This manual is intended to guide healthcare workers in the clinical diagnosis and management of Buruli ulcer, one of the seventeen neglected tropical diseases. The disease is caused by *Mycobacterium ulcerans*, which belongs to the same family of organisms that cause tuberculosis and leprosy.

Since 2004, antibiotic treatment has greatly improved the management of Buruli ulcer and is presently the first-line therapy for all forms of the disease. Guidance for complementary treatments such as surgery, wound care, and prevention of disability are also included. Numerous coloured photographs and tables are used to enhance the manual's value as a training and reference tool.

Implementation of this guidance will require considerable clinical judgement and close monitoring of patients to ensure the best possible treatment outcome. Early detection and early antibiotic treatment are essential for obtaining the best results and minimizing the disabilities associated with Buruli ulcer.

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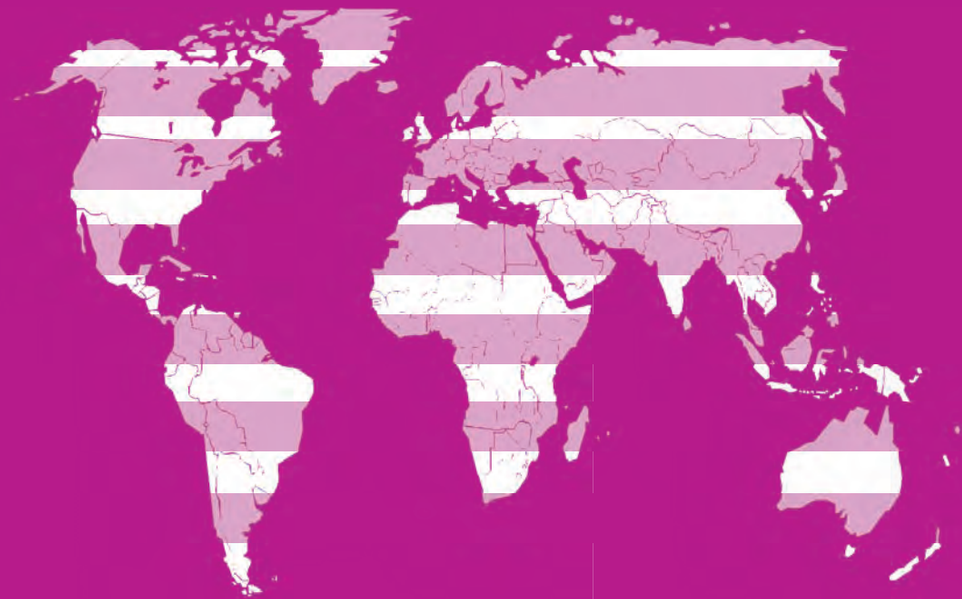
TREATMENT OF *MYCOBACTERIUM ULCERANS* DISEASE (BURULI ULCER)

TREATMENT OF *MYCOBACTERIUM ULCERANS* DISEASE (BURULI ULCER)

GUIDANCE FOR HEALTH WORKERS



World Health Organization

TREATMENT OF *MYCOBACTERIUM ULCERANS* DISEASE (BURULI ULCER)

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WHO Library Cataloguing-in-Publication Data

Treatment of *Mycobacterium ulcerans* disease (Buruli ulcer): guidance for health workers.

1.Buruli ulcer – drug therapy. 2.Buruli ulcer – surgery. 3.Anti-bacterial agents - therapeutic use. 4.*Mycobacterium ulcerans* – drug effects. I.World Health Organization.

ISBN 978 92 4 150340 2 (NLM classification: WC 302)

Printed in Italy

WHO/HTM/NTD/IDM/2012.1

Design & Layout: Patrick Tissot, WHO/HTM/NTD

CONTENTS

ACKNOWLEDGEMENTS

We thank the following for reviewing and making constructive comments on this document:

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Professor Jacques Grosset, Center for Tuberculosis Research, Johns Hopkins University School of Medicine, Baltimore, Maryland, United States of America

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Professor Tjip van der Werf, Physician Specialist, Department of Internal Medicine, Groningen University Medical Centre, Groningen, The Netherlands

The World Health Organization would also like to thank all those who provided photos.

This document was produced with the support of Anesvad, Spain (http://www.anesvad.org).

PREFACE

This document is intended to guide health workers in areas where ***Mycobacterium ulcerans*** disease (Buruli ulcer) occurs, and also those in nonendemic areas, in providing optimal management on the basis of up-to-date knowledge and experience about specific antibiotics and complementary modes of treatment.

Antibiotics are established as first-line therapy for Buruli ulcer; the combination of rifampicin and streptomycin given for 8 weeks is effective in healing small lesions without surgery. The optimal combination of antibiotics and their mode of delivery are still being explored, however, and the role of surgery is evolving as it becomes more readily available and accessible in endemic countries.

The current WHO recommendations for treatment are:

- a combination of specific antibiotics for 8 weeks as first-line treatment for all forms of active disease;
- wound care;
- prevention of disability; and
- surgery to remove necrotic tissue, cover large skin defects and correct deformities.

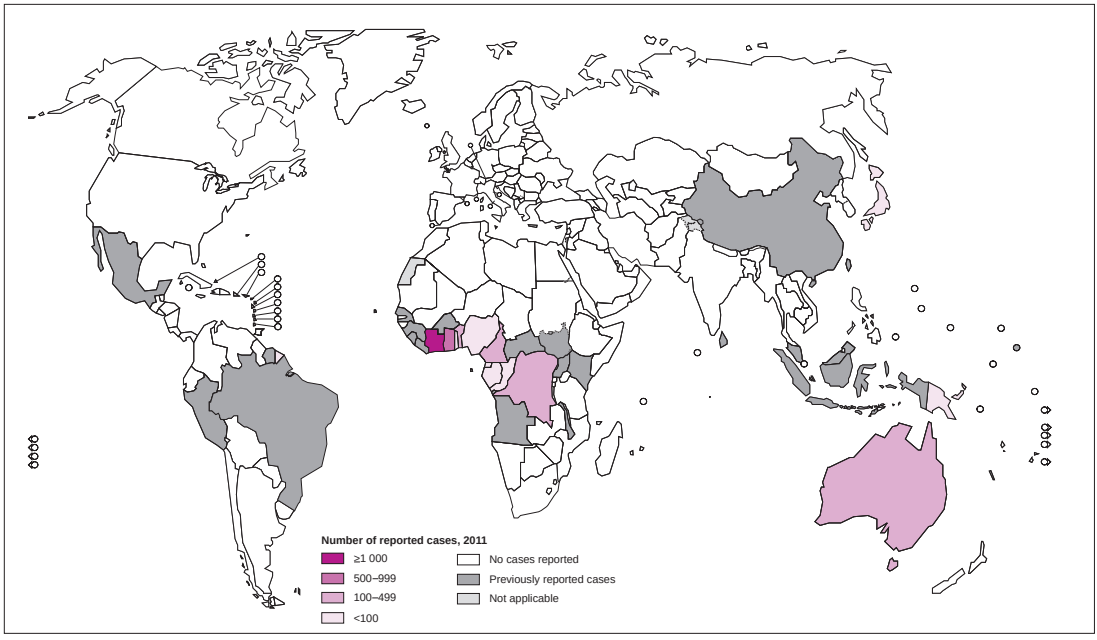
This document, which covers both antibiotics and other treatments, is based on information from field implementation of the first guidance on the role of antibiotics issued by WHO in 2004 (*1*), studies on antibiotic treatment, extensive clinical experience and expert opinion. The guidance is intended to help health workers in affected areas to better manage patients with Buruli ulcer. It will also help those in nonendemic countries or districts confronted with patients who have acquired the infection after travel to endemic areas. Implementation of this guidance will require considerable clinical judgement and close monitoring of patients to ensure the best possible treatment outcome. Early detection and early antibiotic treatment are essential for obtaining the best results and minimizing the disabilities associated with Buruli ulcer.

1. INTRODUCTION

Buruli ulcer, caused by ***Mycobacterium ulcerans***, is largely a problem of the poor in remote rural areas and is an important cause of human suffering. It is the third commonest mycobacterial disease, after tuberculosis and leprosy. WHO began to address this previously neglected disease in 1998 (*2*). In May 2004, the Fifty-seventh World Health Assembly adopted a resolution on Buruli ulcer, which called for intensified research on tools to diagnose, treat and prevent the disease (*3*). Buruli ulcer is one of the group of infectious diseases classified as neglected tropical diseases (*4*).

MacCallum et al. were the first to describe ***M. ulcerans***, in Australia in 1948 (*5*). 'Buruli ulcer' is named after Buruli county (now called Nakasongola) in Uganda, where large numbers of cases were described in the 1960s (*6*). The condition has been reported or suspected in more than 33 countries (*4*), mainly in tropical and subtropical regions, and the number of reported cases is growing. Africa appears to be the worst affected region (*7*), while other important foci are found in Australia (*8,9*), French Guiana (*10*), Peru (11) and Papua New Guinea (12,13). Recently, cases have been reported in Japan (*14–16*). The distribution of Buruli ulcer in 2011 is shown in ***Figure 1***.

FIGURE 1: THE DISTRIBUTION OF BURULI ULCER, WORLDWIDE, 2011



Nearly 50% of the people affected are children under the age of 15 years who live in remote rural areas and have little or no access to health services (*7*). Most patients in endemic areas of Africa present late, with extensive lesions that can cause severe disability (*17*). Health education and early case-finding are resulting in less severe cases than were seen a decade ago (*18*). Although mortality from Buruli ulcer is low, it was estimated in one study that 66% of people with healed lesions had some degree of disability (*19*), and the median age of this group was 12 years.

Until the introduction of antibiotic therapy in 2004, surgery to remove all infected tissue, including a margin of healthy tissue, was regarded as the most effective treatment. Extensive excision followed by skin grafting can involve multiple operations and an average hospitalization of about 3 months (*17*). Rural areas in endemic countries often lack adequate surgical capacity, and prolonged hospitalization stretches the limited bed capacity of health centres, further reducing the number of patients who can be admitted for treatment. In addition, the cost of surgical treatment is far beyond the means of those most severely affected (*17,20*).

The recurrence rates after surgical treatment without antibiotics vary from 16% to 28% (*21,22*); recurrences further inflate treatment costs and undermine patients' confidence in conventional surgical treatment. Since the introduction of antibiotic treatment, recurrence rates of 0–2% have been reported and the requirement for surgical intervention has diminished (*23,24*). Small Buruli lesions can now be cured by antibiotics alone, but research on the optimal use of antibiotics and surgery for all forms of the disease remains a high priority for WHO. The importance of early recognition and treatment has been stressed, and adherence to treatment for the full 8 weeks is essential. Overall, the aims must be to provide effective antibiotic therapy in a village setting with adequate supervision, as well as high-quality wound care and early instigation of simple measures to prevent long-term disability.

EVIDENCE FOR THE EFFICACY OF SPECIFIC ANTIBIOTICS

In 2004, WHO published ***Provisional guidance on the role of specific antibiotics in the management of*** Mycobacterium ulcerans ***disease (Buruli ulcer)*** (*1*), when sufficient evidence had accumulated to suggest that the combination of rifampicin and streptomycin administered for 8 weeks was effective for most patients with Buruli ulcer. This guidance was based on the findings of a study of patients with small early lesions, which showed that, whereas mycobacteria were cultured from excised lesions 2 weeks after the start of antibiotic treatment, cultures were entirely negative at 4, 8 and 12 weeks (*25*). Two observational studies, in Benin (*23*) and Ghana (*24*), subsequently demonstrated that, when outpatients were treated under direct observation as recommended, most lesions healed without requiring surgery, and the recurrence rate was remarkably lower, at less than 3% (*23,24*), than the rates of 16–28% seen previously (*21,22*). Histopathological analyses of tissue samples taken after antibiotic treatment further confirmed the efficacy of the recommended antibiotic treatment (*26*). Oedematous lesions, the most aggressive form of the disease, have also been shown to respond to antibiotic treatment.

Although side-effects of rifampicin and streptomycin have been seen infrequently in studies in Africa, a continuing aim is to design an antibiotic regimen in which no injection is required. The recommended treatment with rifampicin and streptomycin for 8 weeks was compared with the same combination for 4 weeks followed by orally administered rifampicin and clarithromycin for 4 weeks in a prospective randomized study in two hospitals in Ghana; the study showed that the efficacy of the two regimens was comparable (*27*). A small observational study in Ghana showed no difference in outcome when rifampicin and streptomycin were given for only 2 weeks followed by rifampicin and clarithromycin for 6 weeks (*28*). Although a fully oral regimen has not yet been assessed in a clinical trial, observational

studies in Africa (*29*), Australia (*30,31*) and French Guiana (*32*) indicate that all oral regimens are clinically and microbiologically effective. A formal randomized controlled study of rifampicin and streptomycin versus rifampicin and clarithromycin is in progress to establish definitively whether efficacy is preserved when no streptomycin is used (*33*).

