INVITED REVIEW

TUNGIASIS

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SUMMARY

Tungiasis is a neglected parasitic skin disease caused by the permanent penetration of the female sand flea (also called jigger flea) *Tunga penetrans* into the skin of its host. After penetration, most commonly on the feet, the flea undergoes an impressing hypertrophy, and some days later the abdominal segments of the flea have enlarged up to the size of about 1 cm. The flea infestation is associated with poverty and occurs in many resource-poor communities in the Caribbean, South America and Africa. In this review, a historical overview on tungiasis is given. The natural history, pathology, epidemiology, diagnosis, therapy and control of the parasitic skin disease are discussed. It is concluded that tungiasis is an important parasitosis causing considerable morbidity in affected populations. Future studies are needed to increase the knowledge on the biology, pathophysiology, epidemiology, therapy and control of the ectoparasite.

KEYWORDS: Tungiasis; *Tunga penetrans*; Sand flea; Jigger flea.

INTRODUCTION

Tungiasis is a neglected parasitic skin disease caused by the permanent penetration of the female sand flea or jigger flea *Tunga penetrans* into the skin. After penetration, which most commonly takes place on the feet, the flea undergoes an impressing hypertrophy, and some days later the abdominal segments of the flea have enlarged up to the size of about 1 cm. The flea infestation is associated with poverty and occurs in many resource-poor communities in the Caribbean, South America and Africa. In Brazil, tungiasis is called popularly *bicho de pé*, *pulga de bicho* or *pulga de porco*.

HISTORICAL OVERVIEW

Originally, *T. penetrans* occurred only on the American continent. This is the reason why the first descriptions of tungiasis date back to the years of the discovery of the Americas. The first author to mention tungiasis was G. de Oviedo y Valdes who reported the sand flea from Haiti in 1525 (GUYON, 1870; HOEPPLI, 1963; GORDON, 1941). In the 16th century the German Hans Staden spent several years with the Tupinambá indians in south-eastern Brazil and already reported the problems caused by the jigger flea (STADEN VON HOMBERG ZU HESSEN, 1556; TOSTI, 2000). The first scientific description dates back to the early 17th century by Aleixo de Abreu from Brazil (GUERRA, 1968).

Interestingly, *T. penetrans* is one of the few parasites which have spread from the western to the eastern hemisphere. The sand flea has been introduced several times in the 17th, 18th and 19th century to West Africa as a result of the slave trade; however, the flea did not spread over the continent and disappeared after some time (JEFFREYS, 1952; JANSELME, 1908; HENNING, 1904). Finally, *T. penetrans* came to Africa with ballast sand carried by a ship that left from Brazil to Angola in 1872 (HOEPPLI, 1963; HESSE, 1899). Within a few years, the parasite spread from Angola along trading routes and with soldiers in the entire sub-Saharan Africa (HEUKELBACH *et al.*, 2001; HENNING, 1904; HESSE, 1899; GORDON, 1941). In the 19th century travellers to South America, Africa and the Caribbean reported about native communities suffering from severe jigger infestation, eventually leading them to abandon entire villages (HOEPPLI, 1963; HEUKELBACH *et al.*, 2001; BRUCE *et al.*, 1942). They already noted the intense inflammation leading to suppuration, ulcer and gangrene; difficulties in walking were commonly reported (WATERTON, 1973; COTES, 1899; KONCZAKI, 1985; GREY, 1901; HESSE, 1899; BRUCE *et al.*, 1942). The participants of expeditions into Africa at the end of the 19th and the beginning of the 20th century reported natives and also themselves with severe infestation that made many of them almost unable to walk (GREY, 1901; KONCZAKI, 1985). Some military operations in colonial times were prejudiced because the feet of the soldiers were so heavily infested, that they could hardly walk (JOLLY, 1926; GORDON, 1941; HOEPPLI, 1963). At the end of the 19th century

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the sand flea had reached East-Africa, Zanzibar and Madagascar (BLANCHARD, 1899; HESSE, 1899). In 1899, returning British troops brought *T. penetrans* to the Indian Subcontinent. However, the parasite never established there (GORDON, 1941; TURKHUD, 1928; SANE & SATOSKAR, 1985; COTES, 1899).

DECLE (1900) reported vividly the problems encountered in the late 19th century caused by tungiasis in Africa: "*In this village there was not a man, woman or child who was not covered with ulcers*". He continues: "*I found the people starving, as they were so rotten with ulcers from jiggers that they had been unable to work in their fields, and could not even go to cut the few bananas that had been growing.*" These and other observations made him conclude: "*My experience makes me look upon jigger as the greatest curse that has ever afflicted Africa*". Clearly, today the situation is not as dramatic as described in this historical text. However, the historical reports demonstrate the pathology that severe tungiasis can cause. Even today, in resource-poor communities, infestation with individuals harboring hundreds of fleas occurs and severe pathology is common (HEUKELBACH *et al.*, 2001; FELDMEIER *et al.*, 2003).

