

## Editorial

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Having dealt with the commoner afflictions bothering the new world, we are now focusing our attention to segmentally common diseases that have localized presence in the new world. However, even these are threatening the world with the advent of immunosuppressed disease states like HIV/AIDS. This issue's DISEASE DIAGNOSIS features Leishmaniasis. Though otherwise causing low mortality (but high morbidity), in conjunction with HIV - Leishmaniasis acquires a lethal status. What was a disease of the old world or the developing nations is fast spreading its tentacles over the developed world too. Each passing year imposes a burden of fresh 2 million new cases of Leishmaniasis. A detailed clinico-diagnostic approach is presented in the following pages. Colour pictures of the lesions and the parasite, life cycle of the parasite, detailed clinical aspects, signs/ symptoms, diagnostic tests in ample detail and a short therapeutic brief are highlighted for your reference.

We are presenting another of new generation super bugs. MRSA has become a supergerm causing more deaths, even surpassing those caused by AIDS in the developed countries. MRSA was discovered in 1961 in the UK. It is now found worldwide. What are the varieties of MRSA? What are their clinical presentations? How do they differ in diagnostic and therapeutic approaches? Questions that are often being asked by the public at large as well as clinicians are answered in sufficient detail in INTERPRETATION and TROUBLE SHOOTING section tells you just how to get rid of the bug. A task that is important but not difficult. Remember, clinical and para-clinical staff members of British Hospitals have been asked to keep sleeves of their aprons short! Simple well thought remedies prevent. Ideal would be to eradicate and let no carrier endanger the society. Treat all carriers and patients discovered.

We are coming up with unusual articles of contemporary relevance in the forthcoming issues. YOU - our esteemed readers and clients, have requested for these off the rut articles. Honouring your voice we shall be covering more such presentations in near future.

Rest is different but also the same. Bouquet is there with different reasons to laugh along with different words of wisdom. No we don't forget this "pearl" of our communiqué.

## DISEASE DIAGNOSIS

### LEISHMANIASIS

#### Definition

Prevalent on four continents, leishmaniasis refers to various clinical syndromes caused by a vector-borne protozoan and characterized by cutaneous lesions, weight loss, cough, fever, diarrhea, lethargy, and splenomegaly. It's endemic to subtropical countries, particularly those undergoing economic development and man-made environmental changes. Previously regarded as a rural disease, outbreaks of leishmaniasis have been reported in large cities and suburbs of Brazil due to favorable epidemiological conditions, malnutrition, poor sanitation, and population migration.

While leishmaniasis is associated with low mortality, it has a high morbidity rate. It is estimated that 350 million people are exposed to the disease and approximately 12 million are afflicted worldwide. The global annual incidence is estimated at 1.5 to 2 million new cases per year; however, it's now generally accepted that leishmaniasis is grossly under reported. It's considered to be an emerging disease in developed countries, where Leishmaniasis/human immunodeficiency virus (HIV) co-infection is becoming more prevalent due to the acquired immunodeficiency syndrome (AIDS) pandemic and expanded international travel.

#### Scientific classification

**Domain:** Eukaryota, (unranked) Excavata, **Phylum:** Euglenozoa,  
**Class:** Kinetoplastea, **Order:** Trypanosomatida, **Genus:** *Leishmania*

**Species:** *L. aethiopica*, *L. amazonensis*, *L. arabica*, *L. archibaldi* (disputed species), *L. aristedesii*, *L. (Viannia) braziliensis*, *L. chagasi* (syn. *L. infantum*), *L. (Viannia) colombiense*, *L. deanei*, *L. donovani*, *L. enriettii*, *L. equatorensis*, *L. forattinii*, *L. gamhami*, *L. gerbilli*, *L. (Viannia) guyanensis*, *L. herreri*, *L. hertigi*, *L. infantum*, *L. killicki*, *L. (Viannia) lainsoni*, *L. major*, *L. mexicana*, *L. (Viannia) naiffi*, *L. (Viannia) panamensis*, *L. (Viannia) peruviana*, *L. (Viannia) pifanoi*, *L. (Viannia) shawi*, *L. tarentolae*, *L. tropica*, *L. turanica*, *L. venezuelensis*.

#### Origin

The origins of *Leishmania* are unclear. One possible theory proposes an African origin, with migration to the Americas. Another migration from the Americas to the Old World about 15 million years ago, across the Bering Strait land bridge. Another proposes a paleartic origin. Such migrations would entail migration of vector and reservoir or successive adaptations along the way. A more recent migration is that of *L. infantum* from Mediterranean countries to Latin America (there named *L. chagasi*), since European colonization of the New World, where the parasites picked up its current New World vectors in their respective ecologies. This is the cause of the epidemics now evident. One recent New World epidemic concerns foxhounds in the USA.

#### Pathophysiology

*Leishmania* cells have two morphological forms: *promastigote* (with an anterior flagellum) in the insect host, and *amastigote* (without flagella) in the vertebrate host. Infections are regarded as cutaneous, mucocutaneous, or visceral.

*Cutaneous* (localized and diffuse) infections appear as obvious skin reactions. The most common is the *Oriental Sore* (caused by Old World species *L. major*, *L. tropica*, and *L. aethiopica*). In the New World, the most common culprits are *L. mexicana* and *L. (Viannia) braziliensis*. Cutaneous infections are most common in Afghanistan, Brazil, Iran, Peru, Saudi Arabia and Syria. *Mucocutaneous* (espundia) infections will start off as a reaction at the bite, and can go via metastasis into the mucous membrane and become fatal. Mucocutaneous infections are most common in Bolivia, Brazil and Peru.

*Visceral* infections are often recognized by fever, swelling of the liver and spleen, and anemia. They are known by many local names, of which the most common is probably *Kala azar*, and are caused exclusively by species of the *L. donovani* complex (*L. donovani*, *L. infantum* syn. *L. chagasi*) Found in tropical and subtropical areas of all continents except Australia, visceral infections are most common in Bangladesh, Brazil, India, Nepal and Sudan.