In summary, there is now overwhelming evidence that 8 weeks of streptomycin–rifampicin or 4 weeks of rifampicin–streptomycin followed by 4 weeks of rifampicin–clarithromycin or 8 weeks of other oral regimens all achieve recurrence-free healing with an acceptable level of side-effects. This is true for ulcers of all sizes, even without additional surgery to remove necrosis or skin grafting to accelerate healing. Additional information may be obtained from the WHO Fact Sheet published in 2012.[1]

[1] World Health Organization, Fact Sheet 2012: http://www.who.int/mediacentre/factsheets/fs199/en/index.html

2. ANTIBIOTIC TREATMENT

For any patient with strongly suspected Buruli ulcer, specimens should be sent for laboratory confirmation, and the patient should be treated with the recommended combination of rifampicin and streptomycin or rifampicin plus another oral therapy under direct observation for 8 weeks (***Table 1*** and see ***Section 8***). The two antibiotics should always be given in combination to prevent selection of drug-resistant mutants.

Antibiotic treatment of Buruli ulcer is evolving. In addition to the experience with rifampicin and streptomycin, there is growing evidence of the efficacy of some rifampicin-based oral therapies. The purpose of this section is to describe the limited range of antibiotics that can be used in the treatment of Buruli ulcer, awaiting confirmation of the efficacy of full oral antibiotics in ongoing studies.

STANDARD ANTIBIOTIC TREATMENT

Rifampicin at 10 mg/kg body weight by mouth daily for 8 weeks and streptomycin at 15 mg/kg body weight by intramuscular injection daily for 8 weeks (contraindicated in pregnancy)

Antibiotic treatment for pregnant women

A pregnant patient in Benin was successfully treated with a combination of rifampicin and clarithromycin (34). There were subsequently other reports of successful treatment with this combination. The recommendation, based on expert opinion, is therefore: rifampicin at 10 mg/kg body weight by mouth daily for 8 weeks and clarithromycin at 7.5 mg/kg body weight by mouth twice daily for 8 weeks. The extended-release formulation of clarithromycin may be used at 15 mg/kg body weight once daily, although it has yet to be tested.

Antibiotic treatment used in Australia (9,30,31) and French Guiana (32)

The recommended treatment, based on vast clinical practice, is: rifampicin at 10 mg/kg body weight by mouth daily for 8 weeks and clarithromycin at 7.5 mg/kg body weight by mouth twice daily for 8 weeks, or rifampicin at 10 mg/kg body weight by mouth once daily for 8 weeks and moxifloxacin at 400 mg by mouth once daily for 8 weeks (for adults only) (35).

MONITORING AND MANAGING ADVERSE EFFECTS

Most Buruli ulcer patients complete treatment with no significant adverse effects; however, a few patients do experience such effects, and it is therefore important that patients be monitored clinically during treatment so that any adverse effects can be promptly detected and properly managed (***Table 2***). Routine laboratory monitoring may not be necessary, but, when it is clinically indicated, patients should be monitored regularly for adverse effects on the body as a whole (e.g. by hearing, renal and liver function tests).

Health workers can teach patients and their relatives how to recognize the symptoms of common side-effects and encourage them to report any such symptoms.

Adverse reactions to drugs should be recorded on the back of the BU 01 (***Annex 3***) form or in the patient folder.

In general, a patient who develops mild adverse effects should continue treatment, and the symptoms should be treated. Moderate adverse effects may require temporary discontinuation of treatment or adjustment of the dosage and management of symptoms. In cases of severe side-effects, the treatment or the drug should be stopped and the patient urgently referred to hospital for further assessment and treatment.

TABLE 1. DOSAGE OF RIFAMPICIN, STREPTOMYCIN AND CLARITHROMYCIN ACCORDING TO PATIENT BODY WEIGHT

Body weight of patient (kg)	Streptomycin injection (1 g) once daily	Rifampicin (300 mg/tablet)* once daily		Clarithromycin** twice daily (instant release)	
	Dose (g)	Dose (mg)	No. of tablets	Daily dose (mg)	
5–10	0.25	75	0.25	125	5 ml
11–20	0.50	150	0.50	250	10 ml
21–39	0.50	300	1.00	500	1 tablet
40–54	0.75	450	1.50	750	1.5 tablets
> 54	1.00 (maximum)	600 (maximum)	2.00	1000 (maximum)	2 tablets

* Rifampicin syrup may be used
** Extended release formulation of clarithromycin may be used, at 15 mg/kg once daily

TABLE 2. SYMPTOM-BASED APPROACH TO IDENTIFYING AND MANAGING THE SIDE-EFFECTS OF ANTIBIOTICS TREATMENT[a]

Common side-effects	Drug probably responsible	Management
Skin rash with or without itching	Streptomycin Rifampicin	Stop treatment
Deafness (no wax on othoscopy)	Streptomycin	Stop streptomycin
Dizziness (vertigo, ataxia and nystagmus)	Streptomycin	Stop streptomycin
Decreased urine output	Streptomycin	Stop streptomycin
Jaundice (other causes excluded), hepatitis	Rifampicin	Stop rifampicin
Shock, purpura, acute renal failure[a]	Rifampicin	Stop rifampicin
Anorexia, nausea, abdominal pains	Rifampicin	Continue treatment, give drugs with small meals or at night before retiring
Nausea, altered taste	Clarithromycin	Continue treatment
Jaundice (other causes excluded), hepatitis	Clarithromycin	Stop clarithromycin
Tendonitis	Moxifloxacin	Stop moxifloxacin
Nausea, anorexia	Moxifloxacin	Continue treatment
Rash	Moxifloxacin	Stop treatment

From reference (35). The results of studies suggest that side-effects are rare; however, close monitoring of patients and strict observation of this guidance are necessary.

[a] These side-effects occur principally when rifampicin intake is intermittent and the dose exceeds 10 mg/kg.

3. COMPLEMENTARY TREATMENTS

PRESENT ROLE OF SURGERY

All forms of Buruli ulcer—papules, nodules, plaques, oedema and ulcers—however extensive, respond well to antibiotic treatment, although large lesions may be slow to heal and require surgery (debridement, skin grafting and scar revision).

Paradoxical reactions may occur in some cases during or after antibiotic treatment, usually 2–12 weeks after the start of antibiotics, although some may appear much later (> 1 year) after the end of treatment (*37*). Lesions may seem to worsen after initial improvement, new lesions may appear, sometimes on a different part of the body, and non-ulcerative forms, such as nodules (or swelling), plaque and oedema, may ulcerate. This is an immunological response, which usually resolves without treatment other than completion of the standard 8-week course of antibiotics, wound dressing, correct positioning and early movement of the affected part.

Ulcers, whether present initially or occurring during treatment of non-ulcerative lesions, should be managed with regular dressings, good positioning and movement to maintain joint movement until healing is complete. Debridement and skin grafting may be necessary to hasten healing of extensive ulcers.

Wide surgical removal of infected tissue is no longer necessary to achieve microbiological cure: antibiotics have been shown to be fully effective in this respect; however, conservative surgery, in particular debridement and skin grafting, may be needed in some cases to aid healing and to minimize scarring that might limit movement.

In all instances of joint involvement or limitation of movement, appropriate positioning with frequent exercise of the affected joints is essential, and, when possible, the affected part should be used in activities of daily living. In order to prevent permanent impairment, movement should start at the time of diagnosis and might be continued long after antibiotic treatment has been completed. Exercise and movement should cease for 10–14 days after skin grafting to allow the graft to take. Specialized positioning, physiotherapy and other interventions are often needed for severe cases.

PRESENT PRACTICE IN BURULI ULCER MANAGEMENT IN AUSTRALIA

Surgical services and a wide choice of specific antibiotics are readily available in Australia, patients may maintain a strong input into their treatment and there is some variation of established practice between different clinicians, including those in different parts of the country. The following generally applies in the State of Victoria where most *M. ulcerans* disease infections occur. Treatment in other parts of Australia follows a similar pattern.

A common current practice in Victoria is to initially offer all patients a combination of oral antibiotics involving rifampicin plus either clarithromycin or a fluoroquinolone (moxifloxacin or ciprofloxacin). The choice of clarithromycin or a fluoroquinolone is based on factors such as age, co-morbidities, predicted drug tolerance, potential for drug interactions and pregnancy. If no deep structures are involved and they are tolerated, antibiotics are given for 8 weeks.

Surgery is offered if it is considered to be beneficial for wound healing (e.g., by debridement of extensive tissue necrosis) or to lessen scarring or deformity; if antibiotics were contraindicated, refused or not tolerated after less than 4 weeks of total treatment; or at the request of patients to hasten wound healing. Ideally, antibiotics are administered for at least 4 weeks before surgery. Surgical debridement is usually followed by primary or secondary wound closure, by direct suture, free skin graft or flap.

Wounds are monitored closely for paradoxical reactions and, ideally, biopsies of tissue which looks as though it could be infected are examined histopathologically to aid differentiation between paradoxical reactions and treatment failure (remembering that dead organisms may persist for varying times). Mild paradoxical reactions are simply observed but administration of a steroid is probably desirable when severe tissue destruction occurs, in order to protect the integrity of a healing wound or, particularly, a surgical repair. A short course of prednisolone is then given (0.5–1 mg/kg daily, weaned over 4–8 weeks).

GENERAL MANAGEMENT

With full compliance, the antibiotic regimen described above should achieve a high rate of bacteriological cure, making surgical removal of infected tissue no longer essential to get rid of all of the infecting organisms. This also applies when a paradoxical reaction (see above) causes temporary worsening of the clinical condition; full resolution may still be expected over a few weeks or months.

While antibiotics have revolutionized the treatment of Buruli ulcer, additional treatment and care, such as surgery (particularly skin grafting) and early basic management by nurses and physiotherapists to prevent disability (*38*), can minimize complications (especially contractures) and facilitate timely discharge from care and return to normal activities. Adequate pain relief should be provided before the dressings of large ulcers are changed. Secondary bacterial infection, if present, should be treated with appropriate antibiotics.

WOUND CARE, SURGERY AND SCAR MANAGEMENT

All wounds heal better if the following principles are followed (*39*):

- Manage systemic conditions appropriately.
- Protect the wound from trauma.
- Maintain a clean wound base and control infection.
- Maintain a moist wound environment.
- Control peri-wound lymphoedema and oedema.

Small ulcers usually heal without surgical intervention, but larger wounds usually require debridement and skin grafting to hasten healing and to achieve the best possible functional result. Scar tissue resulting from slow normal healing may cause adhesions to and between underlying structures, which limit movement and are painful. Thick or tight scars resist injuries poorly, may limit movement and detract from appearance and function. Their surface is usually dry, may crack or ulcerate and is easily damaged by the sun. Such scars are easily injured during work or play. Note that scars that split frequently or ulcerate may, over many years, develop into squamous-cell carcinomas (*40*).

Good scar management lessens complications. Management may involve moisturizing, massage, elevation, correct positioning of joints, and application of a pressure bandage for up to 1–2 years after natural healing or grafting. A skin graft provides healthy new skin that is stronger and more flexible and is thus better able to withstand minor trauma.

The best time to undertake debridement and skin grafting, when indicated, is yet to be determined. Grafting should be late enough to allow all the *M. ulcerans* organisms to be killed by antibiotics but early enough to promote rapid recovery and a return to normal activities.

Skin grafts should be applied to healthy vascular surfaces. A sound conservative approach is to allow 8 weeks of antibiotic treatment before surgical intervention.

PRESERVATION OF FUNCTION

Restriction of movement by scarring and adhesions is a serious complication, which causes long-term disability. Wounds or lesions at or near joints are highly likely to limit movement and function. Joint stiffness can result if:

- there is oedema or pain: Movement will be difficult and painful, increasing the risk for permanent restriction of movement and thus disability. Management of oedema and pain are therefore important.
- bandaging is incorrect. Tightness may restrict movement, interfere with blood flow and cause oedema. Good wound care permits movement with minimal restriction.
- the affected part is immobilized continuously for a long time: The soft tissues may shorten, limiting movement and thus causing contractures and joint stiffness. Immobilization should be discontinued for short periods for regular exercises and to allow use of the affected part in activities of daily living to preserve function. Regular exercise of the joints near a lesion during antibiotic treatment should continue after the wound has healed.
- there are extensive scars near or across joints: These restrict movement, causing soft tissue and joint contractures that can cause severe deformity. Maintaining full movement of the joints and good scar management prevent disability. In the most severe cases, with thick bands of scar across joints, surgical release and skin grafting are required, with splinting and physiotherapy.

The categories and aims of treatment, the level of the health-care system at which they are provided and the diagnosis required are shown in *Table 3*.