NATURAL HISTORY AND CLINICAL PATHOLOGY

Tunga penetrans is the smallest flea species known with only 1 mm of size (Fig. 1). Both males and females are blood-feeding (WITT *et al.*, 2004), but eventually the female sand fleas penetrate permanently into the skin of its hosts and undergoes an important hypertrophy, expelling hundreds of eggs during a period of two to three weeks (EISELE *et al.*, 2003). Already during penetration the hypertrophy of the flea's abdomen begins, and after some days the abdominal segments reach the size of up to 1 cm (EISELE *et al.*, 2003; GEIGY & HERBIG, 1949). After expulsion of the eggs, the involution of the lesion begins. About three weeks after penetration, the fleas die and eventually are sloughed from the epidermis by skin repair mechanisms (EISELE *et al.*, 2003).

Fig. 1 - Female *Tunga penetrans.*

It is important to understand that infestation with *T. penetrans* is a dynamic process with lesions altering their morphological aspect

continuously. The natural history of tungiasis has been divided into five stages, the so-called Fortaleza Classification (EISELE *et al.*, 2003). In stage I the flea is in *statu penetrandi* (30 min to several hours), and a reddish spot of about 1 mm appears. In stage II the hypertrophy begins and the parasite becomes more obvious as a growing whitish or mother-of-pearl-like nodule (one to two days after penetration). In the protruding rear cone of the flea, the anal-genital opening appears as a central black dot. The lesion is surrounded by an erythema. In stage III the hypertrophy is maximal and becomes macroscopically visible: two days to three weeks after penetration (Fig. 2). A round, watch glass-like patch appears which is frequently accompanied by hyperkeratosis and desquamation of the surrounding skin. Expulsion of eggs and faeces are typical in this stage (Fig. 3). The lesions are usually painful and

Fig. 2 - Single lesion caused by a mature flea (Stage III).

Fig. 3 - Several vital tungiasis lesions on the first toe. Eggs attached to the nail are visible. On the left nail rim, feces are being expelled from a lesion.

produce the sensation of foreign bodies expanding under the skin. In stage IV a black crust covers an involuted lesion with a dead parasite (three to five weeks after penetration). A residual scar in the *stratum corneum* is characteristic for stage V (six weeks to several months after penetration). The usual sequence of development of the neosome, involution of the lesion and stage V formation may be changed by superinfection and manipulation of the lesion by the patient or a carer.

Typically, *T. penetrans* affects the periungual area of the toes, the heels and the soles. However, embedded sand fleas can be found on almost every part of the body, such as the hands, elbows, neck, buttocks and the genital region (Fig. 4) (HEUKELBACH *et al.*, 2002b; HEUKELBACH *et al.*, 2004d; BEZERRA, 1994; VERALDI *et al.*, 1996). If several lesions occur simultaneously they are usually located in clusters. Severe infestations with hundreds of embedded sand fleas are not rare. In single cases lesions may take the aspect of a tumourous growth and in histological sections appear as pseudoepitheliomatous hyperplasia (HEUKELBACH *et al.*, 2004d).

Fig. 4 - Ectopic lesion on the finger of an 8-year-old girl.

Although tungiasis is a self-limited infestation, complications are common in the endemic area (FELDMEIER *et al.*, 2003; HEUKELBACH *et al.*, 2001). Many patients report severe pain, and inflammation and fissures commonly hinders individuals from walking normally (FELDMEIER *et al.*, 2004). Sequels include deformation and loss of toenails, as well as deformation of digits (Fig. 5). The sore in the skin caused by the protruding rear end of the flea is an entry point for pathogenic microorganisms (FELDMEIER *et al.*, 2002). Superinfected lesions lead to formation of pustules, suppuration and ulcers. *Staphylococcus aureus* and streptococci most frequently occur, but other aerobic and anaerobic bacteria (including clostridiae) are also found (FELDMEIER *et al.*, 2002). In non-vaccinated individuals tungiasis may lead to tetanus (OBENGUI, 1989; TONGE, 1989; LITVOC *et al.*, 1991; GRECO *et al.*, 2001; SORIA & CAPRI, 1953).

DIAGNOSIS

The diagnosis of tungiasis is made clinically (HEUKELBACH *et al.*, 2001). Even the untrained physician can diagnose the ectoparasitosis taking into account the typical topographic localisations and the natural history of the disease. The patient typically complains about local

Fig. 5 - Severely infested and inflamed toes with deformation of digits and finger nails. A chain of feces is expelled from the flea at the center.

itching, pain and the sensation of a foreign body. Patients commonly report having walked in infested places such as beaches and farms.

Most lesions occur on the nail rim. Eggs being expelled or eggs attached to the skin and the release of brownish threads of faeces are pathognomonic signs (Fig. 3 and 5). Faeces threads are of a helical structure and often spread into the dermal papillae. A biopsy of the lesion and histopathological examination is not indicated. However, histological sections are often done to confirm the diagnosis in European and North American travellers after their return from the endemic area (FRANCK *et al.*, 2003; SMITH & PROCOP, 2002). The sections usually demonstrate the presence of the parasite, eggs or chitinous fragments (FRANCK *et al.*, 2003; FIMIANI *et al.*, 1990; DOUGLAS-JONES *et al.*, 1995; BURKE *et al.*, 1991; REISS, 1966; POPPITI Jr. *et al.*, 1983; MACIAS & SASHIDA, 2000; SMITH & PROCOP, 2002). In single cases of atypical tungiasis, a biopsy may be indicated, for example lesions with a pseudoepitheliomatous appearance at ectopic sites (HEUKELBACH *et al.*, 2004d).