#### Molecular biology

An important aspect of the *Leishmania* protozoan is its glycoconjugate layer of

lipophosphoglycan (LPG). This is held together with a phosphoinositide membrane anchor, and has a tripartite structure consisting of a lipid domain, a neutral hexasaccharide, and a phosphorylated galactose-mannose, with a termination in a neutral cap. Not only do these parasites develop post-phlebotomus digestion but, it is thought to be essential to oxidative bursts, thus allowing passage for infection. Characteristics of intracellular digestion include an endosome fusing with a lysosome, releasing acid hydrolases which degrade DNA, RNA, proteins and carbohydrates.

#### Leishmania as component of CVBD

*Canine Vector-borne Diseases* (CVBD) covers diseases caused by pathogens transmitted by ectoparasites as ticks, fleas, sand flies or mosquitoes.

Other microorganism-based diseases caused by ectoparasites include *Bartonella*, *Borrelia*, *Babesia*, *Dirofilaria*, *Ehrlichia*, and *Anaplasma* Neutrophil granulocytes - the Trojan horses for *Leishmania* parasites.

The strategy of the "Trojan horse" as a mechanism of pathogenicity of intracellular microorganisms is, to avoid the immune system and its memory function cleverly, with phagocytosis of infected and apoptotic neutrophils by macrophages, employing the non-danger surface signals of apoptotic cells.

Transmitted by the sandfly, the protozoan parasites of the genus *Leishmania major* may switch the strategy of the first immune defense from eating/inflammation/killing to eating/no inflammation/no killing of their host phagocyte and corrupt it for their own benefit. They use the willingly phagocytosing polymorphonuclear neutrophil granulocytes (PMN) rigorously as a tricky hideout, where they proliferate unrecognized from the immune system and enter the long-lived macrophages to establish a "hidden" infection.

#### Uptake and survival

By a microbial infection PMN move out from the bloodstream and through the vessels endothelial layer, to the site of the infected tissue (dermal tissue after fly bite). They immediately start their business there as the first immune response and phagocyte the invader because of the foreign and activating surfaces. In that processes an inflammation emerges. Activated PMN secrete chemokines, IL-8 particularly, to attract further granulocytes and stimulate them to phagocytosis. Furthermore *Leishmania major* increases the secretion of IL-8 by PMN. In the parasites case, that may not sound reasonable at first. We can observe this mechanism on other obligate intracellular parasites, too. For microbes like these, there are several ways to survive inside cells. **Surprisingly, the co-injection of apoptotic and viable pathogens causes by far a more fulminate course of disease than injection of only viable parasites.** Exposing on the surface of dead parasites the anti-inflammatory signal phosphatidylserine, usually found on apoptotic cells, *Leishmania major* switches off the oxidative burst, so killing and degradation of the co-injected viable pathogen is not achieved. In case of *Leishmania* progeny is not generated in PMN, but in this way they can survive and persist untangled on the primary site of infection. The promastigote forms also release LCF (*Leishmania* chemotactic factor) to recruit actively neutrophils but not other leukocytes, for instance monocytes or NK cells. In addition to that, the production of interferon gamma (IFN  $\gamma$ )-inducible protein 10 (IP10) by PMN is blocked in attendance of *Leishmania*, what involves the shut down of inflammatory and protective immune response by NK and Th1 cell recruitment. The pathogens stay viable during phagocytosis since their primary hosts, the PMN, expose **apoptotic cell associated molecular pattern (ACAMP)** signaling "no pathogen".

#### Persistence and attraction

The lifespan of neutrophil granulocytes is quite short. They circulate in bloodstream for about 6 or 10 hours after leaving bone marrow, whereupon they undergo spontaneous apoptosis. Microbial pathogens have been reported to influence cellular apoptosis by different strategies. Obviously because of the inhibition of caspase3-activation *Leishmania major* can induce the delay of neutrophils apoptosis and extend their lifespan for at least 23 days. The fact of extended lifespan is very beneficial for the development of infection because the final host cells for these parasites are macrophages, which normally migrate to the sites of infection within 2 or 3 days. The pathogens are not dronish; instead they take over the command at the primary site of infection. They induce the production by PMN of the chemokines MIP-1 and MIP-1 (macrophage inflammatory protein) to recruit macrophages.

#### Silent phagocytosis

To save the integrity of the surrounding tissue from the toxic cell components and

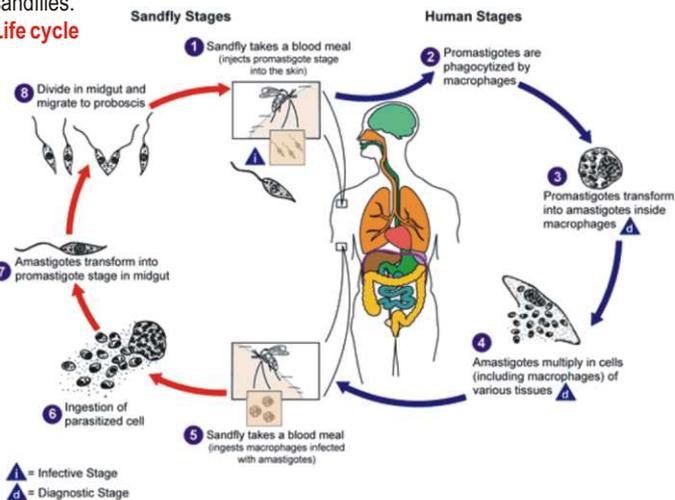
proteolytic enzymes contained in neutrophils, the apoptotic PMN are silently cleared by macrophages. Dying PMN expose the "eat me"-signal phosphatidylserine which is transferred to the outer leaflet of the plasma membrane during apoptosis. By reason of delayed apoptosis the parasites that persist in PMN are taken up into macrophages, employing an absolutely physiological and non-phlogistic process. The strategy of this "**silent phagocytosis**" has following advantage for the parasite: **Taking up** apoptotic cells silences macrophage killing activity leading to a survival of the pathogens. **Pathogens** inside of PMN have no direct contact to the macrophage surface receptors, because they can not see the parasite inside the apoptotic cell. So the activation of the phagocyte for immune activation does not occur.