TABLE 3. CATEGORIES AND AIMS OF TREATMENT, LEVEL OF HEALTH-CARE SYSTEM AND DIAGNOSIS REQUIRED

Treatment category	Form of disease	Treatment	Primary aim	Secondary aim	Level of health-care system	Diagnosis
Category I:	Single small lesion (e.g. nodule, papule, plaque and ulcer < 5 cm in diameter)	Complete antibiotics If at or near a joint, maintain same movement as on unaffected side If surgery is needed in non-critical areas, consider this after 8 weeks of antibiotic treatment	Cure without surgery Cure without movement limitations	Reduce or prevent recurrence	Community, health centres and district hospitals	Strong clinical diagnosis (with or without laboratory confirmation)
Category II:	Non-ulcerative and ulcerative plaque and oedematous forms Single large ulcerative lesion 5–15 cm in diameter	Complete antibiotics, before surgery (if possible) If at or near a joint, maintain same movement as on unaffected side	Cure without surgery Reduce the extent of surgical debridement when needed Cure without movement limitations	Reduce or prevent recurrence	Health centres, district and tertiary hospitals	Strong clinical diagnosis (with or without laboratory confimation)
Category III:	Lesions in the head and neck region, particularly face Disseminated and mixed forms such as osteitis, osteomyelitis, joint involvement Multiple lesions and osteomyelitis Extensive lesion > 15 cm	Complete antibiotics, before surgery (if possible) If at or near a joint, maintain same movement as on unaffected side	Cure without surgery Cure without movement limitations	Reduce or prevent recurrence	District and tertiary hospitals	Strong clinical diagnosis (with or without laboratory confimation)

4. DIAGNOSIS

In an area of known endemicity, an experienced health worker can usually diagnose Buruli ulcer on clinical grounds. (See colour plates, pp 13–41) The following clinico-epidemiological features are important diagnistic tools and may vary (according to geographic area) from different countries and settings. Differences largely depend on the demographical characteristics of the population, level of endemicity and awareness about the disease, extent of active detection efforts and accessibility to treatment.

- Most patients live in and some have travelled to an area of known endemicity.
- Nearly half of patients are children under 15 years of age.

AGE DISTRIBUTION IN YEARS

	<15 years	Mean	Median	Range
Africa	48%	24	15	0.5-90
Australia	10%	50	62	1-96
Japan	19%	41	48	2-81

- About 85% of lesions are on the limbs. Lesions on the upper limbs and other parts of the body are more likely to be confirmed by laboratory methods than lesions on the lower limbs.

LOCATION OF LESIONS

	Upper limb	Lower limb	Other parts of the body
Africa	25%	63%	11%
Australia	31%	64%	5%
Japan	50%	38%	13%

- Differential diagnosis should be considered for lesions on the lower third of the leg, as other causes of ulceration (trauma) may be common. In older patients, venous, arterial and diabetic ulcers should be ruled out.
- Non-ulcerative lesions are almost painless or minimally painful, although ulcers may be painful in the presence of secondary bacterial infection and severe oedema.
- In the absence of secondary bacterial infections or other co-infections in ulcerative lesions, there are often no constitutional symptoms (such as fever).
- Enlarged lymph nodes are not a feature of Buruli ulcer.

DIFFERENTIAL DIAGNOSIS

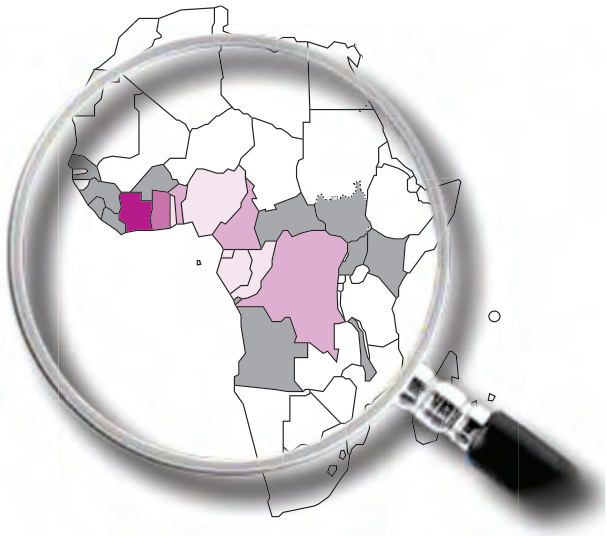
Buruli ulcer can usually be diagnosed on clinical grounds, but other causes of swelling and ulcers, particularly on the lower limb, must be borne in mind. Common differential diagnoses include tropical phagedenic ulcer, necrotizing fasciitis, venous ulcer (especially in the elderly), diabetic ulcer, sickle-cell disease-related ulcers, yaws, cutaneous tuberculosis, leprosy, cutaneous leishmaniasis and malignant ulcer.

Early nodular lesions are occasionally confused with boil, lipoma, ganglion, lymph node tuberculosis, onchocerciasis-related nodules or other subcutaneous infections, such as fungal infections. Papular lesions may initially be confused with an insect bite. Cellulitis may look like oedema caused by ***M. ulcerans*** infection, but the lesions are painful and the patient is febrile.

COLOUR PLATES:

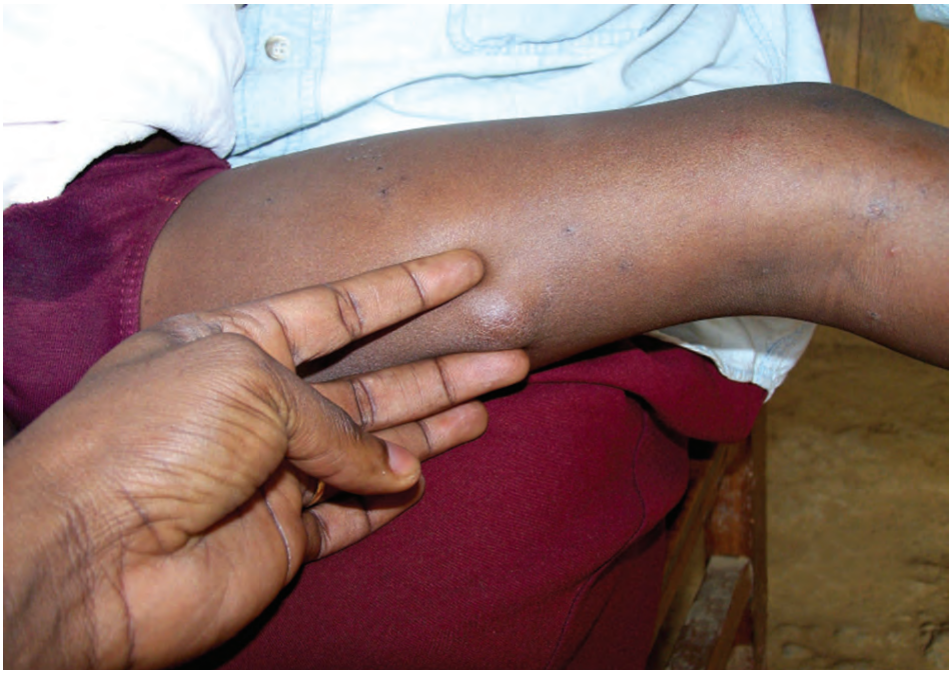
CLINICAL FORMS OF BURULI ULCER IN DIFFERENT ENDEMIC REGIONS

AFRICA



Nodules

Fig. 1



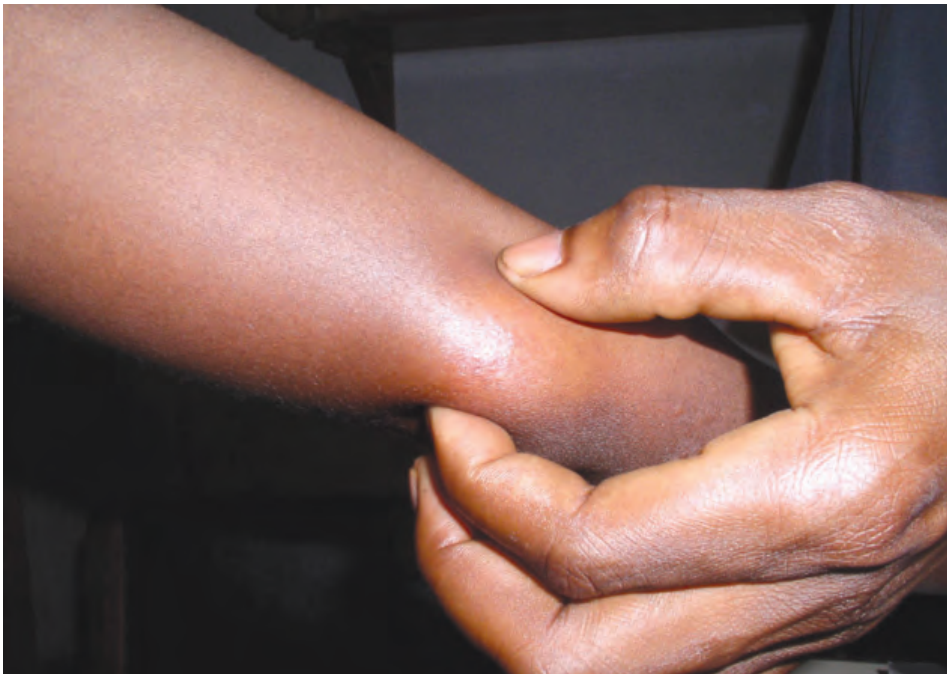
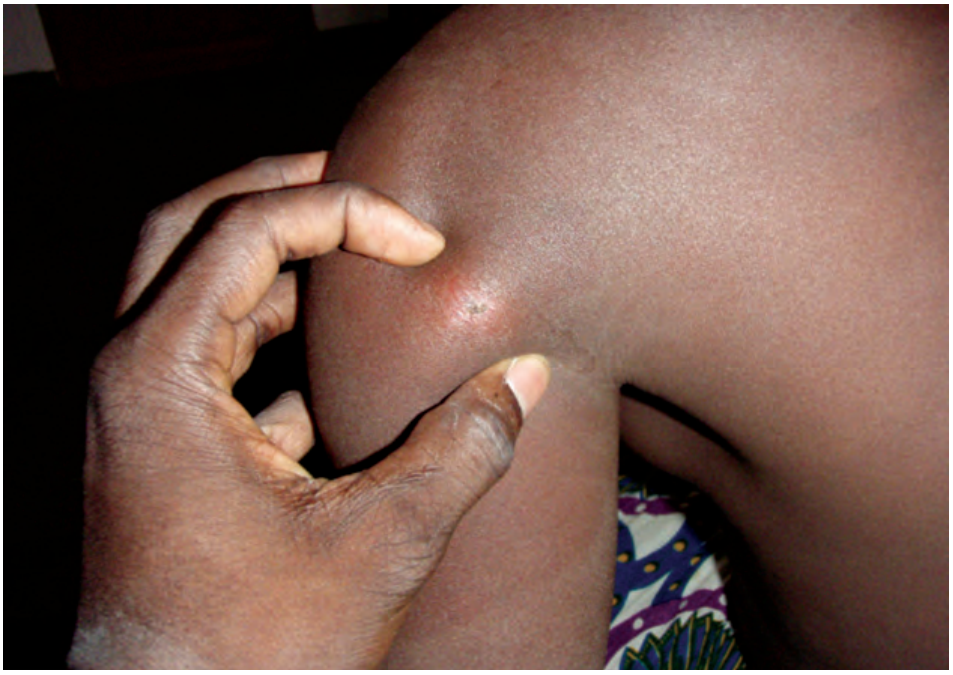


Fig. 2

Fig. 3



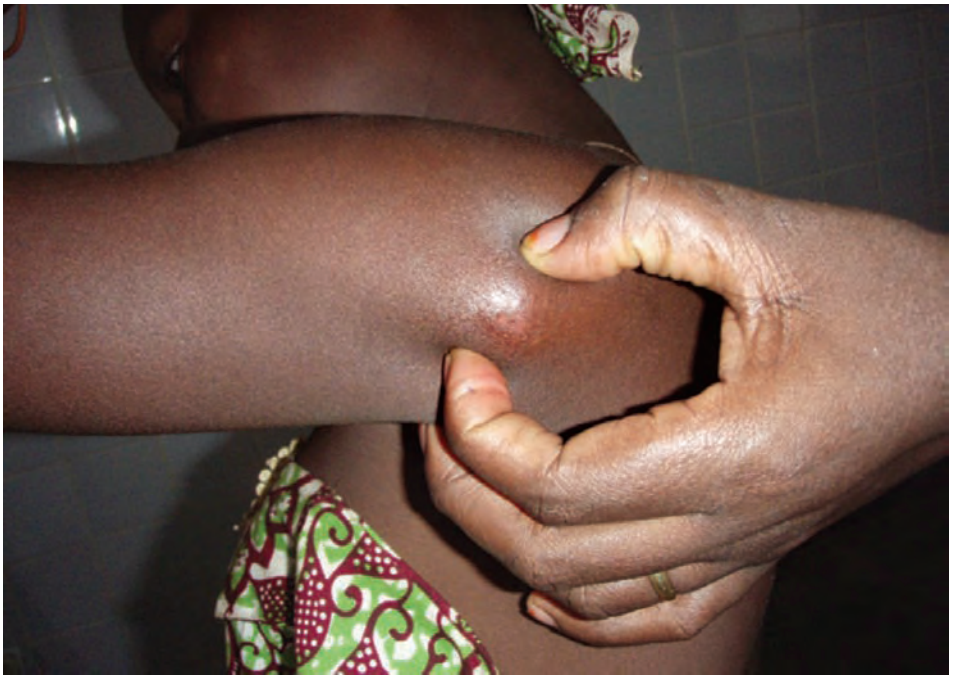
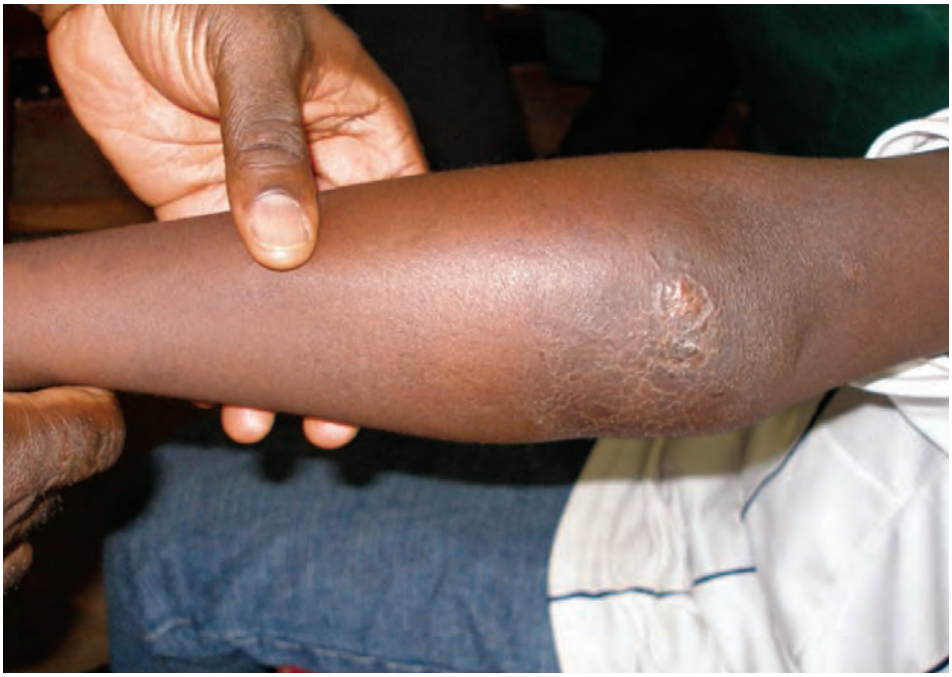


