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Nobody Likes Flies

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Introduction:

Leishmaniasis is a protozoan disease that is common in tropical areas of the globe. Around the world this disease is transmitted from different hosts by various sand-fly species. The most prevalent countries for any type of leishmaniasis are Brazil, India, and Ethiopia[1]. There are three presentations of the disease seen around the world: visceral, mucosal, and cutaneous. Specifically, in the Central American countries of Nicaragua and Costa Rica 1,000-4,999 cases of the cutaneous form present each year[1]. The types of protozoa seen in this disease are classified into new-world and old-world species. The old-world species are typically found in Africa, Asia, and Europe while the new-world are seen in the Americas[2]. Depending on the specific subspecies of leishmaniasis an individual is likely to develop different presentations of leishmaniasis[3]. There are currently about 12 million people afflicted with this disease while 1-2 million cases are expected to develop each year[3]. Leishmaniasis has been seen in 89 countries around the world and because it occurs more frequently in rural and impoverished areas, there is a lack of affordable treatments.

In order to decrease the prevalence and sequelae of cutaneous leishmaniasis (CL) the world each step of the medical process must be evaluated. This paper intends to evaluate the methods of prevention in rural and urban areas, the diagnostic procedures and their necessity, and the various treatment options to properly cure leishmaniasis, dependent on the species. A literature review using online articles and in-person interviews from individuals native to rural areas of Costa Rica will be utilized to compound information. It is the goal of this paper to identify a most appropriate plan for the prevention methods and treatment of individuals with CL.

Background:

Leishmaniasis can be caused by more than twenty different species of protozoa and that leads to various presentations of the disease[1]. As previously stated there are three main forms of leishmaniasis in visceral, mucosal and cutaneous forms and within those there are further subcategories. While visceral is the deadliest form of the disease, cutaneous has the most obvious presentation to patients and providers alike. CL can be further broken down into localized CL, disseminated CL, cutaneous-chondral, and muco-cutaneous leishmaniasis[3]. Apart from muco-cutaneous these forms can be identified primarily by visual appearance of the lesion. How CL presents is based on a few different factors including, the species of protozoan infecting the host, the immunologic ability of the host, and access to treatment. The longer delay to treatment and a decreased immune capability can lead to the more systemic forms of CL, those being disseminated CL, and the sequela form of muco-cutaneous[3].

It is important to understand the life cycle of protozoa to understand how it is transmitted and ultimately how it can be diagnosed. The protozoa begin in a form called amastigote, which is non-flagellated and is often found within the white blood cells of the infected host[3]. The amastigotes are absorbed by the initial bite of a sand-fly and within this vector the amastigote turns into the flagellated promastigote. The promastigote starts as procyclic and then metacyclic, which is the infectious form of the disease[3]. Due to the life cycle of the protozoa there is an incubation period of the disease that can vary from weeks to years. It is because of this fact that the infected host may appear asymptomatic for a long period of time before knowing they have been infected with leishmaniasis. It is also possible for the disease to recur in months or years to come because of the potential latency of the protozoa[3].

The disease is transmitted by sand-flies of many species but most commonly by the species *Phlebotomus*[4]. These sand-flies are known to bite various hosts including humans, domestic animals, and wild mammals and reptiles[3]. Since there are many opportunistic hosts for CL the prevention of sand-flies and their bites can be difficult. Urban environments are usually not conducive to sand-fly habitats, however with continued deforestation of tropical areas the flies that live there may migrate to more populated areas. Another factor to consider for transmission of disease is travelers, both in and out of the country. Individuals that visit the forests of Central America, are bitten, and return home can increase the risk of spreading the disease to others. Though the number of flies that can behave as vectors decreases upon return to urban areas there may be enough insects around to spread the protozoa.

Prevention methods in around the world can vary based on the amount of money one is willing to spend. There currently is not a vaccine available for leishmanial diseases, however there are plans for development of one in the future by the WHO[3]. The goal of this vaccine is to prevent the necessity for expensive treatments and medications. The current recommended prevention methods include: wearing long sleeves, using insect repellents with DEET, wearing clothes that are infused with permethrin, and using fine mesh netting[2]. While wearing long sleeves seems simplistic the hot weather and incidence of outdoor work makes this first recommendation quite difficult to manage. Using insect repellent with DEET is shown to reduce the risk of infection, though which concentration of DEET to use is up to debate[2]. Mesh nettings are commonly used by indigenous and rural communities to prevent mosquitos and other insects from biting while they sleep, though the efficacy of these nettings for sand-flies is possibly decreased due to the smaller size of the sand-fly[2].