Differential diagnoses include verrucae, myiasis, pyogenic infection/abscess, foreign bodies, acute paronychia, cutaneous larva migrans, dermoid cysts, dracontiasis, melanoma, deep mycosis and bites or stings of other injurious arthropods (FRANCK *et al.*, 2003; HEUKELBACH *et al.*, 2001; WARDHAUGH & NORRIS, 1994; GOLOUH & SPILER, 2000; SANUSI *et al.*, 1989).

TREATMENT AND PREVENTION

The standard treatment is surgical extraction of the flea under sterile conditions (HEUKELBACH *et al.*, 2001). Fleas should be extracted as

early as possible to avoid secondary infections. However, this is not an easy task, as it requires a skilled hand and good eye-sight. The opening in the epidermis should be carefully widened with an appropriate instrument such as a sterile needle to enable the extraction of the entire flea. If the flea is torn during extraction or if parts are left in the sore, severe inflammation is the rule. After extraction the sore should be treated with a topical antibiotic. In resource-poor settings, strict hygiene is often not applied and appropriate instruments are unavailable with the consequence that attempts removing the fleas often do more harm than good (FELDMEIER *et al.*, 2003). Tetanus immune status has to be checked, and in case of inappropriate immunization, prophylaxis is indicated.

Daily inspection of the feet and immediate extraction of embedded fleas protect against complications. Closed shoes and socks seem to prevent tungiasis to a certain degree although complete protection cannot be achieved by these means.

At this moment, there is no drug on the market with satisfactory clinical efficacy. A randomized controlled trial realized more than 20 years ago showed a good efficacy of oral niridazole, an anti-schistosomal compound with severe adverse events which has been taken from the market since long (ADE-SERRANO *et al.*, 1982). In the cited study, the therapeutic efficacy of niridazole was claimed to be very good. However, the outcome measures were not well defined and the study showed other methodological problems which limit the interpretation of results. In northeast Brazil many dermatologists claim a good efficacy of ivermectin in tungiasis and support their notion by anecdotal observations. In fact, a case report suggests oral ivermectin given at a single dose (200 µg/kg body weight) to be effective against embedded sand fleas (SARACENO *et al.*, 1999). Additionally, there are several anecdotal reports of health care providers about the efficacy of oral ivermectin for the treatment of tungiasis (HEUKELBACH *et al.*, 2004c). However, a recently conducted randomized controlled trial with oral ivermectin at a relatively high dose (2x300 µg/kg body weight) did not show any efficacy as compared to placebo (HEUKELBACH *et al.*, 2004c). Another trial reported some efficacy of topical ivermectin, metrifonate and thiabendazole as compared to a topical placebo lotion and a control group without treatment (HEUKELBACH *et al.*, 2003b). Other authors suggested oral thiabendazole as an effective drug against embedded sand fleas, but controlled studies are unavailable (CARDOSO, 1981; VALENÇA *et al.*, 1972).

Recently, a case series using a natural repellent based on coconut oil showed an impressive regression of clinical pathology in severely infested patients by prevention of re-infestation (SCHWALFENBERG *et al.*, 2004). The twice-daily application of this plant-based repellent reduced the infestation rate in an area with extremely high transmission rates by almost 90% (FELDMEIER *et al.*, submitted 2005). In endemic communities the use of an effective repellent would probably be a better approach to reduce tungiasis-associated morbidity than treatment after infestation.

EPIDEMIOLOGY AND CONTROL

Tungiasis occurs on the American continent from Mexico to northern Argentina, on several Caribbean islands, as well as throughout sub-Saharan Africa (HEUKELBACH *et al.*, 2001; FRANCK *et al.*,

2003). Single cases are reported from India and southern Italy (SANE & SATOSKAR, 1985; VERALDI *et al.*, 2000). The ectoparasitosis occurs in underdeveloped communities in the rural hinterland, in fishing villages along the coast and in the slums of urban centres. Similar to many other parasitic diseases, the occurrence of severe tungiasis is linked to poverty (HEUKELBACH *et al.*, 2001; HEUKELBACH *et al.*, 2002a). A study assessing risk factors for heavy infestation in a fishing community in Brazil indicated that poor housing is the most important independent factor (MUEHLEN *et al.*, 2005).

In poor communities in Brazil, Trinidad and Nigeria, prevalences ranged between 16% and 54% (ADE-SERRANO & EJEZIE, 1981; CHADEE, 1998; MUEHLEN *et al.*, 2003; WILCKE *et al.*, 2002; CARVALHO *et al.*, 2003; CHADEE, 1994; CHADEE *et al.*, 1991; NTE & EKE, 1995; EJEZIE, 1981). Prevalence and parasite burden are correlated, and commonly individuals harbour dozens - even hundreds - of fleas (Fig. 6) (FELDMEIER *et al.*, 2003). The disease is associated with the presence of sandy soils, but may also be found in banana plantations and in the tropical forest. In Brazil, tungiasis occurs throughout the country, from Yanomami populations in the Roraima State in the far north to rural areas in Rio Grande do Sul State in the far South. Several historical and anecdotal reports indicated a higher incidence of tungiasis in the dry season (COTES, 1899; ATUNRASE *et al.*, 1952; SILVADO, 1908). In fact, there is a clear seasonal variation of infestation with only few cases occurring during the rainy season and a high incidence and consequently prevalence during the dry season (HEUKELBACH *et al.*, 2005).