Fig. 4

Plaques

Fig. 5



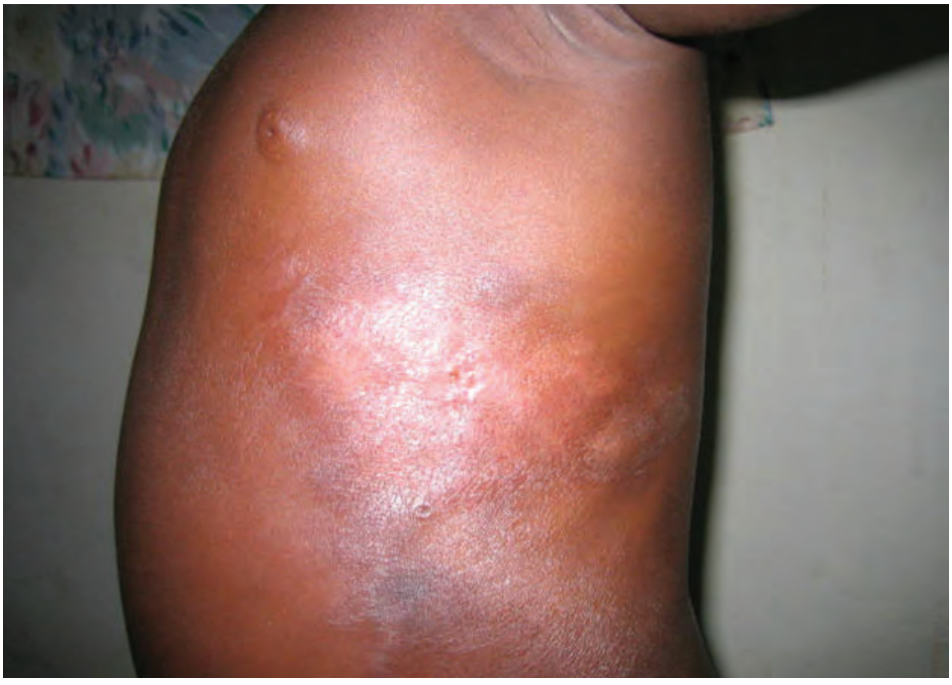
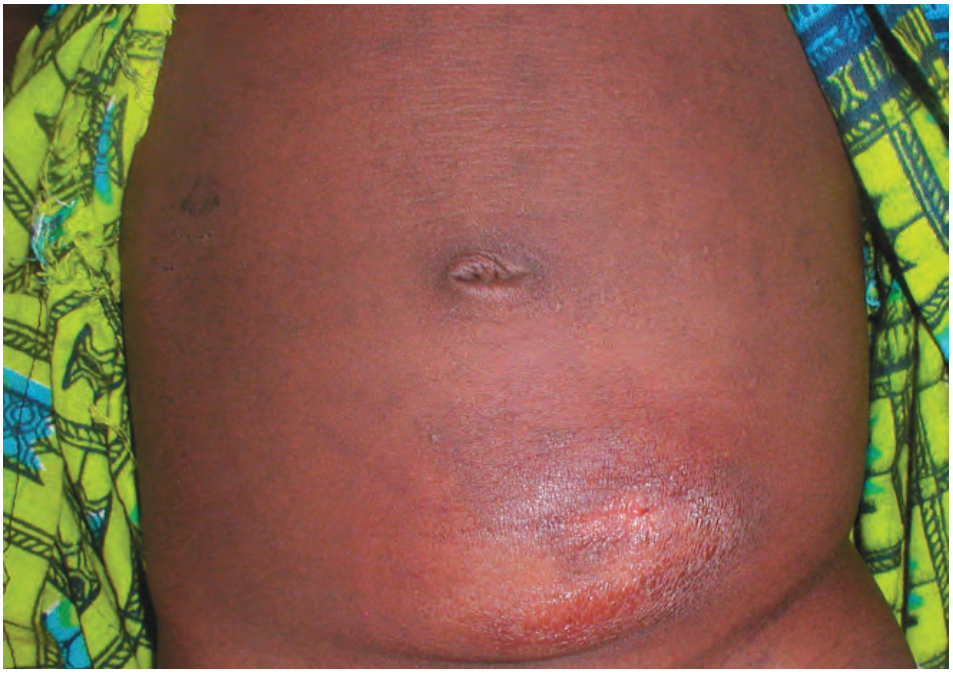


Fig. 6

FIG. 7



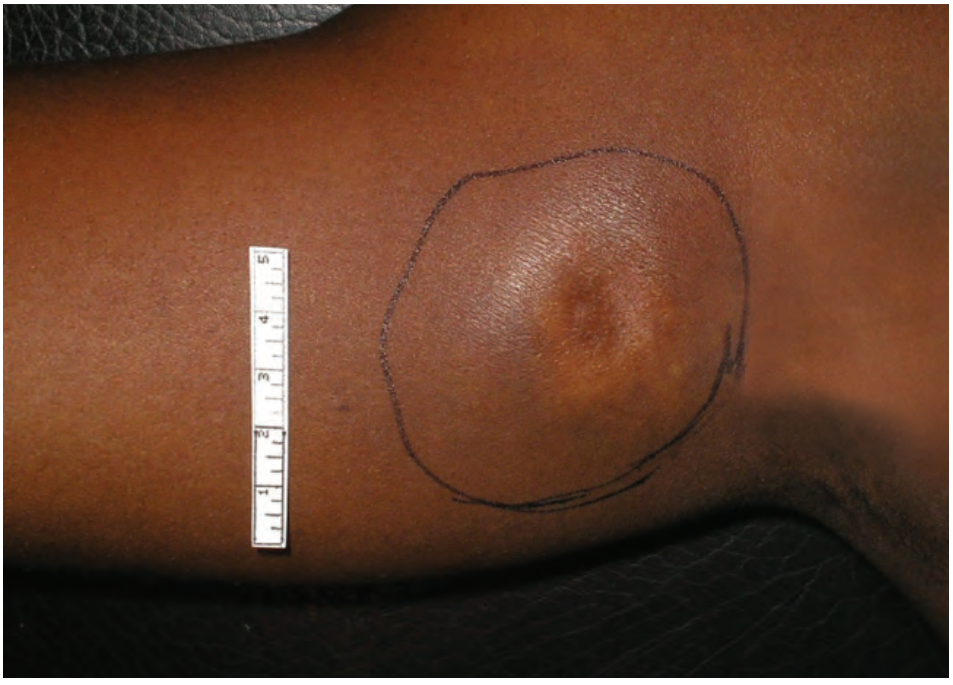
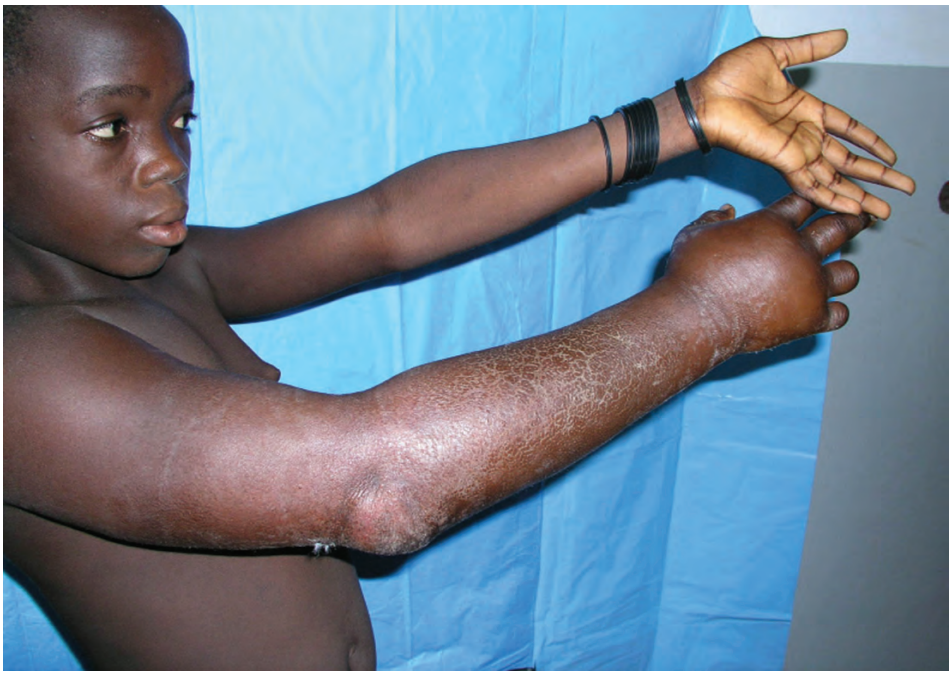


FIG. 8

Oedemas

Fig. 9



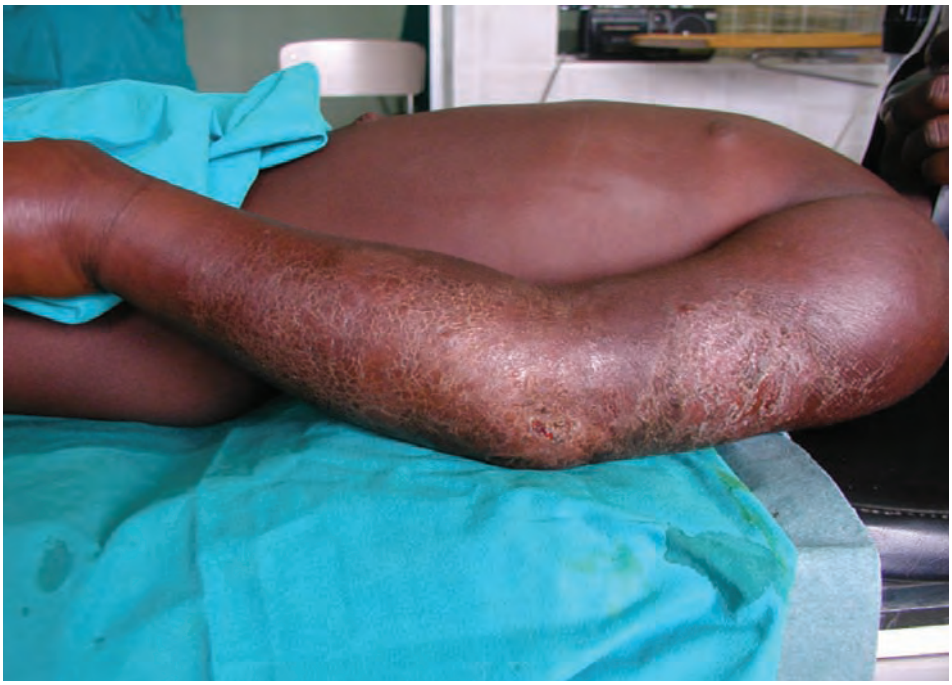
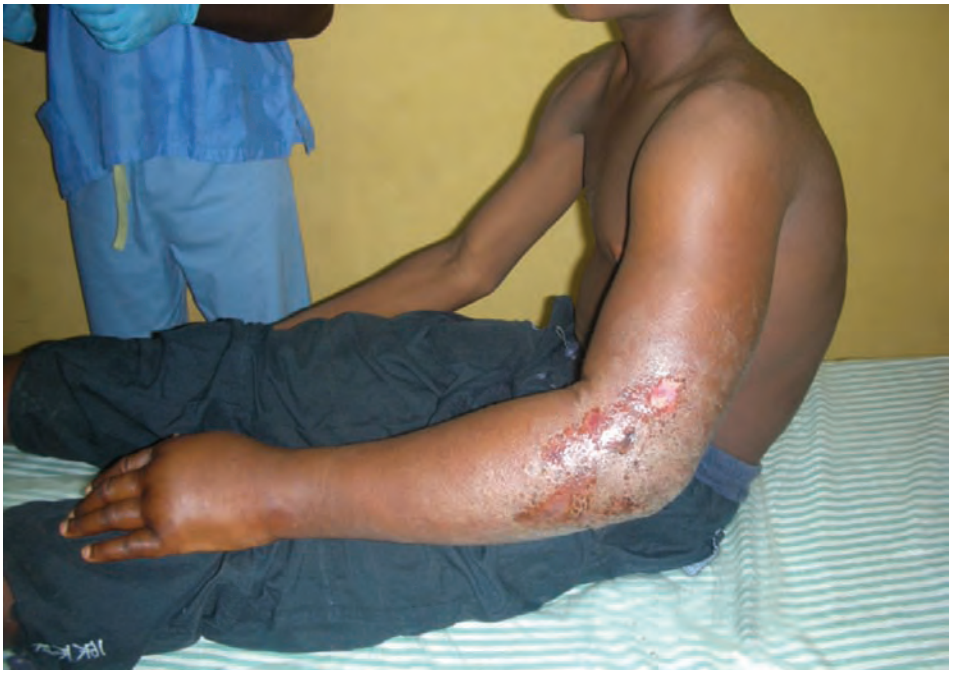