#### Geographic Prevalence

**Primary Distribution:** East and North Africa, Middle East, Southern Europe, Central, South, and East Asia, South America, West Mexico.

**Agent and Vector:** The protozoal parasite species *Leishmania* is transmitted through the bite of female sandflies (phlebotomine) as follows: **Visceral leishmaniasis** or kala-azar is caused primarily by *L. donovani*, *L. chagasi*, or *L. infantum*. Dogs (feral or domesticated) are a reservoir for *L. chagasi*. **Cutaneous leishmaniasis** usually divided into (1) Old World leishmaniasis caused primarily by *L. tropica*, *L. major*, *L. aethiopica*, and (2) New World leishmaniasis caused primarily by *L. mexicana* or *L. braziliensis*. Diffuse cutaneous leishmaniasis is caused primarily by *L. aethiopica* or *L. mexicana*. **Mucocutaneous leishmaniasis** (espundia) is caused primarily by *L. (viannia) braziliensis*. Altogether, there are about 21 leishmanial species that are transmitted by about 30 species of sandflies.

#### Life cycle



Life cycle of the *Leishmaniasis* parasite.

Leishmaniasis is transmitted by the bite of female phlebotomine sandflies. The sandflies inject the infective stage, metacyclic promastigotes, during blood meals (1). Metacyclic promastigotes that reach the puncture wound are phagocytized by macrophages (2), and transform into amastigotes (3). Amastigotes multiply in infected cells and affect different tissues, depending in part on which *Leishmania* species is involved (4). These differing tissue specificities cause the differing clinical manifestations of the various forms of leishmaniasis. Sandflies become infected during blood meals on an infected host when they ingest macrophages infected with amastigotes (5,6). In the sandfly's midgut, the parasites differentiate into promastigotes (7), which multiply, differentiate into metacyclic promastigotes and migrate to the proboscis (8).

#### Causes of Leishmaniasis

*Leishmania*, responsible for human leishmaniasis, is a genus of protozoan's that have a dimorphic life cycle. They occur in mononuclear phagocytes in the body's defense system and multiply intracellularly, resulting in lysis of host cells and infection of other phagocytes. *Leishmania* has also been located in macrophages throughout the reticuloendothelial system in cases of visceral leishmaniasis. Macrophages in skin lesions reveal *Leishmania* in cutaneous leishmaniasis.

Leishmaniasis is transmitted by small, biting sand flies, which are infected with

*Leishmania* and inhabit moist soil, forests, caves, and rodent burrows. Although small rodents and mammals, dogs, foxes, chickens, horses, and humans serve as host reservoirs, the domestic dog is considered to be the principal reservoir. The protozoan is transmitted from one mammalian host to another by the bite of the sand fly, an avid feeder. It strikes humans primarily at night. Fast urbanization, invasion of primary forests, dramatic reductions in the vector's natural ecological space, drought, famine, poor sanitation, overcrowding, and the practice of harboring animal hosts, particularly dogs, close to human domiciles are among the main causes of exposure to and subsequent infection by the *Leishmania* vector.

**Incubation:** Usually 2-6 months or longer. Relapse may occur as many as 10 years after first episode. Local trauma sometimes activates latent infection in cutaneous leishmaniasis.

#### Signs and Symptoms of Leishmaniasis

Leishmaniasis can be divided into four major clinical forms: cutaneous leishmaniasis (CL), mucocutaneous leishmaniasis (ML), diffuse cutaneous leishmaniasis (DCL), and visceral leishmaniasis (VL). Additionally, the first three forms are further classified as New World or Old World, depending on the clinical presentation, species of infective parasite, and geographic location.

**Cutaneous leishmaniasis**, the most common form of infection, manifests as single or multiple ulcerating papules which heal after a few weeks or months, leaving flat, atrophic scars. Regional lymphadenopathy usually accompanies the lesions; fever, malaise, anorexia, and weight loss may also occur. The incubation period for CL may range from two weeks to several months. Resistance to re-infection by the same species of protozoa often occurs.

**Mucocutaneous leishmaniasis** begins with simple cutaneous lesions which progress to form hideously disfiguring lesions of the nose, mouth or pharynx months or years after primary cutaneous infection. ML is responsible for soft tissue, cartilage, and bone destruction, which can lead to nasal obstruction, congestion, discharge, or epistaxis.

**Diffuse cutaneous leishmaniasis**, which closely resembles leprosy and is the most difficult to treat, is the anergic variant of CL. It is characterized by large numbers of parasites in multiple, ulcerating nodules found on the face and extremities. The syndrome may persist for more than 20 years, as the body fails to mount a cell-mediated immune response.

Left untreated, **visceral leishmaniasis** is the deadliest form of *Leishmania*. VL leishmaniasis symptoms include diarrhea, hepatosplenomegaly, lethargy, weight loss, cough, and fever. Some or all of these symptoms may be present, giving the disease a wide range of presentations. In general, symptoms manifest in three to eight months; however, incubation may occur in as little as ten days or extend as long as 34 months. Onset of symptoms may be sudden or gradual.

#### List of symptoms of Leishmaniasis:

The list of signs and symptoms mentioned in various sources for Leishmaniasis includes the symptoms listed below:

**Symptoms of cutaneous leishmaniasis:** Skin sores, Raised edge sores - like a volcano with a central crater, Scabs, Swollen glands, Swollen underarm glands.

**Symptoms of visceral leishmaniasis:** Fever, Weight loss, Enlarged spleen, Enlarged liver, Swollen glands, Bone marrow symptoms, Low blood counts, Anemia, Low white blood cell count, Low platelet count.

