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# LEISHMANIASIS

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I'm Lieutenant Colonel Glen Wortmann, Staff Infectious Disease Physician at the Walter Reed Army Medical Center in Washington D.C, and this briefing will cover Leishmaniasis.

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The objectives for this briefing are: to define leishmaniasis; to describe the clinical presentation of leishmaniasis; to describe how the diagnosis of leishmaniasis is made; and to discuss the available treatment options for leishmaniasis.

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Well, leishmaniasis is actually a group of diseases. It's caused by infection with one of the protozoa parasites of the genus *Leishmania.* Although it's rare for Americans to know about this disease, it is actually one of the five most important diseases worldwide as defined by the World Health Organization, and twenty million people are infected worldwide with this infection.

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This map shows you the geographic distribution of cutaneous disease. The U.S. military used to see a fair number of cases out of Panama when we had a jungle training school in Panama, and as you can see from the red highlighted areas, Afghanistan and Iraq are areas with a high prevalence of disease, and we're seeing most cases out of that area of the world now.

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Visceral disease is not as widespread. There is a small focus of disease in Iraq, but we are not expecting to see any disease or a handful of cases out of Iraq.

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The life cycle of leishmaniasis is complex. The reservoir is a rodent, often times a gerbil or a similar animal. The sand fly bites the rodent for a blood meal; it is a female sand fly. And then a soldier or another person who stumbles in that area happens to be bitten by the sand fly. The person then develops infection at the site of the sand fly bite. The life cycle is then complete when that or a different sand fly would bite that person or the rodent and continue the circle of the life cycle.

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This is the vector. This is a sand fly. It's very distinctive. It has a v appearance to its wings, and the wings are described as being hairy. It's a very small insect, and it does not fly very well. It tends to hop instead of flying. So what we tend to see is a unit will move into an area. This squad will camp in an area near some rubble. They will be bitten by the sand flies. Another squad a hundred meters away which is not in an area of sand flies will be completely uninfected. So the attack rate is very variable depending on how unlucky a person is to camp right where the sand flies exist.

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The clinical presentation. I will go over for cutaneous disease. I will touch on espundia, or mucocutaneous disease, which we're not expecting to see in Iraq, but is a problem in Central America and a couple comments about visceral disease or kala-azar.

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Well, cutaneous disease has some colorful eponyms, which it has acquired over the years. The Baghdad boil is very applicable because of all the cases we are seeing out of Iraq now. Also known as the Aleppo evil or Chiclero's ulcer, it commonly presents as a non-healing ulcer. The incubation period is usually approximately forty days, but it can range from a few days to as long as a year. But for most patients within forty days after they are bitten by a sand fly, they will notice the beginning of a skin lesion.

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I have a quote here from a textbook, which was written in 1944 to put leishmaniasis into perspective. The quote reads: "In some cities the infection is so common and so inevitable that normal children are expected to have the disease soon after they begin playing outdoors. And visitors seldom escape a sore as a souvenir. Since one attack give immunity the oriental sore appearing on an adult person in Baghdad brands him as a new arrival." And this quote written in 1944, fifty years ago, is very applicable to what we're seeing now. Our servicemen are the new arrivals in Baghdad, and sure enough they have an oriental sore. Most, many Iraqi people acquired the disease as children and do not get it again as an adult, so it's uncommon in adults over there. But for the U.S. servicemen who wasn't there as a child to get the infection, they now have the disease as an adult.

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This graph shows you the number of cases that we're seeing, and as you can see from the slope we are seeing a fair number of cases come out of Iraq. We've had a handful of cases out of Afghanistan. Most soldiers are coming out of Iraq at this time.

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This is a typical skin sore from cutaneous leishmaniasis. This soldier was seen last year. It is described as a volcano appearance so there is a central ulcer with a surrounding heaped up margin. The soldier had had this skin lesion for approximately three months. These ulcers typically are not painful, unless they are secondarily infected by bacteria.

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This is another example of some skin lesions. It is not uncommon for patients to have multiple skin lesions, and what is hypothesized is that the *Leishmania* parasite lives in the digestive tract of the sand fly. The female sand fly bites you, attempts to feed but can't swallow the blood because of the parasites in the digestive tract. Therefore it hops over, bites again, hops over, bites again. So it is very common to see multiple bites in just one area of the body.