Fig. 10

Fig. 11



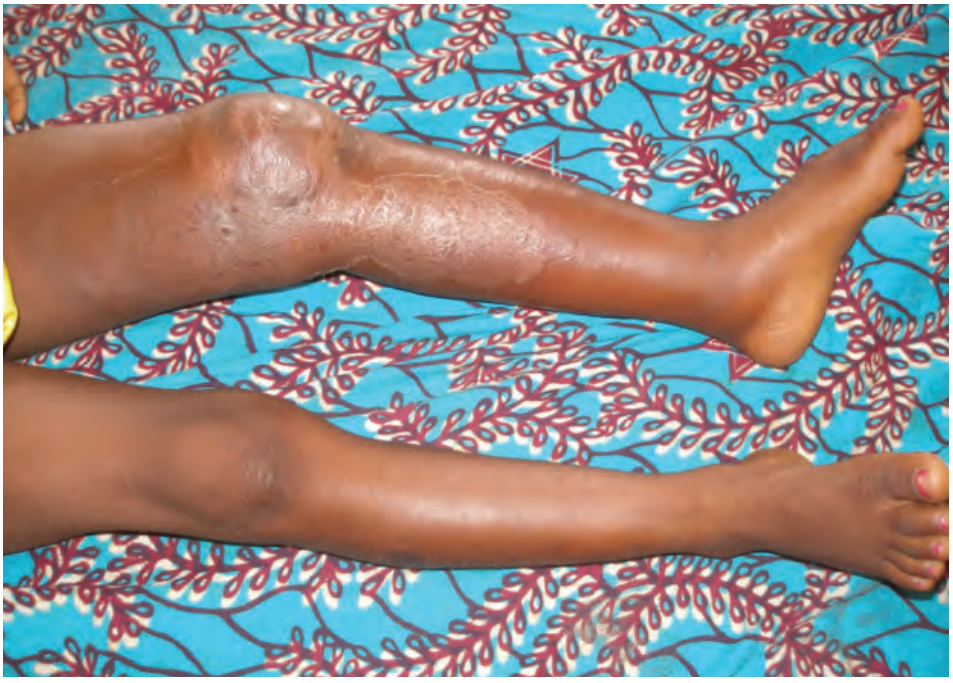
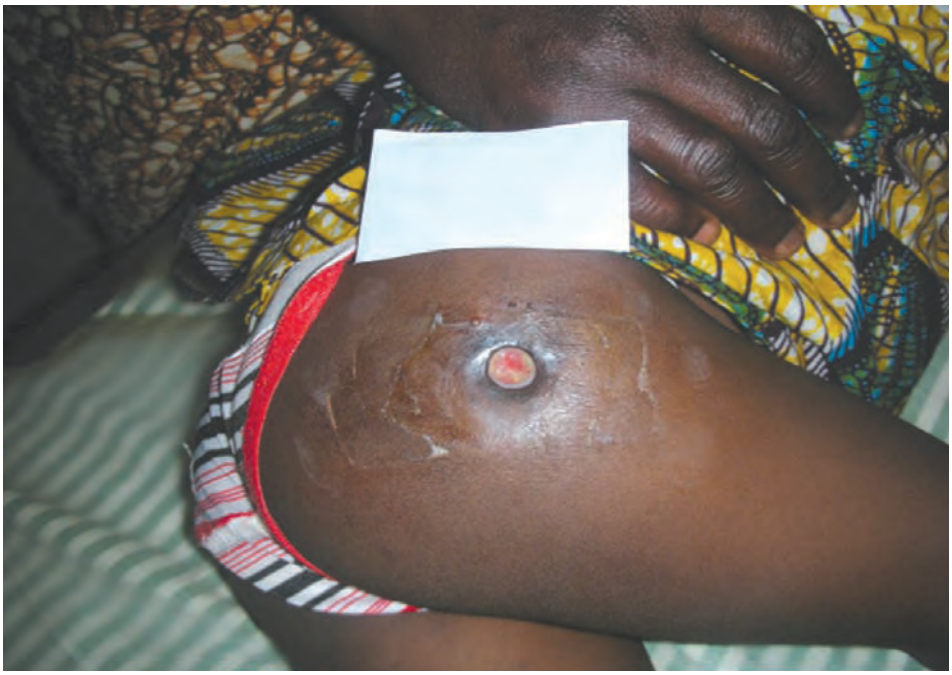


Fig. 12

Small ulcers

Fig. 13



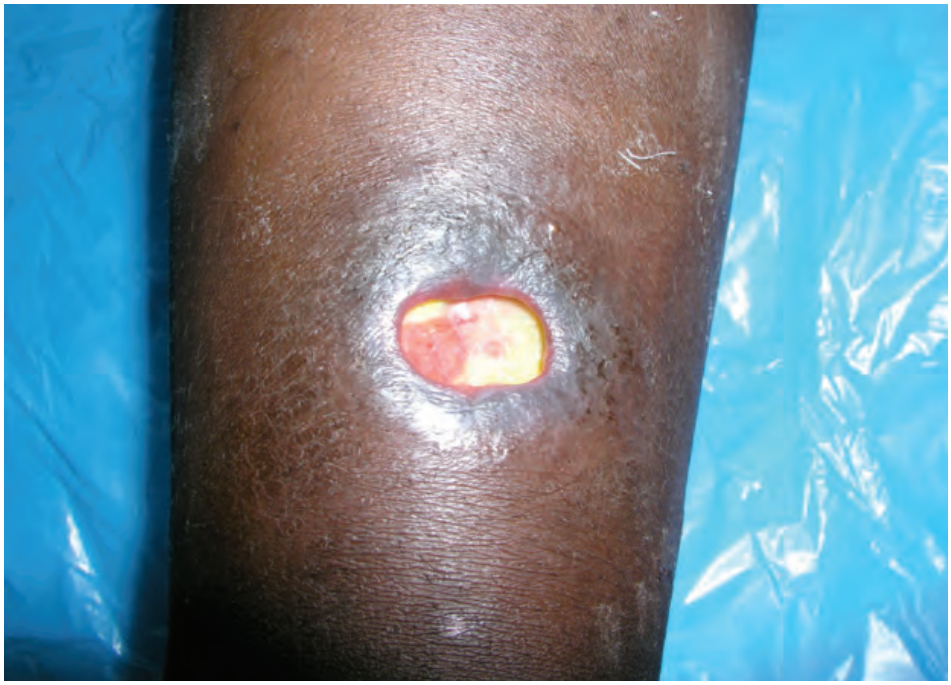
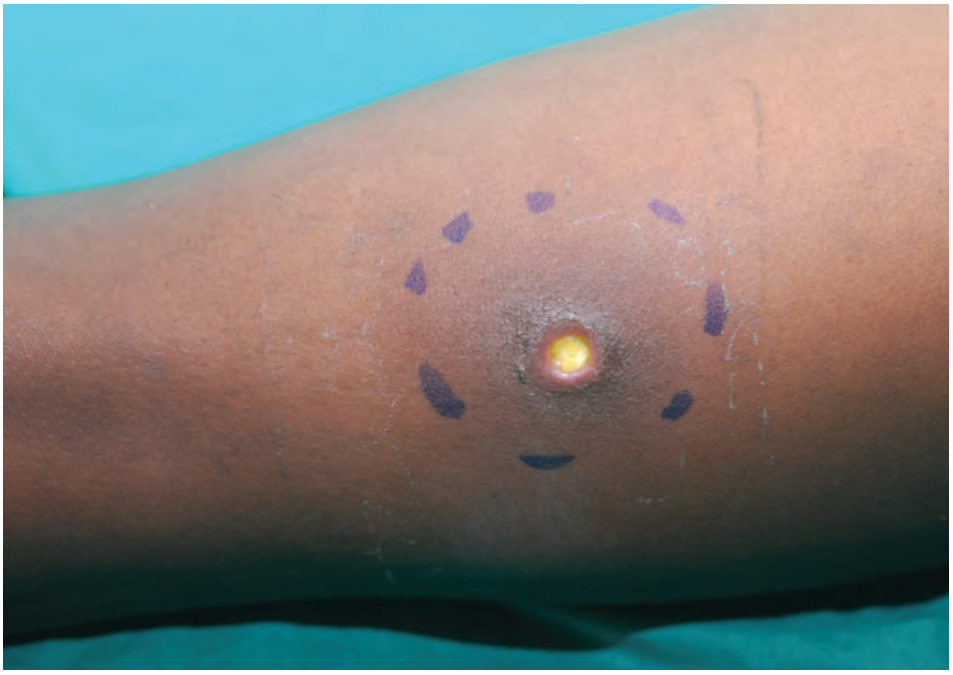


Fig. 14

Fig. 15



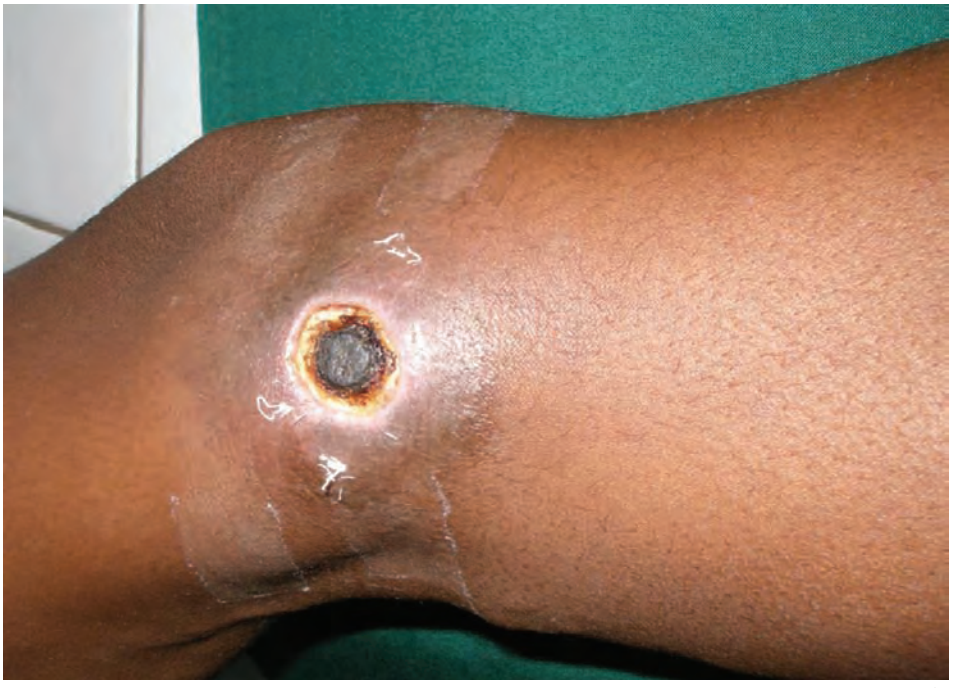
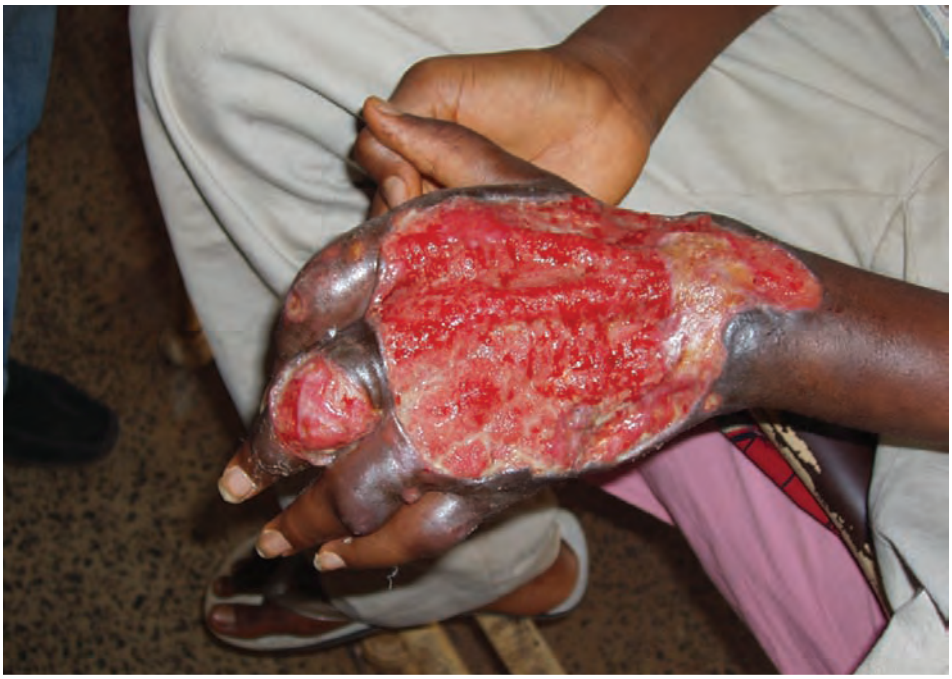