Fig. 6 - Commonly seen in resource-poor communities in endemic areas: the feet of a 10-year-old girl with dozens of penetrated sand fleas.

The animal reservoir plays an important role for transmission dynamics. Domestic animals such as dogs (RIETSCHEL, 1989; HEUKELBACH *et al.*, 2004b; FRANCO DA SILVA *et al.*, 2001b), cats (HEUKELBACH *et al.*, 2004b) and pigs (COOPER, 1967; COOPER, 1976; VERHULST, 1976), but also rats are important reservoirs (HEUKELBACH *et al.*, 2004b). In a slum in Fortaleza (Northeast Brazil), 67% of dogs, 50% of cats and 59% of captured rats were found infested (HEUKELBACH *et al.*, 2004b). In the rural area, pigs and cattle are known reservoirs for *T. penetrans* (VERHULST, 1976; FRANCO DA SILVA *et al.*, 2001a; VAZ & ROCHA, 1946), but its importance seems to have diminished in the last years. Tungiasis

has also been observed in a variety of other host animals such as monkeys (HESSE, 1899; FALKENSTEIN, 1877), sheep (WOLFFHÜGEL, 1910), goats (TRENTINI *et al.*, 2000), sylvatic rodents (KARSTEN, 1865), coatis (WOLFFHÜGEL, 1910) and armadillos (DA FONSECA, 1936; FÜLLEBORN, 1908). The clinical picture and natural history in the animal hosts does not differ considerably from human tungiasis.

Due to the presence of a variety of domestic and sylvatic animals possibly serving as reservoirs, control of tungiasis is difficult to achieve (HEUKELBACH *et al.*, 2002a). Additionally, eggs, larvae and pupae of *T. penetrans* may persist in the environment for a prolonged time, and the reduction of the human and animal reservoir would result in rapid re-infection (HEUKELBACH *et al.*, 2002a). Surface spraying with insecticides has been claimed to be effective, but there is no controlled study to confirm this assumption (MATIAS, 1991), and due to the particular biology of *T. penetrans,* environmental application of insecticides may not be effective. As the flea seems to prefer sandy and shady soil for breeding, floors of houses could be cemented and streets be paved to reduce attack rates (HEUKELBACH *et al.*, 2002a). Improved sanitation and regular waste collection will contribute to reduce incidence and morbidity. These means are clearly very cost-intensive and in many communities not feasible. Health education should focus on secondary prevention, i.e. educating people and the carers of children to inspect daily their feet and take out embedded fleas with an appropriate and sterile instrument (HEUKELBACH *et al.*, 2003a). However, this issue is complicated as many people in the endemic areas consider tungiasis as a nuisance rather than a disease and therefore tend to neglect this ectoparasitosis (HEUKELBACH *et al.*, 2003c).

CONCLUSION AND FUTURE OUTLOOK

In the last few years, knowledge on tungiasis has increased considerably. The natural history has been described in detail, several therapy studies have been conducted, and the epidemiology and morbidity in resource poor settings has been described.

However, there are still many issues to be resolved. The biological habitat of premature stages of the flea and the susceptibility of these stages to insecticides is still not known. The epidemiology of tungiasis in indigenous populations remains enigmatic. The histopathological mechanisms of the inflammatory reaction of the host after infestation is not understood. Studies have to be performed to assess the efficacy and efficiency of various control measures as well as to analyse health care seeking behaviour of different populations. A new flea species, *Tunga trimamillata*, that also parasitizes man has been described recently from Ecuador (PAMPIGLIONE *et al.*, 2004; FIORAVANTI *et al.*, 2003). The lack of data on epidemiology and pathology of this new ectoparasite species calls for future studies.

Recent studies have shown that *T. penetrans* harbour *Wolbachia* bacteria in large numbers (FISCHER *et al.*, 2002; HEUKELBACH *et al.*, 2004a). It may be assumed that the *Wolbachia* of *T. penetrans* are obligatory symbionts similar to those described from other parasites. The role of *Wolbachia* in the biology of *T. penetrans* and in the pathogenesis of tungiasis is not known, but it is likely that *Wolbachia* endobacteria of sand fleas contribute to the severe inflammation constantly found in tungiasis (HEUKELBACH *et al.*, 2004a). Future studies will have to show whether antigens released from parasites actually contribute to the inflammatory reaction commonly observed in patients with tungiasis. Clearly, the presence of *Wolbachia* in sand fleas offers new perspectives for therapy and control. Using appropriate study designs, it remains imperative to increase further the knowledge on the biology, pathophysiology, epidemiology, therapy and control of the sand flea *T. penetrans*.