Despite the preventative measures used, more than 1,000 individuals in Costa Rica and Nicaragua develop CL each year[1]. For patients of rural communities, it can be difficult to reach a medical professional and if the lesion isn't bothersome, they may not consider it necessary. For those that do seek attention, the lesion caused by CL may appear differently depending on what stage it is in. The infection normally begins as a papule or nodule which over time develops into a painless ulcerative lesion. This lesion is noted to have raised margins, a central granulomatous base and possibly a serous discharge. The ulceration may also be associated with localized lymphadenopathy. The most common locations for injury are the sites that are commonly exposed to sand-fly bites: the face, ears, and extremities[5]. It is important for providers to keep in mind how the four types of CL may present differently. The localized form will have one lesion, but there also may be multiple localized CL on one individual. The chondral form is any lesion that affects the ears. The disseminated form will have multiple lesions that are all developing at a similar rate and may appear in all areas of the skin but should not affect internal organs. Finally, the muco-cutaneous form, another systemic type, will have involvement of one or more mucous membranes, typically the nose or the mouth, along with an ulcer that resembles the localized or disseminated types[3]. Because the lesions develop at different rates it is important for providers to remember to do thorough skin and mucous membrane checks for every patient that CL is suspected in.

There are a few different lesions that may look similar to CL including pyoderma gangrenosum, Buruli ulcers, and chronic tropical ulcers caused by Vincent's organisms[6]. To confirm the diagnosis of CL there are two diagnostic test that are commonly performed. The first test is a biopsy of the infected skin which is then observed by light microscopy. If CL is present in large enough numbers a visual representation of the amastigotes should be visible[5]. If the

protozoan yield of amastigotes is too low, the "gold standard" method of real-time PCR can be used. Through PCR the exact species of leishmaniasis can be identified and a treatment plan can be decided upon[4]. There are many species of leishmaniasis that can occur in the "new-world." The main species include *Leishmania mexicana* and *Leishmania viannia,* which includes *Leishmania braziliensis* and *Leishmania panamensis*[5]. *L. mexicana* is typically associated with localized cutaneous forms of CL compared the *L. viannia* species that can be associated with muco-cutaneous presentations and more systemic illnesses[3].

Treatments may not be necessary for individuals with CL depending on certain requirements. The guidelines for treatment vary depending on the source but most agree that CL with dissemination, mucosal involvement, or in locations on the face, ears, or joints should be treated[7]. According to a different source, treatments should be made available to those with lesions over four cm, three or more active lesions, and for those that developed CL in South America[5]. For patients without access to treatment, or do not desire it, as long as the individual was not in an immunocompromised state the wound should resolve on its own. The rate of which the wound will heal on its own depends on the species as well. If *L. mexicana* is the source of the lesion it should heal in three to nine months, however if one of the *L. viannia* species are causing the infection the wound may take from six to fifteen months to heal on its own[2].

If treatment is desired there are many different treatment options available including IV pentavalent antimony, IV liposomal amphotericin B, miltefosine, ketoconazole, fluconazole, itraconazole, topical paramomycin and gentamicin, cryotherapy, and thermotherapy[5]. Though more expensive, the "gold standard" treatment is intravenous pentavalent antimony compound of which there are two, sodium stibogluconate and meglumine antimoniate[3]. These treatments are

considered anti-leishmanial. They have been used for treatment for about half a century and can cause many adverse effects[8]. Some of these adverse effects include local irritation, anorexia, myalgia, arthralgia, nausea, vomiting, and EKG changes[3]. Due to incidence of these side effects many individuals may not be able to tolerate the full treatment plan of twenty-one days. Currently, of the two, only sodium stibogluconate has a generic form, which leads to it being the drug of choice in for many[2].

The choice of alternate systemic therapy often depends on the species of leishmaniasis causing infection. Ketoconazole has been used to cure *L. panamensis,* while IV liposomal amphotericin B is used for *L. braziliensis* and *L. chagasi infantum*[9]. Miltefosine has been studied with a wide variety of species including *L. braziliensis, tropica, and infantum chagasi*[9]. Liposomal amphotericin is the only medication that is safe for pregnancy but is still expensive and has side effects that include fever, chills, renal insufficiency, hypokalemia, and anemia[5]. Miltefosine was first used as a chemotherapy agent in the 1980's but is generally well tolerated. It has been known to cause some nausea, vomiting, headaches, and diarrhea but those symptoms typically abate after the first week of treatment[5].

In one case trial ketoconazole has an efficacy rate of 76% (N=21) compared to sodium stibogluconate which only had a cure rate of 68% (N=19)[9]. In a case report by Dr. Abadir et al. itraconazole was stated to not work for CL and sodium stibogluconate was utilized instead[2]. In a review article by Torres-Guerrero et al. it was suggested that ketoconazole or itraconazole are more efficacious than fluconazole[3]. However, in a third article detailing CL treatment practices in the US by Dr. Eiras et al. ketoconazole or high doses of fluconazole are thought to be useful[5]. Due to these contradicting articles ketoconazole seems to be the most effective of the azole

agents, while the efficacy of fluconazole and itraconazole is debatable[2,3,5]. As is typical with antifungal agents, common adverse effects include GI symptoms and hepatotoxicity[5].