Fig. 16

Large ulcers

Fig. 17



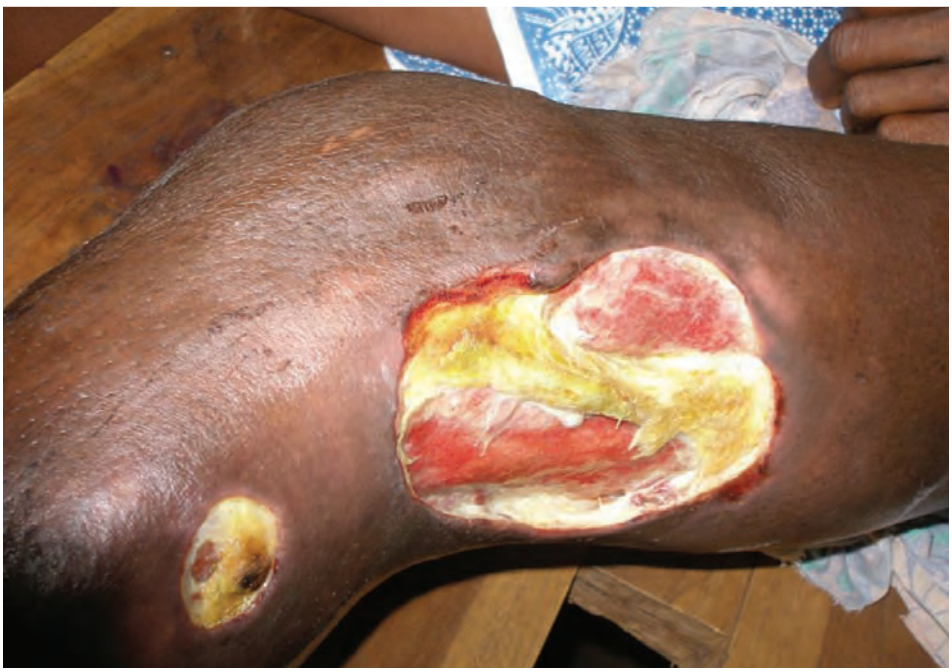
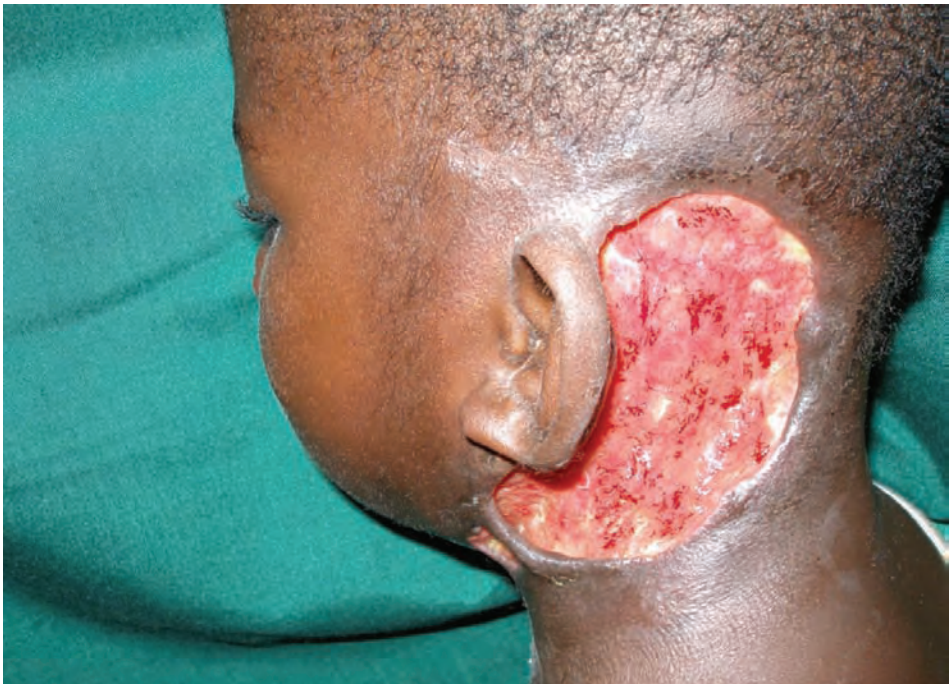


Fig. 18

Fig. 19



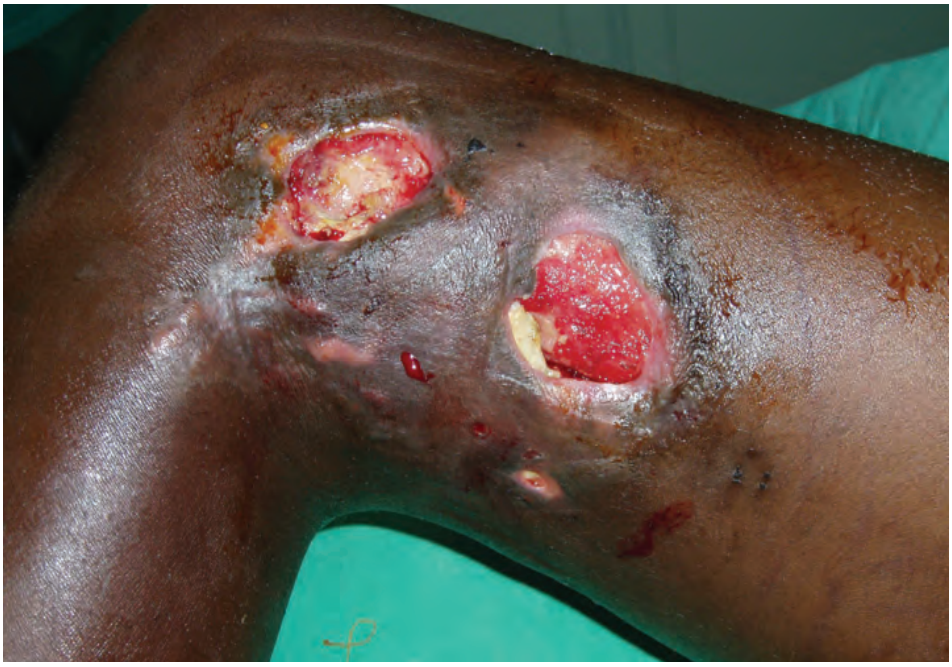


Fig. 20

Lesions on the face

Fig. 21

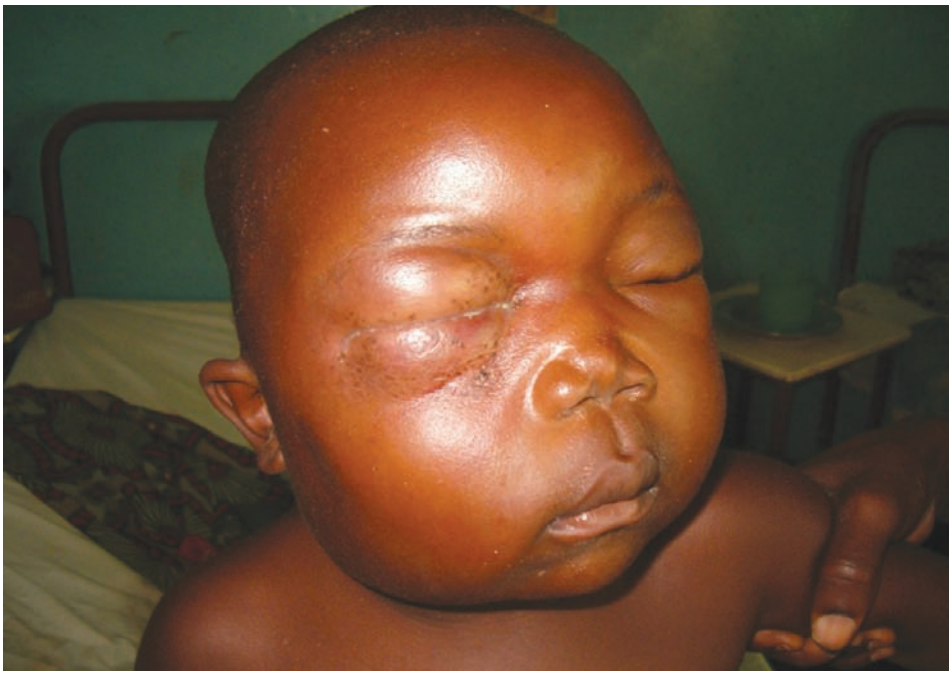
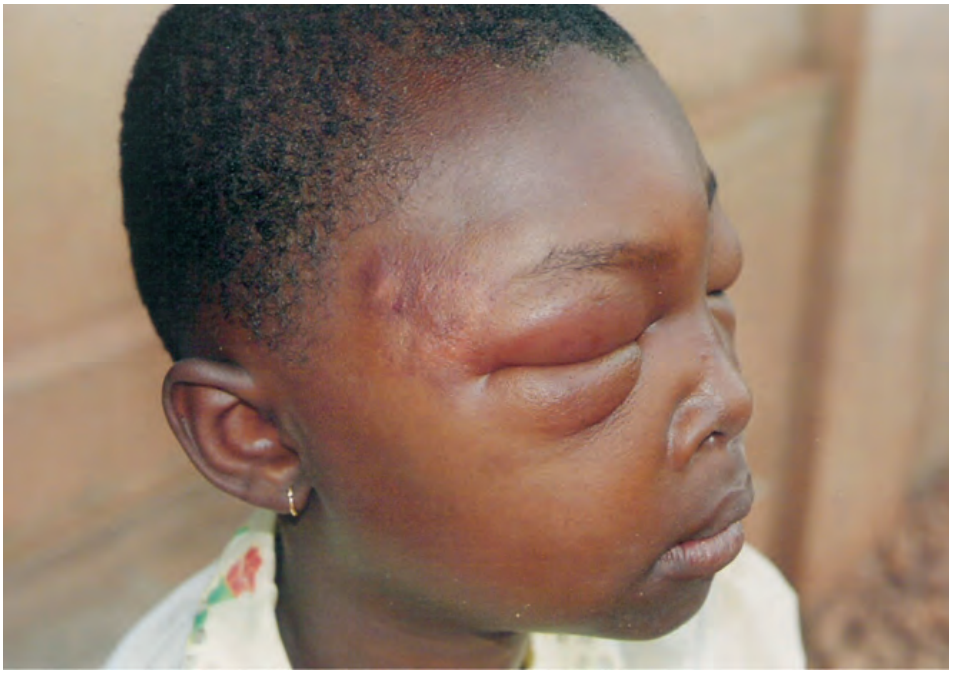