RESUMO

Tungíase

A tungíase é uma ectoparasitose negligenciada causada pela penetração permanente da pulga *Tunga penetrans* (também chamada de bicho de pé) na pele de seu hospedeiro. Depois da penetração, mais comumente localizada nos pés, a pulga se hipertrofia, e alguns dias depois seus segmentos abdominais atingem o diâmetro de até 1 cm. A infestação pela pulga está associada à pobreza e ocorre em muitas comunidades economicamente desfavorecidas no Caribe, na América do Sul e na África. Nesta revisão, é apresentada uma visão histórica da tungíase. A história natural, patologia, epidemiologia, diagnóstico, terapia e controle dessa ectoparasitose são discutidos. Conclui-se que a tungíase é uma importante parasitose causadora de morbidade considerável em populações afetadas. Estudos futuros serão necessários para aumentar o conhecimento sobre a biologia, patofisiologia, epidemiologia, terapia e controle do ectoparasita.

REFERENCES

1. ADE-SERRANO, M.A. & EJEZIE, G.C. - Prevalence of tungiasis in Oto-Ijanikin village, Badagry, Lagos State, Nigeria. **Ann. trop. Med. Parasit., 75:** 471-472, 1981.

2. ADE-SERRANO, M.A.; OLOMOLEHIN, O.G. & ADEWUNMI, A. - Treatment of human tungiasis with niridazole (Ambilhar): a double-blind placebo-controlled trial. **Ann. trop. Med. Parasit., 76:** 89-92, 1982.

3. ATUNRASE, J.O.; AWOBODU, C.A.; FAWOLE, C.A. & ROSANWO, P.O. - Some observations on tungiasis in Yorubaland, Western Nigeria. **W. Afr. med. J., 3:** 181-182, 1952.

4. BEZERRA, S.M. - Tungiasis: an unusual case of severe infestation. **Int. J. Derm., 33:** 725, 1994.

5. BLANCHARD, R.A.E. - Présence de la chique (*Sarcopsylla penetrans*) à Madagascar. **Arch. Parasit., 2:** 627-630, 1899.

6. BRUCE, C.O.; KNIGIN, T.D. & YOLLES, S.F. - A discussion of the chigoe (*Tunga penetrans*) based on experiences in British Guiana. **Milit. Surg., 82:** 446-452, 1942.

7. BURKE, W.A.; JONES, B.E.; PARK, H.K. & FINLEY, J.L. - Imported tungiasis. **Int. J. Derm., 30:** 881-883, 1991.

8. CARDOSO, A. - Generalized tungiasis treated with thiabendazole. **Arch. Derm., 117:** 127, 1981.

9. CARVALHO, R.W.; ALMEIDA, A.B.; BARBOSA-SILVA, S.C. *et al.* - The patterns of tungiasis in Araruama township, state of Rio de Janeiro, Brazil. **Mem. Inst. Oswaldo Cruz**, **98:** 31-36, 2003.

10. CHADEE, D.D. - Tungiasis among five communities in south-western Trinidad, West Indies. **Ann. trop. Med. Parasit.**, **92:** 107-113, 1998.

11. CHADEE, D.D. - Distribution patterns of *Tunga penetrans* within a community in Trinidad, West Indies. **J. trop. Med. Hyg.**, **97:** 167-170, 1994.

12. CHADEE, D.D.; FURLONGE, E.; NARAYNSINGH, C. & LE MAITRE, A. - Distribution and prevalence of *Tunga penetrans* in coastal south Trinidad, West Indies. **Trans. roy. Soc. trop. Med. Hyg.**, **85:** 549, 1991.

13. COOPER, J.E. - An outbreak of *Tunga penetrans* in a pig herd. **Vet. Rec.**, **80:** 365-366, 1967.

14. COOPER, J.E. - Letter: *Tunga penetrans* infestation in pigs. **Vet. Rec.**, **98:** 472, 1976.

15. COTES, E.C. - The jigger or chigoe pest. **Indian med. Gaz.**, **4:** 160-163, 1899.

16. DA FONSECA, F. - Sobre o macho de *Tunga trvassossi* Pinto et Dreyfus, 1927, e o parasitismo de *Euphractes sexcintus* L. por *Tunga penetrans* (L., 1758) (siph., tungidae). **Rev. Entomol.**, **6:** 421-424, 1936.

17. DECLE, L. - **Three years in savage Africa.** London, Methuen, 1900.

18. DOUGLAS-JONES, A.G.; LLEWELYN, M.B. & MILLS, C.M. - Cutaneous infection with *Tunga penetrans*. **Brit. J. Derm.**, **133:** 125-127, 1995.

19. EISELE, M.; HEUKELBACH, J.; VAN MARCK, E. *et al.* - Investigations on the biology, epidemiology, pathology and control of *Tunga penetrans* in Brazil. I. Natural history of tungiasis in man. **Parasit. Res.**, **90:** 87-99, 2003.

20. EJEZIE, G.C. - The parasitic diseases of school children in Lagos State, Nigeria. **Acta trop. (Basel)**, **38:** 79-84, 1981.