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This is another example, and this highlights the size of the skin lesions that we've been seeing. Occasionally we will see large skin lesions, but for most people, it's about an inch to an inch and a half in diameter.

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Although most lesions are described as being ulcerative, some patients have a crusted skin lesion where an ulcer is not apparent, and we've seen a fair number of this type of skin lesion.

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That's a couple slides on mucocutaneous leishmaniasis, also known as espundia. This is commonly reported in the New World with certain types of the parasite. This is a very rare infection, effects 1 to 3% of people, and again this is only out of Central America. We are not expecting any cases to come out of Southwest Asia.

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This was a person from Honduras who we saw two years ago, presented with a chronic lesion in his nose, which had been present for over a year. As you can see there's a lot of scaling there, and he was diagnosed as having espundia.

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Visceral leishmaniasis, known as kala-azar which is Hindi for black sickness or black fever, and that applies to a distinctive skin discoloration that occurs in India with patients who have this infection. The typical presentation is fever, just fever, fever, fever for weeks on end if not months on end. Patients develop an enlarged liver and spleen. They oftentimes are anemic. Usually this affects children, often malnourished children, and it is being increasingly reported in HIV patients. Both young children and HIV patients have abnormal or not the same as adult-level immune systems, and they are more predisposed to get these infections. This infection is fairly uncommon in adults, and we are not expecting to see it in U.S. servicemen. We may see a few cases, but it is not expected to be a problem for U.S. servicemen.

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The picture on the left is a child that was seen several years ago, and the outline shows the enlarged liver and spleen. The other adult picture is a patient in Kenya who had had the infection for three to four months and has a grossly abnormal liver and spleen. This is not a subtle diagnosis. These patients have had fevers for weeks and weeks on end, and it's fairly straightforward to make this diagnosis.

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So, to go into diagnosis. For cutaneous disease or skin disease, your physician needs to take a sample of the skin ulcer. We need to get a piece of tissue. And that can be done either with a scraping or your physician would take a scalpel blade and just scrape across the ulcer. It can be done by an aspirate where your physician would take a needle and inject into the ulcer and then withdraw some fluid or a punch biopsy where a core is taken out of the skin lesion for diagnosis and culture. The sensitivity and the literature ranges from 75 to 90%. Out of Iraq, our sensitivity has been close to 90%. There is an investigational PCR test. This test amplifies the DNA of the *Leishmania* parasite and is available as a research assay in several labs. But for most people the diagnosis is made by taking a biopsy, scrapping aspirate punch biopsy, spreading it on a smear and looking under the microscope to see if you can see the parasite.

For visceral disease, we also rely on tissue sampling, and the tissue that we sample typically is a bone marrow or a splenic aspirate. Overseas in India or in Kenya, a splenic aspirate is commonly done, that's where a physician will stick a needle into the spleen for a sample. In the U.S., we're

not as familiar with that procedure, and we tend to do a bone marrow biopsy. We would look for the parasite under the microscope and also attempt to culture it. There is a available test off the blood, a serology test called the rK39 or Kalazar Detect™ test which in some studies has been shown to be very good. That is a commercially available test, which can be purchased by a lab to use. It's a very simple test to do, very similar to a pregnancy test and is fairly straightforward.

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This is what your physician would be looking for under the microscope. This is a white blood cell, a macrophage. The large areas just a nucleus but all those small areas around the nucleus are the amastigotes. Leishmaniasis has a very typical pattern of a nucleus and something called the kinetoplast, and your physician would look under the microscope, and if he saw a macrophage containing these amastigotes that would give you a diagnosis of leishmaniasis.

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This is another example here of two macrophages, side-by-side. Both of them are stuffed with amastigotes.

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At certain reference labs, there is culture available, and your physician would take your skin biopsy, drop it in some media and when the parasite grows it actually grows as something known as a promastigote. There is a long tail or a flagella which grows, and these will actually swim around in culture. This is the stage of the parasite which lives in the sand fly, and then when it's infected into a mammal, it changes into an amastigote.