Topical antibiotics like paramomycin have varying efficacy rates with reports anywhere from 4% - 93% being observed[10]. It has been demonstrated that though the efficacy varies, paramomycin alone is still better than placebo and even greater cure rates occur when paramomycin is combine with methylbenzethonium chloride (MBCL) or gentamicin sulfate[10,11]. Though generally safe for local use, a few adverse effects include application site erythema, edema, and pain[11]. These reactions are decreased by the addition of gentamicin, but more commonly seen with the MBCL formula[10,11].

Finally, for individuals that seek the more conservative route or cannot tolerate medications, cryotherapy and thermotherapy have been used advance the healing process. Cryotherapy is a common treatment for localized lesions in the US, by way of liquid nitrogen[6]. As a conservative method of thermotherapy, objects such as silver nitrate, brown sugar oil, candle wax, and heated metal objects have been applied to lesions with reported healing of the wound, though these reports are from solely by word of mouth without any proof of evidence[12]. In other parts of the world, studies focused on more controlled methods including hot baths, laser therapy and infrared light were utilized, but one of the most studied methods of heating is seen by using radiofrequency therapy, which is the use of a device to heat a localized area with radio waves[12]. In a study performed in 2015 in Brazil 13 out of 15 patients had complete cure of CL 3 months after treatment[12]. The side effects experienced by radiofrequency therapy include pain, itching, burning, and possibly blisters[12].

Methods:

Research on leishmaniasis as a whole was performed on international informative websites run by the WHO and the CDC. From there specific information about CL was selected and used for more advanced searches. The research database PubMed was used to find two generalized articles about CL with points detailing prevention, history and physical exam, diagnosis, and treatment. Using references from those articles and further details about the specific treatments, another article was discovered with information on diagnostic procedures and seven more were found describing various treatment practices.

In-person interviews were conducted as part of a large group in Costa Rica with various individuals. Information was gathered from individuals from the Longo Mai community and a woman from the BriBri tribe. The woman from the BriBri tribe was a representative that was familiar with using natural herbs and remedies to avoid insects and thwart diseases. One individual from Longo Mai was a farmer with a wealth of information on how the crops were treated and cared for. The second individual was a leader of Longo Mai and demonstrated which natural remedies were used and for what purpose. Though none of these individuals were familiar with leishmaniasis by name they did recognize that diseases are commonly caused by flies and mosquitos and that their natural cocktails are effective for preventative measures. Further questions about treatments for these conditions was not requested due to the fact that leishmaniasis could not be identified specifically.

Discussion:

General types of prevention methods were found by online research and interviews with people from rural areas of Costa Rica. Specific information on the prevention styles listed were

not detailed in the articles referenced by this paper and did not appear after thorough search requests. According to a woman from the Costa Rican indigenous tribe, BriBri, a common way to avoid insect bites is to use a form of fumigation around communal areas. She stated that a combination of bitter plants, such as lemongrass, are boiled in a pot. The steam that is released from the mixture is released around doors and windows to keep insects away.

A similar statement was shared by individuals from the rural Longo Mai community in Costa Rica. They also have mentioned using plants to ward away bothersome pests. Like the BriBri tribe, the field workers use bitter plant cocktails to keep insects away from crops and themselves. A farmer from Longo Mai discussed three methods for dispersing the repellent. The first method, and the simplest, is by simply dipping a brush into the repellent and spreading the bitter water amongst the leaves of the plant. He mentioned that this style is the cheapest, but it also takes a long time to spread the mixture. The second style is by use of steam, similar to the BriBri tribe and the third way is through mixing the repellent directly into the soil. It was noted that the steam method is typically the most effective, but also takes more effort to boil the water and buy supplies for dispersing the steam. It was also mentioned by a leader of the Longo Mai community that citronella is commonly grown around houses to keep mosquitos and flies away.

This material gathered from citizens of less inhabited areas of Costa Rica provided details on the distribution of natural repellents, but the exact composition was not discussed due to language barrier, lack of time, and the informants' inability to reprise the details. The use of any preventative measure is suggested by professionals, but the actual use of these techniques is probably more limited than it seems. One factor that obstructs prevention is the cost of the method like permethrin infused clothing and insect repellent containing DEET. It is also important to consider the comfortability of the individual when wearing long sleeves in the heat

of Central America. Another barrier to prevention is knowledge of the method, for example how to concoct a solution for natural repellent or which type of netting can best prevent insect bites.