Fig. 22

Fig. 23



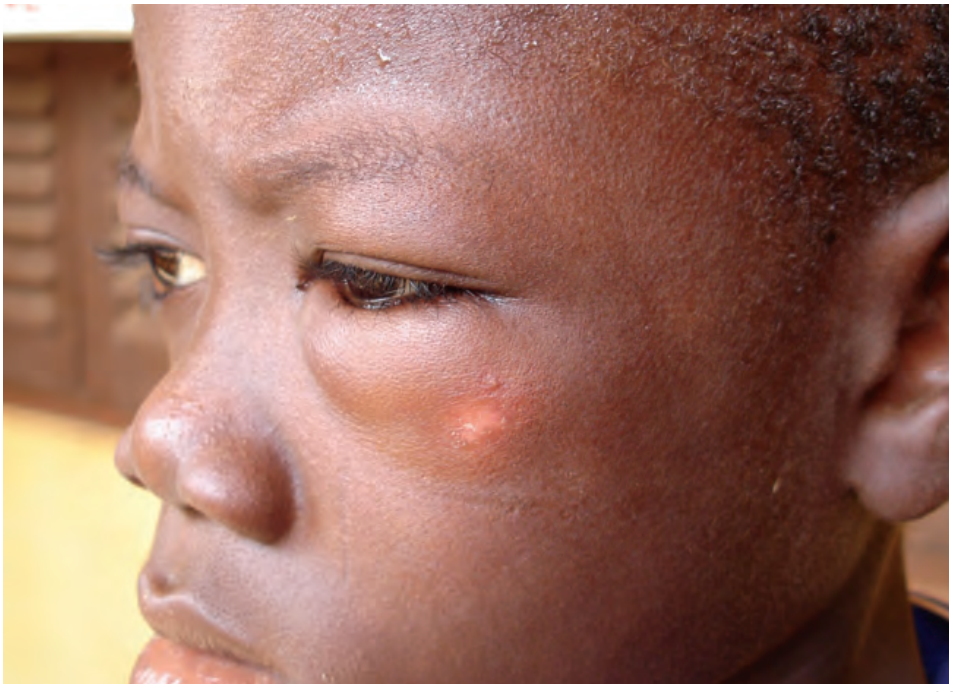
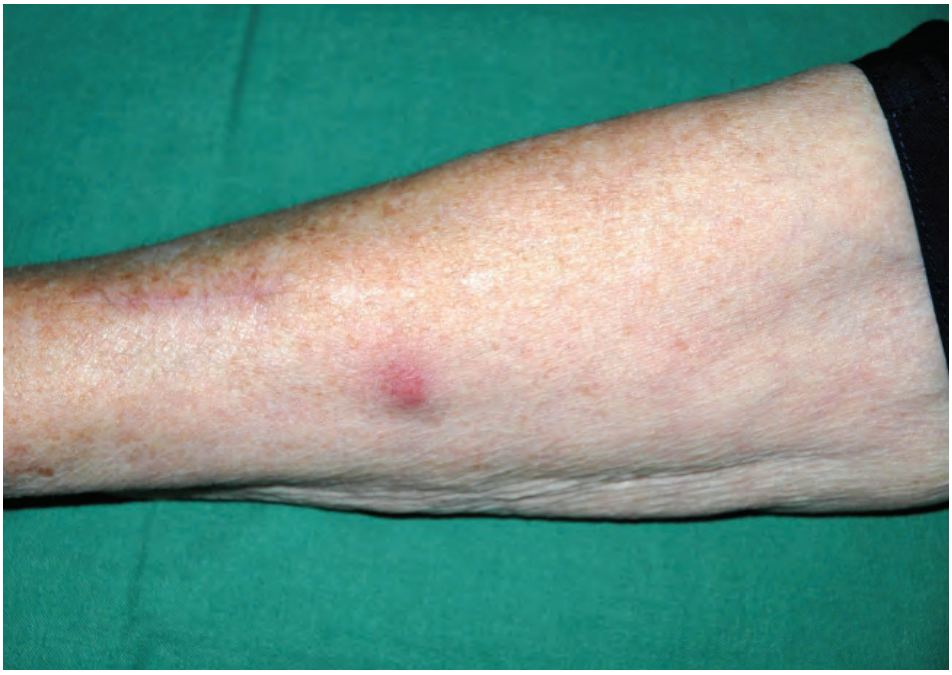


Fig. 24

AUSTRALIA

Small ulcers

Fig. 25



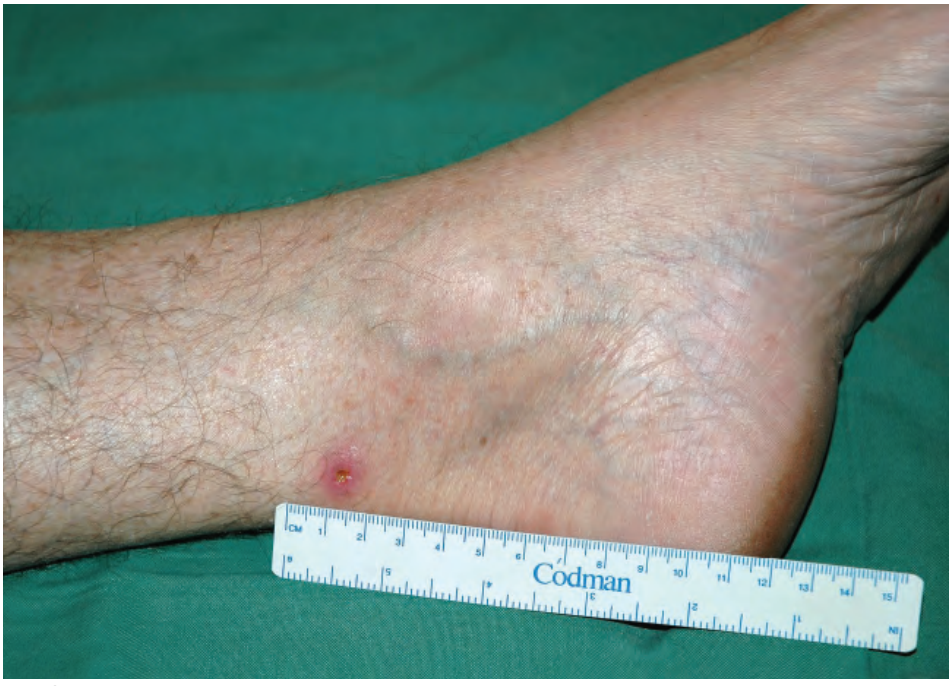
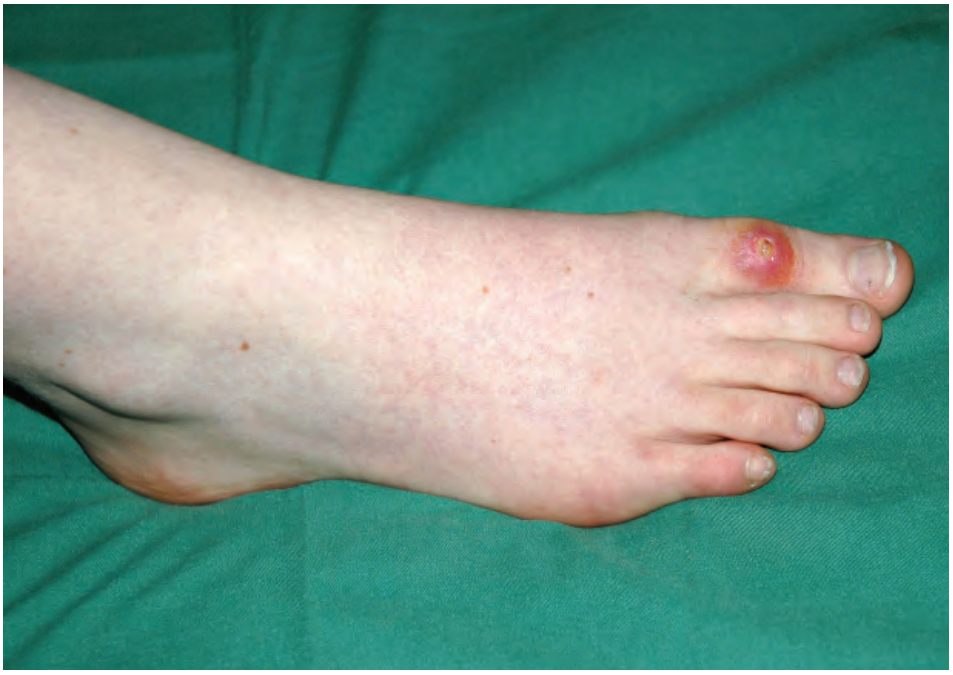


Fig. 26

FIG. 27



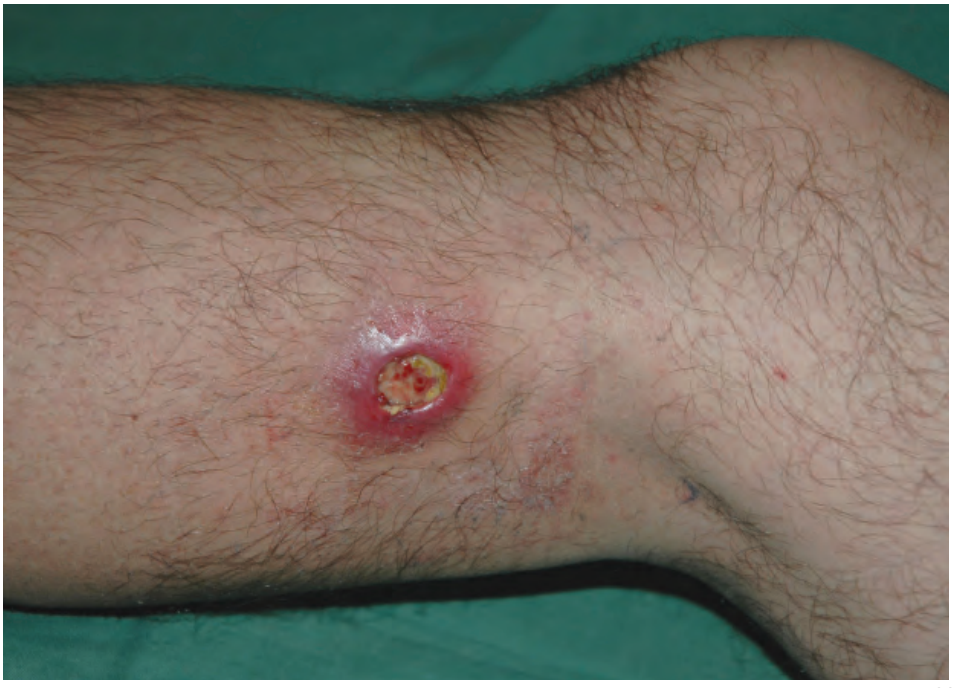
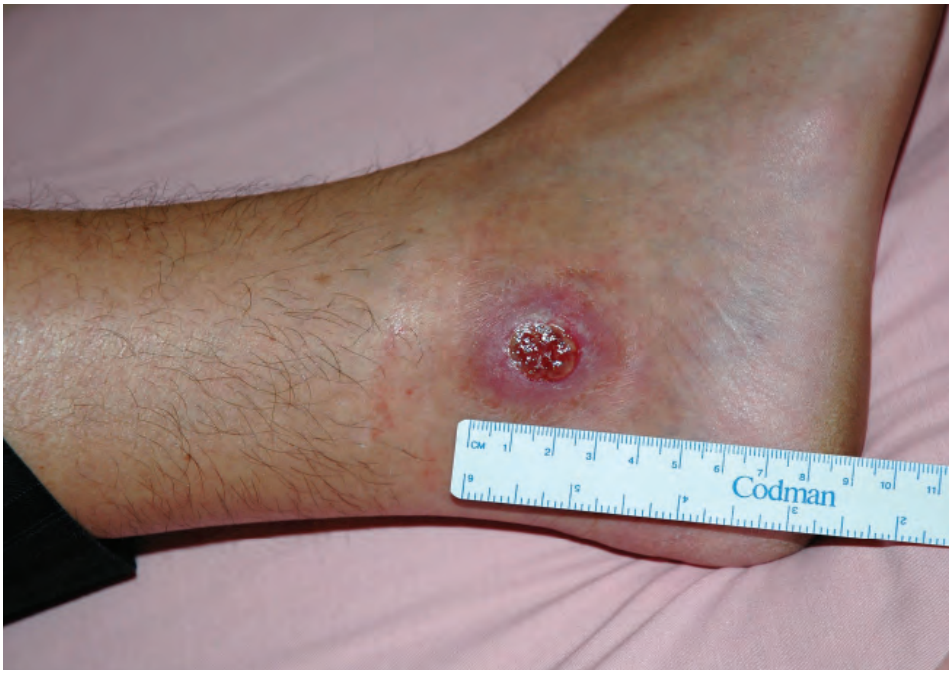


