

Buruli ulcer

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Buruli ulcer

(also known as the **Bairnsdale ulcer**, **Searls ulcer**, or **Daintree ulcer**^{[1][2][3]}) is an infectious disease caused by

Buruli ulcer



Buruli ulcer on the ankle of a person from Ghana.

Classification and external resources

Specialty	Infectious disease
ICD-10	A31.1 (http://apps.who.int/classifications/icd10/browse/2016/en#/A31.1) (ILDS A31.120)
ICD-9-CM	031.1 (http://www.icd9data.com/getICD9Code.ashx?icd9=031.1)
DiseasesDB	8568 (http://www.diseasesdatabase.com/ddb8568.htm)
Patient UK	Buruli ulcer (http://patient.info/doctor/Buruli-Ulcer)
MeSH	D054312 (https://www.nlm.nih.gov/cgi/mesh/2017/MB_cgi?field=uid&term=D054312)

Mycobacterium ulcerans.^[4] The early stage of the infection is characterised by a painless nodule or area of swelling.^[4] This nodule can turn into an ulcer.^[4] The ulcer may be larger inside than at the surface of the skin,^[5] and can be surrounded by swelling.^[5] As the disease worsens, bone can be infected.^[4] Buruli ulcers most commonly affect the arms or legs;^[4] fever is uncommon.^[4]

M. ulcerans releases a toxin known as mycolactone, which decreases immune system function and results in tissue death.^[4] Bacteria from the same family also cause tuberculosis and leprosy (*M. tuberculosis* and *M. leprae*, respectively).^[4] How the disease is spread is not known.^[4] Sources of water may be involved in the spread.^[5] As of 2013 there is no effective vaccine.^{[4][6]}

If people are treated early, antibiotics for eight weeks are effective in 80%.^[4] The treatment often includes the medications rifampicin and streptomycin.^[4]

Clarithromycin or moxifloxacin are sometimes used instead of streptomycin.^[4] Other treatments may include cutting out the ulcer.^{[4][7]} After the infection heals, the area typically has a scar.^[6]

Buruli ulcers occurs most commonly in rural sub-Saharan Africa especially Cote d'Ivoire, but can also occur in Asia, the Western Pacific and the Americas.^[4] Cases have occurred in more than 32 countries.^[5] About five to six thousand cases occur every year.^[4] The disease also occurs in a number of animals other than humans.^[4] Albert Ruskin Cook was the first to describe buruli ulcers in 1897.^[5]

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Signs and symptoms

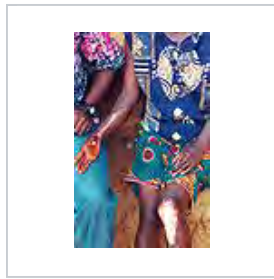
The infection in most instances presents as a painless lump just under the skin. In southern Australia, the presentation is more often as a pimple in the skin (dermis) rather than under it. The infection is mostly in the limbs, most often in exposed areas, but not on the hands or feet. In children, all areas may be involved, including the face or abdomen. A more severe form of infection produces diffuse swelling of a limb, which, unlike the papule or nodule, can be painful and accompanied by fever. Infection may frequently follow physical trauma, often minor trauma such as a small scratch.



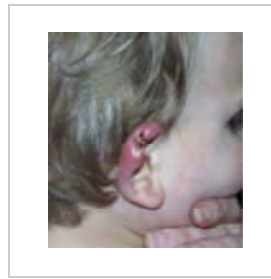
Buruli ulcer on the hand of a person from Peru. A) nonulcerative edematous lesion on the right middle finger as first seen B) ulcerated lesions on the right middle finger about 4 weeks later C) extensive debridement, 5.5 weeks after first seen D) cured lesion 5 months after first seen, 1 month after autologous skin graft



A typical Buruli ulcer on the left hand of a 17-year-old boy in Nigeria



Healed Buruli ulcer lesions in a Ghanaian woman



Ear of an 18-month-old child with culture- and PCR-confirmed Buruli ulcer



Buruli ulcer in a long-term traveler to Senegal

Cause

The disease is caused by *Mycobacterium ulcerans*.^[4] It often occurs in close proximity to water bodies, but no specific activities that bring people into contact with water have been identified (i.e. fetching of water, fishing, washing, bathing, etc.). The mode of transmission of Buruli ulcer is not entirely known. Recent evidence suggests insects may be involved in the transmission of the infection.^[8] These insects are aquatic bugs belonging to the genus *Naucoris* (family Naucoridae) and *Diplonychus* (family Belostomatidae). Trauma is probably the most frequent means by which *M. ulcerans* is introduced into the skin from surface contamination.^[9] The initial trauma can be as slight as a hypodermic needle puncture or as severe as gunshot or exploding land mine wounds.^[10] Other studies have suggested aerosol spread but these are not proven.^[11] In Australia, animals such as koalas and possums are naturally infected.^{[12][13]} Epidemiological evidence has not clearly supported person-to-person transmission. However, Muelder & Nourou found that 10 out of 28 patients had relatives who had also had the disease, and cautioned against the dismissal of person-to-person transmission.^[14] Given the number of patients who shed large numbers of bacilli from their wounds and live in very close contact with relatives, more cases should have been observed. The cases reported by Muelder & Nourou could perhaps have been exposed to a common source of infection, and there might also be genetic component to sensitivity to the disease.