21. FALKENSTEIN - Über das Verhalten der Haut in den Tropen, ihe Pflege und Krankheiten.**Virchows Arch. path. Anat.**, **71:** 421-440, 1877.

22. FELDMEIER, H.; EISELE, M.; SABOIA-MOURA, R.C. & HEUKELBACH, J. - Severe tungiasis in underprivileged communities: case series from Brazil. **Emerg. infect. Dis.**, **9:** 949-955, 2003.

23. FELDMEIER, H.; EISELE, M.; VAN MARCK, E. *et al.* - Investigations on the biology, epidemiology, pathology and control of *Tunga penetrans* in Brazil. IV. Clinical and histopathology. **Parasit. Res.**, **94:** 275-282, 2004.

24. FELDMEIER, H.; HEUKELBACH, J.; EISELE, M. *et al.* - Bacterial superinfection in human tungiasis.**Trop. Med. int. Hlth**, **7:** 559-564, 2002.

25. FIMIANI, M.; REIMANN, R.; ALESSANDRINI, C. & MIRACCO, C. - Ultrastructural findings in tungiasis. **Int. J. Derm.**, **29:** 220-222, 1990.

26. FIORAVANTI, M.L.; PAMPIGLIONE, S. & TRENTINI, M. - A second species of Tunga (Insecta, Siphonaptera) infecting man: *Tunga trimamillata*. **Parasite**, **10:** 282-283, 2003.

27. FISCHER, P.; SCHMETZ, C.; BANDI, C. *et al.* - *Tunga penetrans*: molecular identification of *Wolbachia* endobacteria and their recognition by antibodies against proteins of endobacteria from filarial parasites. **Exp. Parasit.**, **102:** 201-211, 2002.

28. FRANCK, S.; FELDMEIER, H. & HEUKELBACH, J. - Tungiasis: more than an exotic nuisance. **Travel Med. infect. Dis.**, **1:** 159-166, 2003.

29. FRANCO DA SILVA, L.A.; SANTANA, A.P.; BORGES, G.T. *et al.* - Aspectos epidemiológicos e tratamento da tungíase bovina no município de Jataí, Estado de Goiás. **Ciênc. anim. bras.**, **2:** 65-67, 2001a.

30. FRANCO DA SILVA, L.A.; TEIXEIRA BORGES, G.; SANTANA, A.P. *et al.* - Alguns aspectos epidemiológicos e profiláticos da tungíase em cães de Jataí, GO. **Rev. Pat. trop.**, **30:** 69-73, 2001b.

31. FÜLLEBORN, F. - Untersuchungen über den Sandfloh. **Arch. Schiffs- u. Tropenkr.**, **6:** 269-273, 1908.

32. GEIGY, R. & HERBIG, A. - Die Hypertrophie der Organe beim Weibchen von *Tunga penetrans*. **Acta trop. (Basel)**, **6:** 246-262, 1949.

33. GOLOUH, R. & SPILER, M. - A paraungual tumor? No, just tungiasis. **Radiol. Oncol.**, **34:** 35-39, 2000.

34. GORDON, R. M. - The jigger flea. **Lancet**, **2:** 47-49, 1941.

35. GRECO, J.B.; SACRAMENTO, E. & TAVARES-NETO, J. - Chronic ulcers and myasis as ports of entry for *Clostridium tetani*. **Braz. J. infect. Dis.**, **5:** 319-323, 2001.

36. GREY, G. - The Kafue river and its headwaters. **Geogr. J.**, **18:** 62-77, 1901.

37. GUERRA, F. - Aleixo de Abreu [1568-1630], author of the earliest book on tropical medicine describing amoebiasis, malaria, typhoid fever, scurvy, yellow fever, dracontiasis, trichuriasis and tungiasis in 1623. **J. trop. Med. Hyg.**, **71:** 55-69, 1968.

38. GUYON, M. - Note accompagnant la présentation d'un ouvrage intitulé: Histoire naturelle et médicale de la Chique, *Rhynchoprion penetrans* (Oken). **C. R. Acad. Sci. (Paris)**, **70:** 785-792, 1870.

39. HENNING, G. - Zur Geschichte des Sandflohs (*Sarcopsylla penetrans* L.) in Afrika. **Naturw. Wochenschrift**, **20:** 310-312, 1904.

40. HESSE, P. - Die Ausbreitung des Sandflohs in Afrika. **Geogr. Z. (Hettner),** 522-530, 1899.

41. HEUKELBACH, J.; BONOW, I.; WITT, L.H. *et al.* - High infection rate of *Wolbachia* endobacteria in the sand flea *Tunga penetrans* from Brazil. **Acta trop.**, **92:** 225-230, 2004a.

42. HEUKELBACH, J.; COSTA, A.M.L.; WILCKE, T. *et al.* - The animal reservoir of *Tunga penetrans* in severely affected communities of north-east Brazil. **Med. vet. Entomol.**, **18:** 329-335, 2004b.

43. HEUKELBACH, J.; DE OLIVEIRA, F.A. & FELDMEIER, H. - Ectoparasitoses e saúde pública: desafios para controle. **Cadern. Saude públ.**, **19:** 1535-1540, 2003a.