**Skin lesions, Scar:** Localized adenopathy, Red skin macula, Red skin nodules, Shallow skin ulcer, Mucosal lesions in mouth, Mucosal lesions in nasopharyngeal area. **Fever, Anorexia, Weight loss, Enlarged spleen, Enlarged liver, Lymphadenopathy, Anemia, Leukopenia, Thrombocytopenia, Hemorrhage, Hypergammaglobulinemia.**

#### Clinical Findings: Visceral Leishmaniasis or Kala-Azar

**Signs and Symptoms:** Cardinal signs of visceral leishmaniasis (VL) are prolonged fever, splenomegaly, anemia, leukopenia, or hypergammaglobulinemia. A cutaneous nodule may or may not appear at the site of the bite within several days of inoculation. If present, the nodule remains, but in most cases, no other symptoms are present for at least several months. Systemic symptoms include gradual onset fever that often rises and falls twice/day, fatigue, weight loss, dizziness, cough, and diarrhea. Visceral manifestations include pronounced splenomegaly (hard, non-tender) and to a lesser extent hepatomegaly. Other manifestations may include generalized lymphadenopathy; hyperpigmented skin of the forehead, abdomen, hands, and feet in light-skinned persons; skin lesions in dark-skinned persons; signs of

bleeding (petechiae, epistaxis, bleeding gums); jaundice and ascites; and progressive wasting. Onset may also be acute, with the above manifestations appearing a few weeks after infection.

**Differential Diagnosis:** Brucellosis, leprosy, schistosomiasis, trypanosomiasis (African), leukemia, lymphoma, malaria, typhoid, liver diseases, other entities.

**Complications:** Progressive wasting or intercurrent infections (e.g., pneumonia, tuberculosis, diarrhea) may lead to death. Post kala-azar cutaneous leishmaniasis may occur as many as 10 years after the first episode. Lesions may resemble Hansen's disease and include hypopigmented macules, nodules, and erythematous patches. Leishmaniasis may occur as an opportunistic infection in immunocompromised persons. The disease may also be passed from an asymptomatic mother to her child. **Laboratory Findings:** Leukopenia, hypergammaglobulinemia, hypoalbuminemia; thrombocytopenia with hemorrhagic fever.

**Diagnosis:** Presence of cardinal signs noted above, in addition to living in or visiting endemic area lead to suspicion of leishmaniasis. The organism is present in bone marrow or splenic aspirate (most sensitive), blood, and nasopharyngeal secretions. If parasites are present in sufficient concentration, light microscopy of giemsa-stained slides reveals amastigotes, the tissue form of the parasite. Direct agglutination and ELISA are positive early and the leishmanin skin test is positive only after active disease.

#### Clinical Findings: Cutaneous Leishmaniasis

**Signs and Symptoms:** Cutaneous leishmaniasis (CL) is characterized by single or multiple lesions typically progress from papules to nodules to non-ulcerated dry plaques or ulcers (with raised indurated border and central depression) that usually are painless unless secondarily infected. The appearance of lesions depends largely on the host's immune response. Lesions are sometimes described as wet or dry. Distribution may be a single primary lesion, multiple primary lesions, and/or satellite lesions. Low-grade fever, regional lymphadenopathy and/or lymphangitis, and lesion pruritis or pain may be present. Most new world cutaneous lesions are ulcers as are some old world cutaneous lesions. In many cases, healing is spontaneous within months or years of onset. In other cases, however, the disease is progressive with visceral manifestations or spreading skin lesions. Photo: Cutaneous leishmaniasis.



**Complications:** Mucosal leishmaniasis may occur as a sequela of new world cutaneous leishmaniasis. Diffuse cutaneous leishmaniasis (DCL) is characterized by non-ulcerating nodules over the entire body, resembling lepromatous leprosy and is usually associated with *L. mexicana* or *L. aethiopica* infection. Diffuse cutaneous leishmaniasis (DCL) tends to be refractory to treatment. Leishmaniasis recidivans is recurrent leishmaniasis that is resistant to treatment. Cutaneous leishmaniasis may occur as an opportunistic infection in immunocompromised persons. **Laboratory Findings:** There are no specific laboratory findings characteristic of primary CL.

**Diagnosis:** Presence of cardinal signs noted above and geographic risk lead to suspicion of leishmaniasis. The organism is present in histopathologic studies of slit skin smears or in cultures - though neither is highly reliable. Leishmanin skin test is positive only after active disease.

**Differential Diagnosis:** Numerous primary and secondary skin diseases/conditions such as other tropical ulcers, impetigo, infected insect bites, leprosy, lupus vulgaris, tertiary syphilis, yaws, blastomycosis, skin cancer, and others.

#### Clinical Findings: Mucocutaneous Leishmaniasis (Espundia)

**Signs and Symptoms:** Mucocutaneous leishmaniasis (MCL) is a sequela of new world cutaneous leishmaniasis and results from direct extension or hematogenous or lymphatic metastasis to the nasal or oral mucosa. In most cases, naso-oropharyngeal symptoms appear several years after resolution of the primary lesion(s), but may also appear while the primary lesions are still present or decades later. Manifestations of mucocutaneous leishmaniasis include chronic nasal symptoms, especially of the anterior nasal septum (leading to development of the characteristic "tapir nose") and progressing to extensive naso-oropharyngeal destruction. Secondary bacterial (or fungal) infections and associated problems are common.

**Complications:** Mucosal leishmaniasis is, itself, a complication. Secondary

infections and associated problems are common. **Laboratory Findings:** There are no specific laboratory findings characteristic of MCL.

**Diagnosis:** Presence of cardinal signs, positive history, and geographic risk lead to suspicion of mucocutaneous leishmaniasis. Diagnosis is difficult because amastigotes are scarce in the usual sources (scrapings, tissue aspirates, biopsy). Culture and serologic tests are usually necessary.

**Differential Diagnosis:** paracoccidioidomycosis, polymorphic reticulosis, Wegener's granulomatosis, lymphoma, histoplasmosis, yaws, gummatous syphilis, tuberculosis, nasopharyngeal carcinoma, other destructive lesions.