After considering the various suspected agents, Portaels *et al.* proposed the hypothesis that human beings, as well as domestic and wild animals, could be contaminated or infected by biting insects such as water bugs.^[15] Aquatic bugs are cosmopolite insects found throughout temperate and tropical regions especially rich in freshwater. They represent about 10% of all species of Hemiptera associated with water and belong to two series of the suborder Heteroptera: the Nepomorpha, which include four superfamilies whose members spend most of their time under water, and the Naucoridae, which include a single family, the Naucoridae, whose members are commonly termed creeping water bugs.

Whether found in temperate countries like France or tropical ones like Ivory Coast, aquatic bugs exhibit the same way of life, preying, according to their size, on mollusks, snails, young fish, and the adults and larvae of other insects that they capture with their raptorial front legs and bite with their rostrum. These insects can inflict painful bites on humans as well. In the Ivory Coast, where Buruli ulcer is endemic, the water bugs are present in swamps and rivers, where human activities such as farming, fishing, and bathing take place. Present findings^[16] describing the experimental transmission of *M. ulcerans* from water bugs to mice are in good agreement with the possibility of this mode of transmission to humans by bites.

Also in strong support of this hypothesis was the localization of *M. ulcerans* within the salivary glands of Naucoridae.^[16] Local physiological conditions of this niche appear to fit the survival and the replication needs of *M. ulcerans* but not those of other mycobacteria. Surprisingly, infiltration of the salivary glands of Naucoridae by *M. ulcerans* does not seem to be accompanied by any tissue damage similar to the ulcerative skin lesions developed by bitten individuals and mediated by the cytotoxic activity of the mycolactone^[17] and other toxins produced by *M. ulcerans*.^[18] The inactivation of the latter toxins could be the result of salivary enzymatic activities, which remain to be determined.

Mycobacterium ulcerans was first cultivated and characterized from the environment in 2008.^[19]

Pathology

The disease is primarily an infection of subcutaneous fat, resulting in a focus of necrotic (dead) fat containing myriads of the mycobacteria in characteristic spherules formed within the dead fat cells. Skin ulceration is a secondary event.

M. ulcerans releases a lipid toxin, mycolactone, which functions as an immune suppressant, necrotising agent and activator of cellular death.^{[20][21]}

Healing may occur spontaneously but more often the disease is slowly progressive with further ulceration, granulation, scarring, and contractures. Satellite infection may occur with other nodules developing and infection may occur into bone. Although seldom fatal, the disease results in considerable morbidity and deformity.

Th1-mediated immune responses are protective against *M. ulcerans* infection, whereas Th2-mediated responses are not.

Diagnosis

The diagnosis of Buruli ulcer is usually based on the characteristic appearance of the ulcer in an endemic area. If there is any doubt about the diagnosis, then PCR using the IS2404 target is helpful, but this is not specific for *M. ulcerans*. The Ziehl-Neelsen stain is only 40–80% sensitive, and culture is 20–60% sensitive. Simultaneous use of multiple methods may be necessary to make the diagnosis.^[22]

Prevention

There is no specific vaccine for *Myocobacterium ulcerans*.^[6] The Bacillus Calmette-Guérin vaccine may offer temporary protection.^[4]

Treatment

If treated early antibiotics for eight weeks are effective in 80% of people.^[4] This often includes the medications rifampicin and streptomycin.^[4] Clarithromycin or moxifloxacin are sometimes used instead of streptomycin.^[4]

Treatment may also include cutting out the ulcer.^[7] This may be a minor operation and very successful if undertaken early. Advanced disease may require prolonged treatment with extensive skin grafting. Surgical practice can be dangerous in the developing countries where the disease is common.

Epidemiology

The infection occurs in well-defined areas throughout the world, mostly tropical areas — in several areas in Australia, in Uganda, in several countries in West Africa, in Central and South America, in southeast Asia and New Guinea. It is steadily rising as a serious disease, especially in West Africa and underdeveloped countries, where it is the third leading cause of mycobacterial infection in healthy people, after tuberculosis and leprosy.