44. HEUKELBACH, J.; DE OLIVEIRA, F.A.; HESSE, G. & FELDMEIER, H. - Tungiasis: a neglected health problem of poor communities. **Trop. Med. int. Hlth**, **6:** 267-272, 2001.

45. HEUKELBACH, J.; EISELE, M.; JACKSON, A. & FELDMEIER, H. - Topical treatment of tungiasis: a randomized, controlled trial. **Ann. trop. Med. Parasit.**, **97:** 743-749, 2003b.

46. HEUKELBACH, J.; FRANCK, S. & FELDMEIER, H. - Therapy of tungiasis: a double-blinded randomized controlled trial with oral ivermectin. **Mem. Inst. Oswaldo Cruz**, **99:** 873-876, 2004c.

47. HEUKELBACH, J.; MENCKE, N. & FELDMEIER, H. - Cutaneous larva migrans and tungiasis: the challenge to control zoonotic ectoparasitoses associated with poverty. **Trop. Med. int. Hlth**, **7:** 907-910, 2002a.

48. HEUKELBACH, J.; SAHEBALI, S.; VAN MARCK, E. *et al.* - Pseudoepitheliomatous hyperplasia in ectopic tungiasis: an unusual case. **Braz. J. infect. Dis.**, **8:** 465-468, 2004d.

49. HEUKELBACH, J.; VAN HAEFF, E.; RUMP, B. *et al.* - Parasitic skin diseases: health care-seeking in a slum in north-east Brazil. **Trop. Med. int. Hlth**, **8:** 368-373, 2003c.

50. HEUKELBACH, J.; WILCKE, T.; HARMS, G. & FELDMEIER, H. - Seasonal variation of tungiasis in an endemic community. **Amer. J. trop. Med. Hyg.**, **72:** 145-149, 2005.

51. HEUKELBACH, J.; WILCKE, T.; EISELE, M. & FELDMEIER, H. - Ectopic localization of tungiasis. **Amer. J. trop. Med. Hyg.**, **67:** 214-216, 2002b.

52. HOEPPLI, R. - Early references to the occurrence of *Tunga penetrans* in Tropical Africa. **Acta trop. (Basel)**, **20:** 143-152, 1963.

53. JANSELME, E. - Note sur l'existence de la chique dans l'Afrique occidentale au XVIII siècle. **France méd.**, **55:** 424-425, 1908.

54. JEFFREYS, M.D.W. - *Pulex penetrans*: the jigger's arrival and spread in Africa. **S. Afr. J. Sci.**, **48:** 249-255, 1952.

55. JOLLY, G.G. - An entomological episode of the East African Campaign. **Indian med. Gaz.**, **61:** 164-165, 1926.

56. KARSTEN, H. - Beitrag zur Kenntnis des *Rhynchoprion penetrans*. **Virchows Arch. path. Anat.**, **32:** 269-292, 1865.

57. KONCZAKI, J. - The Emin Pasha Relief Expedition (1887-1889): some comments on disease and hygiene. **Canad. J. Afr. Studies**, **19:** 615-625, 1985.

58. LITVOC, J.; LEITE, R.M. & KATZ, G. - Aspectos epidemiológicos do tétano no estado de São Paulo (Brasil). **Rev. Inst. Med. trop. S. Paulo**, **33:** 477-484, 1991.

59. MACIAS, P.C. & SASHIDA, P.M. - Cutaneous infestation by *Tunga penetrans*. **Int. J. Derm.**, **39:** 296-298, 2000.

60. MATIAS, R.S. - Verificação da eficácia de diferentes inseticidas no controle ambiental de *Tunga penetrans*. **Rev. Soc. bras. Med. trop.**, **24:** 31-36, 1991.

61. MUEHLEN, M.; FELDMEIER, H.; WILCKE, T.; WINTER, B. & HEUKELBACH, J. - Identifying risk factors for tungiasis and heavy infestation in a resource-poor community in Northeast Brazil. **Trans. roy. Soc. trop. Med. Hyg.**, 2005. (in press).

62. MUEHLEN, M.; HEUKELBACH, J.; WILCKE, T. *et al.* - Investigations on the biology, epidemiology, pathology and control of *Tunga penetrans* in Brazil. II. Prevalence, parasite load and topographic distribution of lesions in the population of a traditional fishing village. **Parasit. Res.**, **90:** 449-455, 2003.

63. NTE, A.R. & EKE, F.U. - Jigger infestation in children in a rural area of Rivers State of Nigeria. **W. Afr. J. Med.**, **14:** 56-58, 1995.

64. OBENGUI - La tungose et le tétanos au C.H.U. de Brazzaville. **Dakar Med.**, **34:** 44-48, 1989.

65. PAMPIGLIONE, S.; TRENTINI, M.; FIORAVANTI, M.L. & GUSTINELLI, A. - Differential diagnosis between *Tunga penetrans* (L., 1758) and *T. trimamillata* Pampiglione et al., 2002 (Insecta, Siphonaptera), the two species of the genus *Tunga* parasitic in man. **Parasite**, **11:** 51-57, 2004.