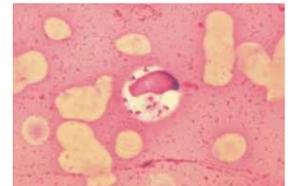
#### Diagnosis for Leishmaniasis

Diagnosis of all forms of leishmaniasis is most accurately accomplished via staining and identification of the parasite from specimens obtained from skin punch biopsy or scrapings from the base of an ulcer, spleen and bone marrow aspirates, and lymph node biopsy. Specific antibodies may be detected via the indirect immunofluorescent test (IFAT), the enzyme linked immunosorbent assay (ELISA), and the direct agglutination test (DAT). Occasionally, skin testing with leishmanial antigens may be employed. Polymerase chain reaction has proven to be highly sensitive and specific as well. Staining tissue with monoclonal antibodies is species specific; however, it is available only in research laboratories. The **differential diagnoses** to consider include: sporotrichosis, chromomycosis, lobomycosis, cutaneous tuberculosis, atypical mycobacterial infection, syphilis, yaws, leprosy, sarcoidosis, neoplasm, malaria, typhoid fever, typhus, acute Chagas' disease, acute schistosomiasis, miliary tuberculosis, amebic liver abscess, brucellosis, histoplasmosis, infectious mononucleosis, leukemia, lymphoma, agnogenic myeloid metaplasia, hepatosplenic schistosomiasis, prolonged *Salmonella* bacteremia, and tropical splenomegaly from chronic malaria. Leishmaniasis can be safely excluded from those who are not international travelers or immigrants of endemic areas.

#### Leishmania

##### Treatment for Leishmaniasis

Pentavalent antimonial compounds are the drugs of choice for treating visceral and cutaneous leishmaniasis. It is administered I.M. or I.V. over a 5- to 28-day period, depending on the type of leishmaniasis as well as the presence of drug-related signs of toxicity. Amphotericin B is employed in cases of resistant strains of VL. Pentamidine is considered a second-line agent, due to increasing resistance and prolonged course of therapy.



*Leishmania donovani* in bone marrow cell.

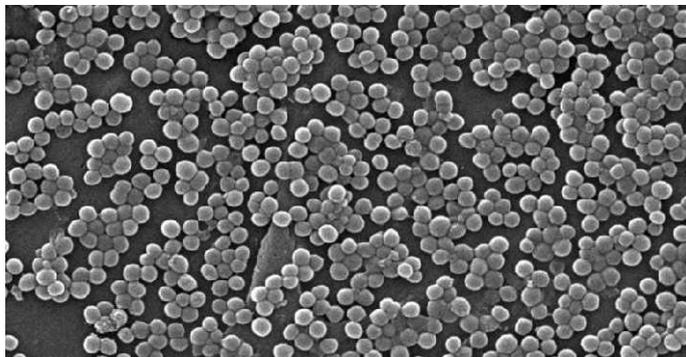
#### Special Considerations and Prevention Tips for Leishmaniasis

In the absence of prophylactic drug treatment for leishmaniasis, the best treatment is prevention. Instruct travelers to endemic areas to minimize sand fly exposure by avoiding outdoor activities when sand flies are most active (dusk to dawn); covering all exposed skin with netting; applying repellents such as DEET, lemon essential oils, or 2% neem oil to the skin and under the edges of clothing; and using permethrin-impregnated clothing.

**Some more Tips:** **Monitor** skin lesions for signs and symptoms of bacterial infection. **Utilize** appropriate personal protective gear. **Instruct** patients to avoid touching skin lesions to avoid complications. **Monitor** for adverse effects of pentavalent antimonial agents, such as arthralgia, myalgia, nausea, vomiting, abdominal pain, headache, rash, pancreatitis, anemia, leukopenia, thrombocytopenia, and renal insufficiency. **Monitor** weekly transaminase, lipase, complete blood count (CBC), and creatinine levels. Transaminase levels greater than or equal to 4 to 5 times the upper limits of normal necessitate discontinuation of pentavalent antimonial therapy. **Monitor** weekly electrocardiograms for QT interval prolongation, T-wave inversions, or significant dysrhythmia with pentavalent antimonials. **Observe** for adverse effects of amphotericin therapy, which include nausea, vomiting, malaise, anemia, hypokalemia, hypomagnesemia, and nephrotoxicity. Be prepared to monitor frequent CBCs, potassium and magnesium levels, and blood urea nitrogen and creatinine levels. **Monitor** the patient for side effects of pentamidine therapy, which include hypoglycemia followed by diabetes, hypotension with too rapid infusion, nausea, vomiting, abdominal pain, and headache. **Be** prepared to provide emotional support for coinfecting HIV/VL patients as their prognosis is poor.

## INTERPRETATION

### MRSA (METHICILLIN-RESISTANT STAPHYLOCOCCUS AUREUS)



Electron micrograph of MRSA

#### Scientific classification

**Domain:** Bacteria. **Kingdom:** Bacteria. **Phylum:** Firmicutes. **Class:** Bacilli. **Order:** Bacillales. **Family:** Staphylococcaceae. **Genus:** *Staphylococcus*. **Species:** *S. aureus*

#### Binomial name: *Staphylococcus aureus*

**Methicillin-resistant *Staphylococcus aureus* (MRSA)** (usually pronounced in short as "Mursa" or spelled out as MRSA), is a bacterium responsible for difficult-to-treat infections in humans. It may also be referred to as **multiply-resistant *Staphylococcus aureus*** or **oxacillin-resistant *Staphylococcus aureus* (ORSA)**. The organism is often sub-categorized as community-acquired MRSA (CA-MRSA) or hospital-acquired MRSA (HA-MRSA) depending upon the circumstances of acquiring disease, based on current data that these are distinct strains of the bacterial species.