Map with number of reported cases of Buruli ulcer in 2009.

The disease is more likely to occur where there have been environmental changes such as the development of water storages, sand mining, and irrigation.

Buruli ulcer is currently endemic in Benin, Côte d'Ivoire, Ghana, Guinea, Liberia, Nigeria, Sierra Leone and Togo.^[23] In Ghana, 1999 data indicated that the prevalence rate of the disease in the Ga West District was 87.7 per 100,000, higher than the estimated national prevalence rate at 20.7 per 100,000 generally, and 150.8 per 100,000 in the most disease-endemic districts.^[24]

Geographical distribution

Buruli ulcer has been reported from at least 32 countries around the world, mostly in tropical areas:

- West Africa: Benin, Burkina Faso, Côte d'Ivoire, Ghana, Liberia, Nigeria, Togo, Guinea, Sierra Leone.
- Other African Countries: Angola, Cameroon, Congo, Democratic Republic of Congo, Equatorial Guinea, Gabon, Sudan, Uganda.
- Western Pacific: Australia, Papua New Guinea, Kiribati.
- Americas: French Guyana, Mexico, Peru, Surinam.
- Asia: China, Malaysia, Japan.

In several of these countries, the disease is not considered to be a public health problem, hence the current distribution and the number of cases are not known. Possible reasons include:

- the distribution of the disease is often localized in certain parts of endemic countries;
- Buruli ulcer is not a notifiable disease
- In most places where the disease occurs, patients receive care from private sources such as voluntary mission hospitals and traditional healers. Hence the existence of the disease may not come to the attention of the ministries of health.

It most commonly occurs in Africa: Congo and Cameroon in Central Africa, Côte d'Ivoire, Ghana and Benin in West Africa. Some Southeast Asian countries (Papua New Guinea) and Australia have major foci, and there have been a few patients reported from South America (French Guyana and Surinam) and Mexico. Focal outbreaks have followed flooding, human migrations,^[25] and man-made topographic modifications such as dams and resorts. Deforestation and increased basic agricultural activities may significantly contribute to the recent marked increases in the incidence of *M. ulcerans* infections, especially in West Africa, where the disease is rapidly emerging.

Race, age and sex

Buruli ulcer commonly affects poor people in remote rural areas with limited access to health care. The disease can affect all age groups, although children under the age of 15 years (range 2–14 years) are predominantly affected. There are no sex differences in the distribution of cases among children. Among adults, some studies have reported higher rates among women than males (Debacker *et al.* accepted for publication). No racial or socio-economic group is exempt from the disease. Most ulcers occur on the extremities; lesions on the lower extremities are almost twice as common as those on the upper extremities. Ulcers on the head and trunk accounted for less than 8% of cases in one large series.^[26]

History

James Augustus Grant, in his book *A Walk across Africa* (1864), describes how his leg became grossly swollen and stiff with later a copious discharge. This was almost certainly the severe edematous form of the disease, and is the first known description of the infection. Buruli ulcer disease was identified in 1897 by Sir Albert Cook, a British physician, at Mengo Hospital in Kampala, Uganda. A detailed description of the disease was written in 1948 by Professor Peter MacCallum and his colleagues, who were treating patients from the Bairnsdale district, near Melbourne, Australia. They

were the first to identify *Mycobacterium ulcerans* as the pathogen causing it. The disease was so named after Buruli County in Uganda (now called Nakasongola District), because of the many cases that occurred there in the 1960s.^[27] The incidence of the disease has recently been rising in tropical Africa.

In March 2008, researchers announced the first isolation of *M. ulcerans* from the environment.^[19] This suggested that the disease might be transmitted via contact with the environment rather than person to person.^[19] The entire genome of *M. ulcerans* has been sequenced.

Other names





Other names include Bairnsdale ulcer, Searls ulcer, Daintree ulcer,^{[1][2][3]} Kumusi ulcer,^[28] and mycoburuli ulcers.^[29] Searls was one of the first physician who first described it.^[30]

See also

- Neglected diseases

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Further reading

- Merritt, R. W.; Walker, E. D.; Small, P. L. C.; Wallace, J. R.; Johnson, P. D. R.; Benbow, M. E.; Boakye, D. A. (2010). Phillips, Richard O, ed. "Ecology and Transmission of Buruli Ulcer Disease: A Systematic Review". *PLoS Neglected Tropical Diseases*. **4** (12): e911. doi:10.1371/journal.pntd.0000911. PMC 3001905 . PMID 21179505.

External links

- World Health Organization buruli ulcer page (http://www.who.int/mediacentre/factsheets/fs199/en/)
- "*Mycobacterium ulcerans*". *NCBI Taxonomy Browser*. 1809.

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