reported leishmaniasis cases of laboratory transmission, with the parenteral route being the most frequent means of exposure, followed by animal bites, primarily from experimental animals. In one affected population, the average age of leishmaniasis cases due to work-related accidents was 30, and four of the affected individuals were students [80].

According to the CDC, the *Leishmania* parasite is considered to be a Biosafety Level 2 (BSL-2) organism, which implies that the individual transmission rate is moderate, and low in the case of a community. Therefore, *Leishmania* can cause disease in humans or animals without being considered a serious risk for laboratory staff. Although exposure can lead to serious infection, effective treatments are available and the risk is limited [82]. Potentially infectious parasites can be found in blood, tissues, exudates and infected arthropods, and they can be transmitted through wounds, micro-abrasions, accidental parenteral inoculation or transmission by arthropods [80]. Therefore, it is recommended that all staff having contact with potentially infectious material use protective equipment and that the handling of potentially infectious waste be carried out in accordance with appropriate regulations and good clinical/laboratory practices [80, 82]. In the case of staff with compromised immune systems, it is recommended that they avoid work with live organisms [82].

3. Conclusions

The *Leishmania* parasite can survive in a wide range of temperatures and pH conditions, which has allowed it to adapt to the diverse conditions encountered within different vector and host species. In recent years, transmission pathways other than those based on vector species have been described, including invasive procedures for therapeutic purposes, sexual practices, pregnancy, drug practices and work-related accidents among health/research staff members, all of which have led to an increase in the number of reported leishmaniasis cases. However, considering that the latency period of the parasite within the host can last up to one year, there are likely more infected individuals than those that have been reported. Because leishmaniasis is not considered to be a disease that can be transmitted between individuals without the intervention of a vector species, laboratory tests for the presence of these parasites to rule out prospective donors are not carried out prior to in most invasive therapeutic procedures. However, in the case of patients with immunodeficiency, the possibility of contracting the disease is significantly increased. Furthermore, during pregnancy, changes to the immune system can allow for the transmission of the parasite from the mother to the fetus. It should also be noted that maternal-fetal infection can also be of sexual origin. Among drug addicts, it was demonstrated that syringe sharing is a significant source of infection. Finally, in addition to populations exposed in endemic areas, staff working in the health or research sectors should also be considered as populations at risk of acquiring this disease.

Taken together, there is a clear need for the health system to reevaluate the global situation concerning leishmaniasis transmission and to implement strategies to reduce the exposure of individuals to *Leishmania* infections.

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Author details

Miroslava Avila-García, Javier Mancilla, Enrique Segura-Cervantes and Norma Galindo-Sevilla*

National Institute for Perinatology, Department of Infectious Diseases and Perinatal Immunology, Mexico City, Mexico

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