MRSA is a resistant variation of the common bacterium *Staphylococcus aureus*. It has evolved an ability to survive treatment with beta-lactam antibiotics, including penicillin, methicillin, and cephalosporins. MRSA is especially troublesome in hospital-acquired (nosocomial) infections. In hospitals, patients with open wounds, invasive devices, and weakened immune systems are at greater risk for infection than general public. Hospital staff who do not follow proper sanitary procedures may inadvertently transfer bacterial colonies from patient to patient.

MRSA was discovered in 1961 in the UK. It is now found worldwide. MRSA is often referred to in the press as a superbug.

#### Morbidity and mortality

##### *Supergerm deaths soar, surpass AIDS in the developed countries*

It has been difficult to quantify the degree of morbidity and mortality attributable to MRSA. A 2004 study showed that patients in the United States with *S. aureus* infection, on average, had three times the length of hospital stay (14.3 vs. 4.5 days), incurred three times the total cost, and experienced five times the risk of in-hospital death than in patients without this infection. In a study, it has been concluded that MRSA bacteremia is associated with increased mortality as compared with MSSA bacteremia. In addition, studies report a death rate of 34% within 30 days among patients infected with MRSA, a rate similar to the death rate of 27% seen among MSSA-infected patients.

In developed countries MRSA infection is held responsible for more deaths as compared each year than AIDS.

#### Clinical presentation and concerns

*S. aureus* less commonly colonizes the anterior nares (the nostrils), although the respiratory tract, open wounds, intravenous catheters, and urinary tract are also potential sites for infection. Healthy individuals may carry MRSA asymptomatically for periods ranging from a few weeks to many years. Patients with compromised immune systems are at a significantly greater risk of symptomatic secondary infection.

MRSA can be detected by swabbing the nostrils of patients and isolating the bacteria found inside. Combined with extra sanitary measures for those in contact with infected patients, screening patients admitted to hospitals has been found to be effective in minimizing the spread of MRSA. Many people who are symptomatic present with pus-filled boils and occasionally with rashes.

About 75 percent of CA-MRSA infections are localized to skin and soft tissue and usually can be treated effectively; however CA-MRSA strains display enhanced virulence, spreading more rapidly and causing illness much more severe than traditional HA-MRSA infections, which can affect vital organs and lead to widespread infection (sepsis), toxic shock syndrome and necrotizing ("flesh-eating") pneumonia. This is thought to be due to toxins carried by CA-MRSA strains, such as PVL and PSM. It is not known why some healthy people develop CA-MRSA skin infections that are treatable whereas others infected with the same strain develop severe infections or die.

#### Treatment

CA-MRSA often results in abscess formation that requires incision and drainage. Before the spread of MRSA into the community, abscesses were not considered contagious because it was assumed that infection required violation of skin integrity and the introduction of staphylococci from normal skin colonization. However, newly emerging CA-MRSA is transmissible (similar, but with very important differences) from hospital-acquired MRSA. CA-MRSA is less likely than other forms of MRSA to cause cellulitis.

Both CA-MRSA and HA-MRSA are resistant to traditional anti-staphylococcal beta-lactam antibiotics, such as cephalexin. CA-MRSA has a greater spectrum of antimicrobial susceptibility, including to sulfa drugs, tetracyclines, and clindamycin. HA-MRSA is resistant even to these antibiotics and often is susceptible only to vancomycin. Newer drugs, such as linezolid (belonging to the newer oxazolidinones class), may be effective against both CA-MRSA and HA-MRSA.

Vancomycin and teicoplanin are glycopeptide antibiotics used to treat MRSA infections. Teicoplanin is a structural congener of vancomycin that has a similar activity spectrum but a longer half-life ( $t_{1/2}$ ). Because the oral absorption of vancomycin and teicoplanin is very low, these agents must be administered intravenously to control systemic infections. Treatment of MRSA infection with vancomycin can be complicated, due to its inconvenient route of administration. Moreover, many clinicians believe that the efficacy of vancomycin against MRSA is inferior to that of anti-staphylococcal beta-lactam antibiotics against MSSA.

Several newly discovered strains of MRSA show antibiotic resistance even to vancomycin and teicoplanin. These new evolutions of the MRSA bacterium have dubbed vancomycin intermediate-resistant *Staphylococcus aureus* (VISA). Linezolid, quinupristin/dalfopristin, daptomycin, and tigecycline are used to treat more severe infections that do not respond to glycopeptides such as vancomycin. MRSA infections can be treated with oral agents, including linezolid, rifampicin+fusidic acid, rifampicin+fluoroquinolone, pristinamycin, cotrimoxazole (trimethoprim-sulfamethoxazole), doxycycline or minocycline, and clindamycin.

A new antibiotic, called platensimycin, has demonstrated successful use against MRSA. An entirely different and promising approach is phage therapy which has a reported efficacy against up to 95% of tested *Staphylococcus* isolates.

It has been reported that maggot therapy to treat MRSA infection has been successful. Studies in diabetic patients reported significantly shorter treatment times than those achieved with standard treatments.

It has also been reported that early infections - characterized by a boil that resembles a spider bite - may be arrested with an ichthammol salve, which

## TROUBLESHOOTING

### PREVENTION OF MRSA INFECTIONS

#### FAQs For the Workplace

##### Can you get MRSA from someone at work?

MRSA is transmitted most frequently by direct skin-to-skin contact or contact with shared items or surfaces that have come into contact with someone else's infection (e.g., towels, used bandages).

MRSA skin infections can occur anywhere. However, some settings have factors that make it easier for MRSA to be transmitted. These factors, referred to as the **5 C's**, are as follows: **C**rowding, frequent skin-to-skin **C**ontact, **C**ompromised skin (i.e., cuts or abrasions), **C**ontaminated items and surfaces, and lack of **C**leanliness. Locations where the **5 C's** are common include schools, dormitories, military barracks, households, correctional facilities, and daycare centers.

##### If you have MRSA, can you go to work?

Unless directed by a healthcare provider, workers with MRSA infections should not be routinely excluded from going to work.