66. POPPITI Jr., R.; KAMBOUR, M.; ROBINSON, M.J. & RYWLIN, A.M. - *Tunga penetrans* in South Florida. **Sth. med. J. (Bgham, Ala.)**, **76:** 1558-1560, 1983.

67. REISS, F. - Tungiasis in New York City. **Arch. Derm.**, **93:** 404-407, 1966.

68. RIETSCHEL, W. - Beobachtungen zum Sandfloh (*Tunga penetrans*) bei Mensch und Hund in Französisch-Guayana. **Tierärztl. Praxis**, **17:** 189-193, 1989.

69. SANE, S.Y. & SATOSKAR, R.R. - Tungiasis in Maharashtra (a case report). **J. postgrad. Med.**, **31:** 121-122, 1985.

70. SANUSI, I.D.; BROWN, E.B.; SHEPARD, T.G. & GRAFTON, W.D. - Tungiasis: report of one case and review of the 14 reported cases in the United States. **J. Amer. Acad. Derm.**, **20:** 941-944, 1989.

71. SARACENO, E.F.; BAZARRA, M.L.G.; CALVIELLO, R.C. *et al.* - Tungiasis: tratamiento de un caso con ivermectina. **Arch. argent. Derm.**, **49:** 91-95, 1999.

72. SCHWALFENBERG, S.; WITT, L.H.; KEHR, J.D. *et al.* - Prevention of tungiasis using a biological repellent: a small case series. **Ann. trop. Med. Parasit.**, **98:** 89-94, 2004.

73. SILVADO, J. - O bicho de pé. **Brasil méd.**, **25:** 84, 95-96, 97, 1908.

74. SMITH, M.D. & PROCOP, G.W. - Typical histologic features of *Tunga penetrans* in skin biopsies. **Arch. Path. Lab. Med.**, **126:** 714-716, 2002.

75. SORIA, M.F. & CAPRI, J.J. - Tetanos y "piques". **Prensa med. argent.**, **40:** 4-11, 1953.

76. STADEN VON HOMBERG ZU HESSEN, H. - **Wahrhaftige Historia und Beschreibung einer Landschaft der wilden, nacketen, grimmigen Menschenfresser Leuten, in der Neuen Welt America gelegen.** Frankfurt am Main, Weigand Hahn, 1556.

77. TONGE, B.L. - Tetanus from chigger flea sores. **J. trop. Pediat.**, **35:** 94, 1989.

78. TOSTI, A. - La Tunga ed i cannibali Tupinamba. **G. ital. Derm. Venereol.**, **135:** 653-654, 2000.

79. TRENTINI, M.; PAMPIGLIONE, S.; GIANNETTO, S. & FINOCCHIARO, B. - Observations about specimens of *Tunga* sp. (Siphonaptera, Tungidae) extracted from goats of Ecuador. **Parassitologia**, **42:** 65, 2000.

80. TURKHUD, D.A. - A case of sweating blood. **Indian med. Gaz.**, **63:** 51, 1928.

81. VALENÇA, Z.O.; CARDOSO, A.E.C. & CARDOSO, A.S. - Tunguiase generalizada: relato de dois casos tratados com thiabendazol. **Derm. ibero lat.-amer.**, **3:** 375-378, 1972.

82. VAZ, Z. & ROCHA, U.F. - *Tunga penetrans* (L., 1758), "bicho de pé" em gado bovino. **Livro de homenagem a R.F. Almeida**, **40:** 327-332, 1946.

83. VERALDI, S.; CAMOZZI, S. & SCARABELLI, G. - Tungiasis presenting with sterile pustular lesions on the hand. **Acta derm.-venereol. (Stockh.)**, **76:** 495, 1996.

84. VERALDI, S.; CARRERA, C. & SCHIANCHI, R. - Tungiasis has reached Europe. **Dermatology**, **201:** 382, 2000.

85. VERHULST, A. - *Tunga penetrans* (*Sarcopsylla penetrans*) as a cause of agalactia in sows in the Republic of Zaire. **Vet. Rec.**, **98:** 384, 1976.

86. WARDHAUGH, A.D. & NORRIS, J.F. - A case of imported tungiasis in Scotland initially mimicking verrucae vulgaris. **Scot. med. J.**, **39:** 146-147, 1994.

87. WATERTON, C. - **Wanderings in South America the North-West of the United States and the Antilles, in the years 1812, 1816, 1820 and 1824 with original instruction for the perfect preservation of birds and for cabinets of natural history.** Oxford, University Press, 1973. p. 108-109.

88. WILCKE, T.; HEUKELBACH, J.; CESAR SABOIA, M.R. *et al.* - High prevalence of tungiasis in a poor neighbourhood in Fortaleza, Northeast Brazil. **Acta trop.**, **83:** 255-258, 2002.

89. WITT, L.H.; LINARDI, P.M.; MECKES, O. *et al.* - Blood-feeding of *Tunga penetrans* males. **Med. vet. Entomol.**, **18:** 439-441, 2004.

90. WOLFFHÜGEL, K. - Die Flöhe (Siphonaptera) der Haustiere. **Z. Infektionskrankheiten der Haustiere**, **8:** 354-382, 1910.