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What about treatment? It's important to realize that this infection, the cutaneous disease, is a self-limited infection. In many areas of the world, treatment is not available. This is a common disease in children. Children have it for five, six months, and it goes away even without therapy. The only thing treatment does is make it go away faster. Your options would be no treatment if you had a very small lesion which was already healing on its own, we would recommend no treatment because we can't make it any better than it already is. If you have a small lesion which is not healing that well and you want it to go away faster, we could freeze it with some liquid nitrogen, and there is a device known as the ThermoMed™ device, which is FDA-cleared for this use, which microwaves the area of skin to get rid of the infection. There is a pill known as fluconazole, which we commonly use for fungal infections which is available. It does not have the FDA licensure for this indication but is available and physicians commonly use medicines off licensure. It's known as off label use for this infection. And there was a study done in Saudi Arabia which showed it was 80% effective three months after treatment compared to 34% of patients who had no therapy. So it is moderately efficacious. The treatment is once a day for six weeks. At the end of six weeks, the cure rate is 30%, but then over the next two to three months the cure rate improves to 80%. So it is a slowly effective therapy and would be an option for some patients.

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Finally, Pentastam®, or sodium stibogluconate, is a drug which is not licensed by the FDA for use in the United States. It is extensively used in other countries for use and is available in the United States under a protocol known as an IND. That protocol is held by the Center for Disease Control and at this time by the Walter Reed Army Medical Center. If you are a civilian your physician would call the Center for Disease Control, and the medicine would be mailed out to your doctor. If you're military at this time, you're asked to come to Walter Reed for treatment. The treatment is between ten and twenty days; it depends on what parasite we isolate from you as well as the extent of your disease. If you have fairly modest disease, we would recommend ten days of

therapy. If you have extensive disease especially disease on your face or your hands, we would give you twenty days of therapy. The cure rate in our hands is over 90%, but it is not 100%. We have had a few patients get treated and then relapse with the infection. The options at that point would be another course of Pentastam® or perhaps the liquid nitrogen, the ThermoMed™ therapy or the fluconazole. This drug has some known toxicities. It elevates the pancreatic enzymes in almost 97% of patients. It causes joint pains in over half of patients and liver irritation in almost two thirds of patients. It is not a therapy which we give lightly and for many patients treatment with local therapy or no treatment would be preferable to getting this medication. However, if you have extensive disease, Pentastam® would be the recommended therapy for you.

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For visceral disease, the treatment is either AmBisome® or Pentastam®. AmBisome® is known as liposomal amphotericin, and it actually has an FDA licensure for this indication. So any physician in the United States can give this drug for visceral disease. Treatment for visceral disease is much more straightforward than treatment for cutaneous disease. There's a medicine called AmBisome®, or liposomal amphotericin, which has been approved by the FDA for the treatment of visceral disease. The protocol is fairly straightforward. Medication is given on days one through five, day fourteen and day twenty-one. This drug has a fairly well known safety profile. It is fairly well tolerated and is very efficacious. Pentastam® is also available and is the drug that we used to give before AmBisome® was approved. It requires twenty-eight days of therapy. In some areas of the world, such as India there has been drug resistance to Pentastam® and so AmBisome® has become the first choice for most physicians in treating visceral disease.

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So in summary, the most likely presentation of leishmaniasis in a returning soldier or serviceman would be cutaneous leishmaniasis. And the chief complaint is a non-healing skin lesion. So what you would notice or your family member would notice would be a skin lesion that just doesn't go away.

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For the physicians, what we would recommend is empiric routine wound care, which might consist of antibiotics if the wound appears infected and local wound care. If after two to three weeks there's no improvement, then you should consider that this may be cutaneous leishmaniasis. We would be happy to field any phone calls from physicians or patients regarding this potential infection. The assets that we have at Walter Reed are the Armed Forces Institute of Pathology, which has expertise in reading slides, as well as the Walter Reed Army Institute of Research, which has the availability to culture the organism as well as a PCR which can be done as a research test. We also currently hold the treatment protocol for Pentastam.

The phone numbers for the Infectious Disease Clinic at Walter Reed are (202) 782-6740.

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If you have questions you should, you can also contact the DoD Deployment Health Clinical Center at the Walter Reed Army Medical Center. The phone number and the website are on the slides.