Exclusion from work should be reserved for those with wound drainage ("pus") that cannot be covered and contained with a clean, dry bandage and for those who cannot maintain good hygiene practices.

Workers with active infections should be excluded from activities where skin-to-skin contact with the affected skin area is likely to occur until their infections are healed.

##### What should you do if you think you have a staph or MRSA infection?

See your healthcare provider/ physician or surgeon and follow your healthcare provider's advice about returning to work.

##### If you have staph, or a MRSA skin infection, what can you do to prevent the spread of MRSA at work and at home?

You can prevent spreading staph or MRSA skin infections to others by following these steps:

**Cover your wound.** Keep areas of the skin affected by MRSA covered. Keep wounds that are draining or have pus covered with clean, dry bandages. Follow your healthcare provider's instructions on proper care of the wound. Pus from infected wounds can contain staph and MRSA, so keeping the infection covered will help prevent the spread to others. Bandages or tape can be discarded with the regular trash.

**Clean your hands.** You, your family, and others in close contact should wash their hands frequently with soap and warm water or use an alcohol-based hand sanitizer, especially after changing the bandage or touching the infected wound.

**Do not share personal items.** Avoid sharing personal items such as uniforms, personal protective equipment, clothing, towels, washcloths or razors that may have had contact with the infected wound or bandage.

**Talk to your doctor.** Tell any healthcare providers who treat you that you have or had a staph or MRSA skin infection.

##### What should you do if you suspect that your uniform, clothing, personal protective equipment or workstation have become contaminated with MRSA?

Wash uniforms, clothing, sheets and towels that become soiled with water and laundry detergent. Drying clothes in a hot dryer, rather than air-drying, also helps kill bacteria in clothes. Use a dryer to dry clothes completely.

Cleaning contaminated equipment and surfaces with detergent-based cleaners or Environmental Protection Agency (EPA)-registered

disinfectants is effective at removing MRSA from the environment. Because cleaners and disinfectants can be irritating and exposure has been associated with health problems such as asthma, it is important to read the instruction labels on all cleaners to make sure they are used safely and appropriately. Where disinfection is concerned, more is not necessarily better.

##### What can employers do to prevent the spread of staph or MRSA at the workplace?

Place importance on worker safety and health protection in the workplace  
Ensure the availability of adequate facilities and supplies that encourage workers to practice good hygiene

Ensure that routine housekeeping in the workplace is followed

Ensure that contaminated equipment and surfaces are cleaned with detergent-based cleaners or Environmental Protection Agency (EPA)-registered disinfectants.

#### Other FAQs About MRSA

##### Transmission and Risk:

##### Who gets staph or MRSA infections?

Approximately 25% to 30% of the population is colonized (when bacteria are present, but not causing an infection) in the nose with staph bacteria. Staph infections, including MRSA, occur most frequently among persons in hospitals and healthcare facilities (such as nursing homes and dialysis centers) who have weakened immune systems. These healthcare-associated staph infections include surgical wound infections, urinary tract infections, bloodstream infections, and pneumonia.

##### How common are staph and MRSA infections?

Staph bacteria are one of the most common causes of skin infection in the developed countries and are a common cause of pneumonia, surgical wound infections, and bloodstream infections. The majority of MRSA infections occur among patients in hospitals or other healthcare settings; however, it is becoming more common in the community setting. Data from a prospective study in 2003, suggests that 12% of clinical MRSA infections are community-associated, but this varies by geographic region and population.

##### Signs and Symptoms:

##### What does a staph or MRSA infection look like?

Staph bacteria, including MRSA, can cause skin infections that may look like a pimple or boil and can be red, swollen, painful, or have pus or other drainage. More serious infections may cause pneumonia, bloodstream infections, or surgical wound infections.

*Staphylococcus aureus*, often referred to simply as "staph," is a type of bacteria commonly carried on the skin or in the nose of healthy people. Sometimes, staph can cause an infection. Staph bacteria are one of the most common causes of skin infections in the United States. Most of these skin infections are minor (such as pustules and boils) and can be treated without antibiotics. However, staph bacteria also can cause serious infections (such as surgical wound infections, bacteremia / septicemia, and pneumonia).

Methicillin-resistant *Staphylococcus aureus* (MRSA) refers to types of staph that are resistant to a type of antibiotic methicillin. MRSA is often resistant to other antibiotics, as well. While 25% to 30% of the population is colonized with staph (meaning that bacteria are present, but not causing an infection with staph), approximately 1% is colonized with MRSA.

Staph infections, including MRSA, occur most frequently among persons in hospitals and healthcare facilities (such as nursing homes and dialysis centers) who have weakened immune systems. These healthcare-associated staph infections include surgical wound infections, urinary tract infections, bacteremia / septicemia, and pneumonia.

Staph and MRSA can also cause illness in persons outside of hospitals and healthcare facilities. MRSA infections that are acquired by persons who **have not** been recently (within the past year) hospitalized or had a medical procedure (such as dialysis, surgery, catheters) are known as community-associated MRSA infections. Staph or MRSA infections in the community are usually manifested as skin infections that look like pimples or boils and occur in otherwise healthy people.



Usual presentation of MRSA infections

#### Prevention:

**How can I prevent staph or MRSA skin infections?**

Practice good hygiene:

Keep your hands clean by washing thoroughly with soap and water or using an alcohol-based hand sanitizer.

Keep cuts and scrapes clean and covered with a bandage until healed.

Avoid contact with other people's wounds or bandages.

Avoid sharing personal items such as uniforms and personal protective equipment.

#### Treatment:

##### Are staph and MRSA infections treatable?

Yes. Many staph skin infections may be treated by draining the abscess or boil and may not require antibiotics. Drainage of skin boils or abscesses should only be done by a healthcare provider.

However, some staph and MRSA infections are treated with antibiotics. If you are given an antibiotic, take all of the doses, even if the infection is getting better, unless your doctor tells you to stop taking it. Do not share antibiotics with other people or save unfinished antibiotics to use at another time.