Though the mainstay for diagnosis of CL is PCR, there is a challenge for some individuals in Costa Rica to get to a clinic or to pay for a lesion in which may heal on its own. Since there is a chance for resolution of the disease, it is easy to see how patients with CL would choose not to get an official diagnosis by PCR or biopsy. It may be possible, with the right information, for the individual to identify a bite by a sand-fly and how the lesion could present if infected, though the exact species of sand-fly and species of leishmaniasis would not be possible. Despite the barriers to availability of diagnosis it is still recommended that individuals with concerning lesions seek medical attention. Though rare in Central America, it is fairly common for species of leishmaniasis in Brazil to present in the visceral form which is deadly[3].

Deciding on a treatment option may be difficult or simplistic depending on the individual's stance on getting treated. If the patient chooses not to utilize medical treatment their options are limited to cryotherapy, thermotherapy, or waiting for the lesion to heal on its own. Waiting for a lesion to heal could take months to years and even if one lesion does heal another may recur[3]. This is still going to be a popular option for those that aren't bothered by a scarred appearance on their skin. Finding an effective method for cryotherapy would remain quite difficult in rural regions of Central America, though liquid nitrogen may be available for use in larger cities. The uses of thermotherapy in rural areas around the world are likely to be used in Central American countries as well, especially non-specific styles such as hot baths, candle wax, and heated metals. One issue with the study of radiofrequency therapy to heal CL ulcers is the relatively small patient population. Another problem with the study itself is that the way

radiofrequency is used is not described and may differ depending on the provider that is utilizing the therapy.

Pentavalent antimony compounds are noted to be available worldwide and used frequently as the mainstay for CL. Which drug is available depends on your region but the efficacy of both sodium stibogluconate and meglumine antimoniate are noted to be higher than every other treatment method available[2,3,5,6]. According to a case study and review by Dr. Abadir et al. the efficacy of either pentavalent antimony is equivocal and the cure rate for first time use was 76.5%, with a second dose the cure rate increased to 91.5%[2]. Since these medications are the gold standard they are studied in the context of CL more often and compared to other medications more frequently. There is one study in which another medication has a higher efficacy, ketoconazole had 8% higher cure rate when compared to sodium stibogluconate[9]. The issue with this study is that each trial had very small population sizes and it is commonly known that the pentavalent antimony treatment plan requires a more rigorous adherence with more difficult side effects[3,9].

Though the sample size was small ketoconazole did prove to be comparably efficacious to the gold standard. Other studies agree that ketoconazole may be a good alternative to antimonial compounds when looking at cost or availability[3,5]. A provider should remain cautious of the use of itraconazole and fluconazole due to conflicting information. There may be inherent bias in the authors of these articles demonstrating which antifungal treatment works best, especially since efficacy rates for the azole groups are not mentioned. It would be an interesting study for future researchers to compare the cure rates of each of these three antifungals in treating CL.

Liposomal amphotericin B and miltefosine are most likely not used frequently in Central America due to their high cost[12]. These medications appear to be fairly effective in treating CL when paired with a specific species that is likely to susceptible to it. In one study a cure rate was achievable for every patient that completed follow-up, however the reason for patients dropping out is not listed[9]. The patients may have dropped out due to the nephrotoxicity of amphotericin B or simply because they no longer wished to be a part of the study. Overall these medications should be considered for treatment if the individual can afford to pay it, if pentavalent antimony is unavailable, or if a patient is pregnant (amphotericin specifically).

Topical antibiotics should also be used cautiously with their varying efficacy ratings[10]. Though they are demonstrated to be better than placebo, the provider should not recommend these medications without consideration of resistance. A combination with paramomycin is seen to have greater cure rates with either MBCL or gentamicin sulfate most likely due to the increased coverage of infectious agent[11,12]. Since the application of the treatment is more simplistic and cheaper than other medications, it may be used more commonly in areas with limited access to medical care.

Conclusion:

Overall cutaneous leishmaniasis is a disease that can be disfiguring and disrupting to individuals across the world. Though it may be difficult to access information for those in rural communities in Central America it is important for providers to provide information in an attempt to spread details about sand-fly bites and CL. Preventative guidelines should be addressed primarily in an effort to decrease the incidence of the disease. Hopefully the development of antileishmanial vaccines by the WHO will be supported and completed in the

near future, but these vaccines should also be made available, at no cost, to anyone in an endemic area.

If any treatment is possible, based on the research above, the gold standard medication of a pentavalent antimony compound should be the first choice. All of the medications included in this article have been compared to at most two other medications. A useful research topic for the future would be a collective study comparing the efficacy of multiple different medications for CL. Another topic for research would be the development of a new pentavalent antimony compound. Little is currently known about the structures of these compounds and if more information can be gathered then perhaps a new medication could be developed with an increased efficacy and a decreased risk for side effects. Though these thoughts may be idealistic, it is important to continue education of the general population and research on a disease that afflicts so many individuals worldwide and maybe, someday, leishmaniasis will become a disease of the past.

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