If after visiting your healthcare provider the infection is not getting better after a few days, contact them again. If other people you know or live with get the same infection tell them to go to their healthcare provider.

(...to be continued)

## BOUQUET

### In Lighter Vein

○ Through the pitch-black night, the captain sees a light dead ahead on a collision course with his ship. He sends a signal:

"Change your course ten degrees east."

The light signals back: "Change yours, ten degrees west."

Angry, the captain sends: "I'm a Navy captain! Change your course, sir!"

"I'm a seaman, second class," comes the reply. "Change your course, sir."

Now the captain is furious. "I'm a battleship! I'm not changing course!"

There's one last reply. "I'm a lighthouse. Your call."

○ See if you can do this. Read each line aloud without making any mistakes. If you make a mistake you **MUST** start over or it won't work.

This is this cat

This is is cat

This is how cat

This is to cat

This is keep cat

This is a cat

This is dumbass cat

This is busy cat

This is for cat

This is forty cat

This is seconds cat

Now go back and read the **THIRD** word in each line from the top...

○ A little boy was taken to the dentist. It was discovered that he had a cavity that would have to be filled.

"Now, young man," asked the dentist, "what kind of filling would you like for that tooth?"

"Chocolate, please," replied the youngster

○ A man & wife entered a dentist's office. The Wife said, "I want a tooth pulled. I don't want gas or Novocain because I'm in a terrible hurry. Just pull the tooth as quickly as possible." You're a brave woman said the dentist. Now, Show me which tooth it is. The wife turns to her husband and says, "Open your mouth and show the dentist which tooth it is, dear."

### Wisdom Whispers

- ◆ The foolish man seeks happiness in the distance, the wise grows it under his feet.
- ◆ At the height of laughter, the universe is flung into a kaleidoscope of new possibilities.
- ◆ The bird of paradise alights only upon the hand that does not grasp.
- ◆ Happiness is nothing more than good health and a bad memory.
- ◆ The secret of happiness is to make others believe they are the cause of it.
- ◆ You don't stop laughing because you grow old. You grow old because you stop laughing.
- ◆ He who laughs, lasts!
- ◆ Laugh at yourself first, before anyone else can.
- ◆ The most profound joy has more of gravity than of gaiety in it.
- ◆ Grief can take care of itself, but to get the full value of a joy you must have somebody to divide it with.
- ◆ Life is just a mirror, and what you see out there, you must first see inside of you.
- ◆ It's not true that life is one damn thing after another; it is one damn thing over and over.
- ◆ "Politics is the art of looking for trouble, finding it everywhere, diagnosing it incorrectly, and applying the wrong remedies."

### Brain Teasers

1. The largest cell in the myeloid series is.  
A. Myeloblast B. Promyelocyte C. Myelocyte D. Metamyelocyte
2. In erythroid series mitotic division occurs upto which stage?  
A. Pronormoblast B. Early normoblast  
B. Intermediate normoblast D. Late normoblast
3. A reticulocyte matures into an RBC in ... days  
A. 1-2 B. 2-5 C. 5-10 D. 10-20
4. In myeloid series granules first appear in .. stage  
A. Myeloblast B. Promyelocyte C. Myelocyte D. Metamyelocyte
5. A normal female's blood should show at least ... typical drumsticks in 500 neutrophils  
A. 2 B. 4 C. 6 D. 10
6. The largest cell of erythroid series is..  
A. Polychromatic normoblast B. Basophilic normoblast  
C. Orthochromatic normoblast D. Pronormoblast

Answers: 1.C, 2.C, 3.A, 4.B, 5.C, 6.D

## TULIP NEWS

**MALASCAN AND TULIP'S FEBRILE ANTIGEN SET****- TWO MORE STARS IN THE HORIZON**

True to its corporate line - **Innovative Excellence**, Tulip Group is constantly introducing innovative products designed to changing market trends and customer requirements.

Adding products with new improved technology for better performance and customer convenience is what keeps Tulip Group ahead of competition.

We would like to take this opportunity to unfold to our privileged customers some of our remarkable achievements.

**Did you know?**

**.. that Tulip Group was the first Indian diagnostic company to introduce**

**Liquid, stable Prothrombin reagent**

**Latex based RAC tests without serum dilutions**

**Matrix Gel system for Blood grouping and typing**

**Indigenously manufactured Immunoturbidimetry Reagents**

**Indigenously manufactured dRVVT test for Kaolin clotting time for lupus anticoagulant (LA) detection**

**and many more...**

Continuing our trend of innovations we have recently introduced

**TULIP'S FEBRILE ANTIGEN SET**

Tulip's Febrile antigen set can be used for the detection of antibodies encountered in febrile diseases like Salmonellosis, Brucellosis and Rickettsia.

These new emerging febrile diseases are often missed out in diagnosis due to non availability of specific diagnostic procedure/kit. Always prompt in response, Tulip Group launched the much needed Tulip's Febrile antigen set to diagnose PUO's.

Tulip's Febrile antigen set is available in 6 x 5 ml format and contains the following antigens

*S. typhi 'O'*  
*S. paratyphi 'H'*  
*S. paratyphi 'AH'*  
*S. paratyphi 'BH'*  
*Brucella abortus*  
*Proteus Ox19*

The test method employed is Widal test for detection of Salmonellosis and Weil-Felix test method for Rickettsial diseases.

Closely following the launch of Tulip's Febrile antigen set, Zephyr Biomedicals, A Tulip Group company introduced another major product

**MALASCAN**

Malascan Pf/Pan is rapid self performing, qualitative, two site sandwich immunoassay, utilising whole blood for the detection of *P. falciparum* specific histidine rich protein-2 (Pf HRP-2) and pan specific aldolase. This test can be used for differentiation of *P. falciparum* and other malarial species in whole blood samples

Malascan Pf/Pan is available in convenient pack sizes of One Test, 10 Tests and 25 Tests.

**Tulip Diagnostics (P) Ltd's****Zephyr Biomedical's**

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