FIG. 28

Fig. 29



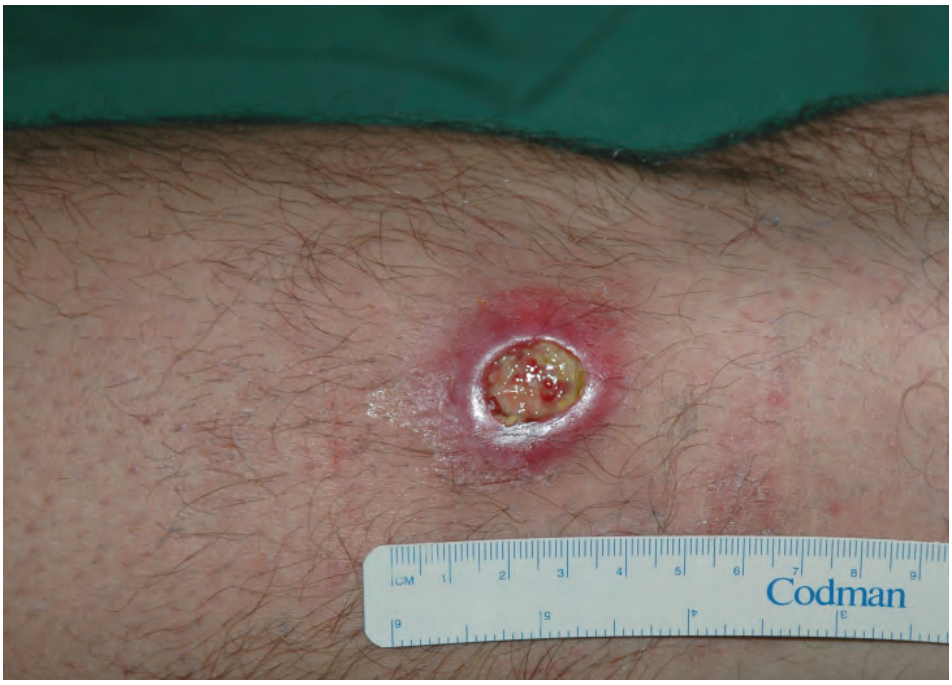
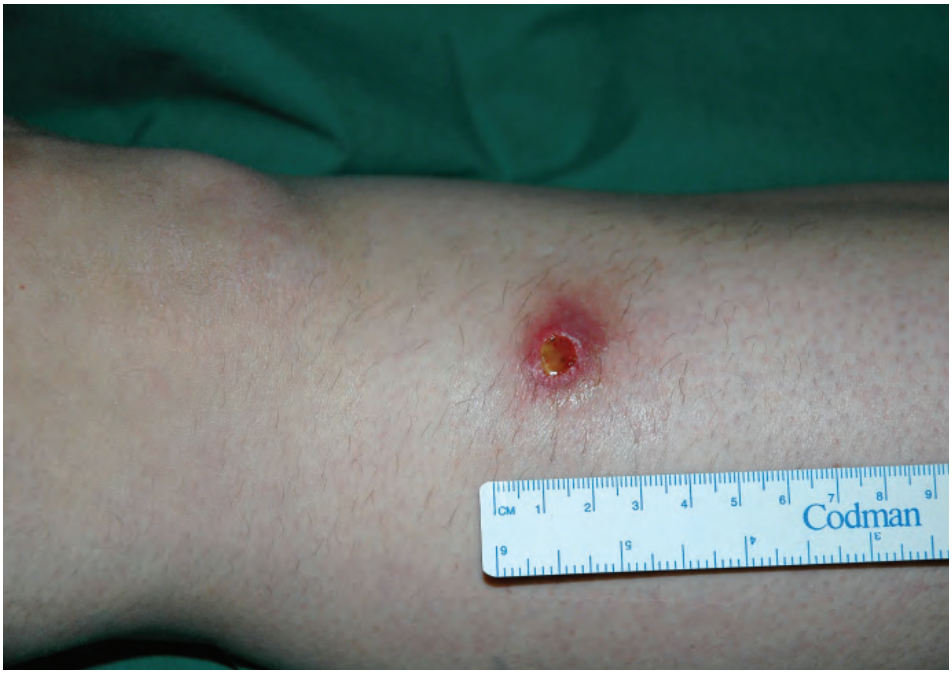


Fig. 30

Fig. 31



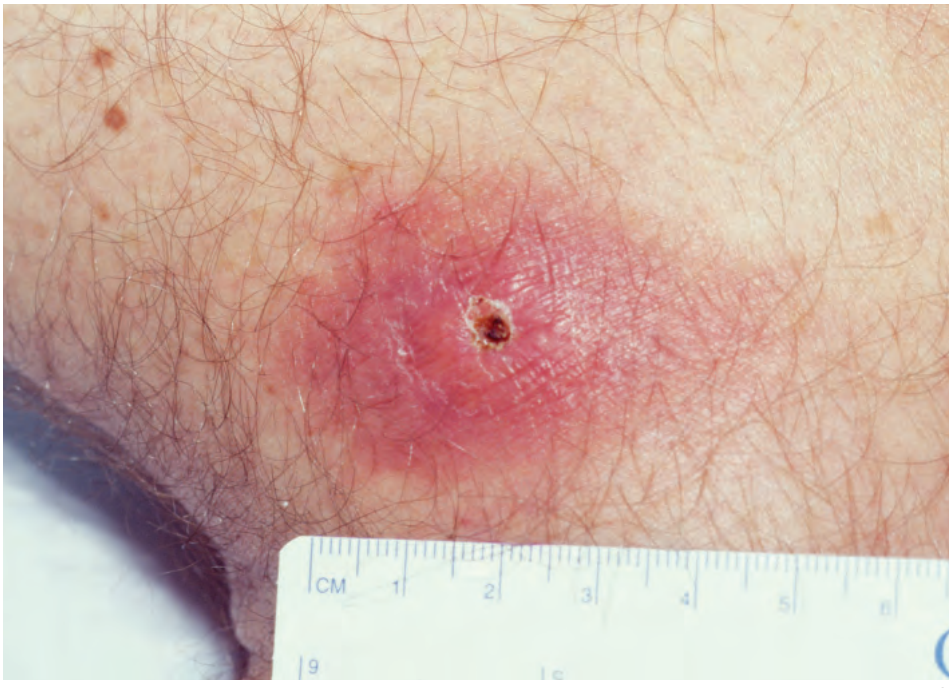
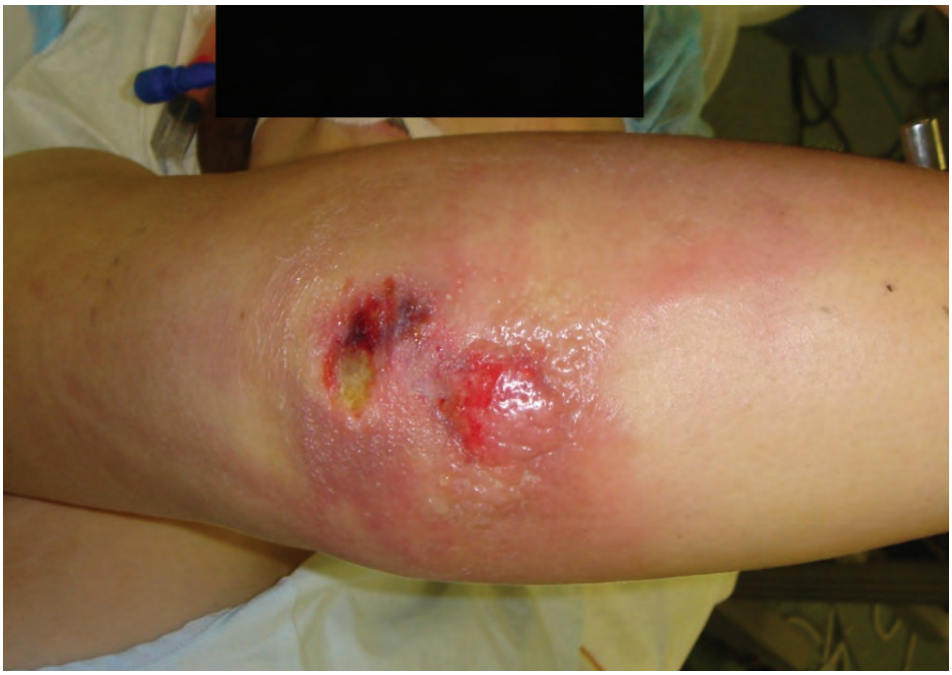


Fig. 32

JAPAN

Fig. 33



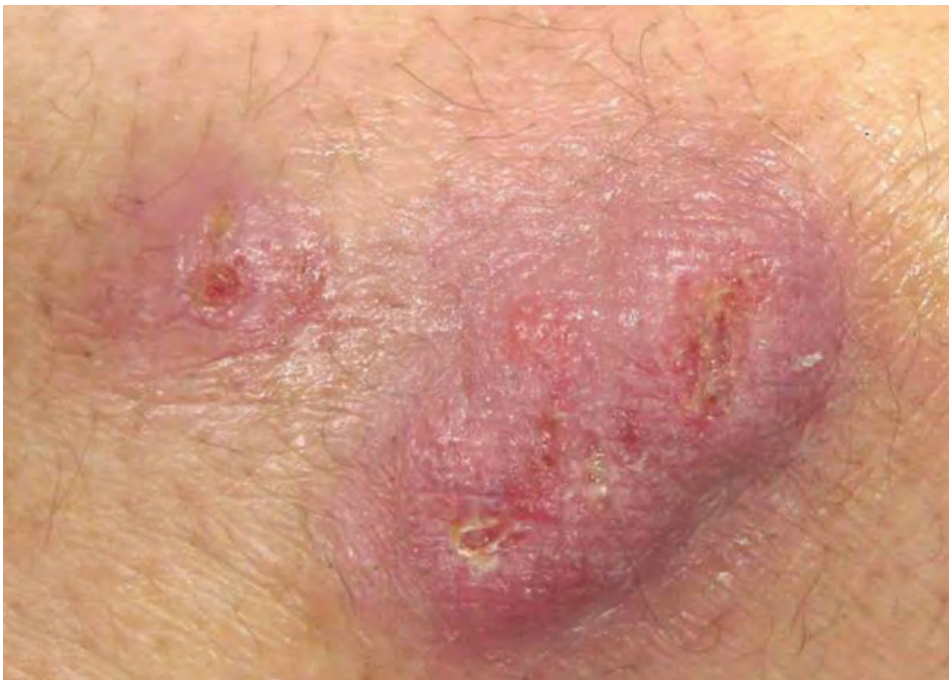
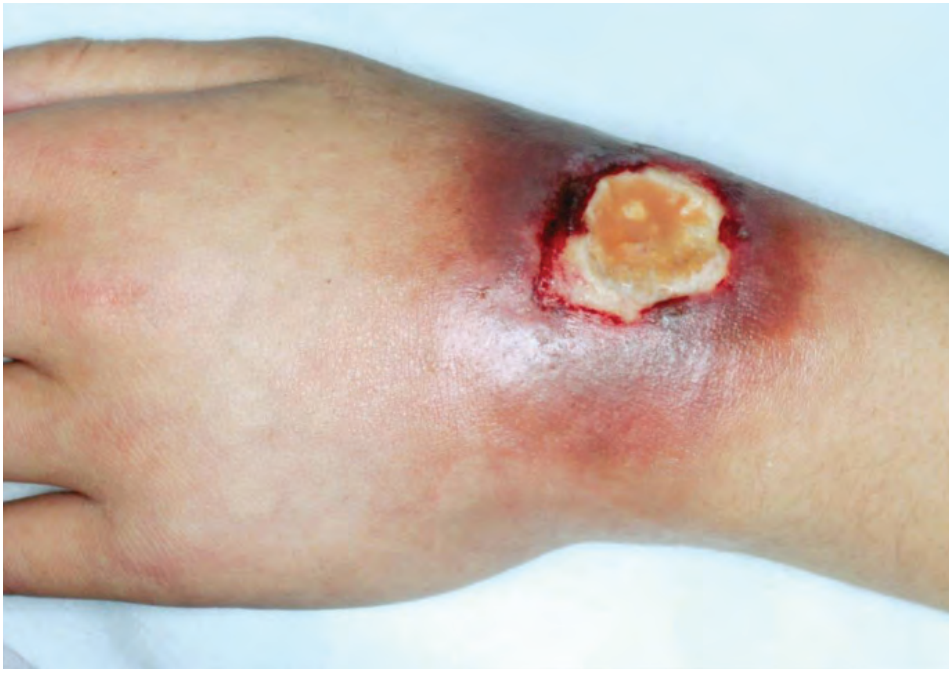


Fig. 34

FIG. 35



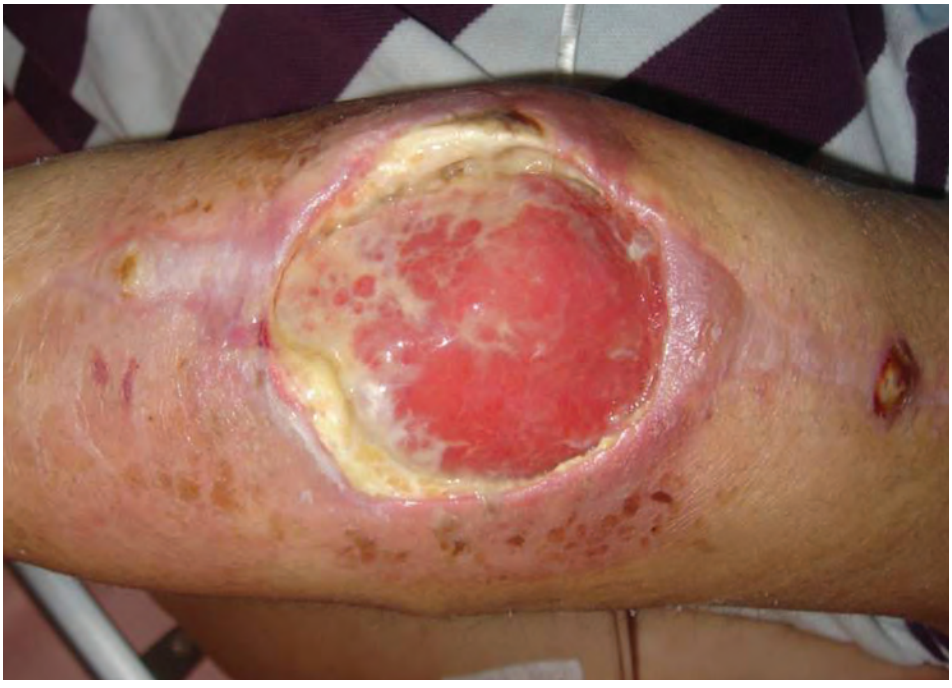
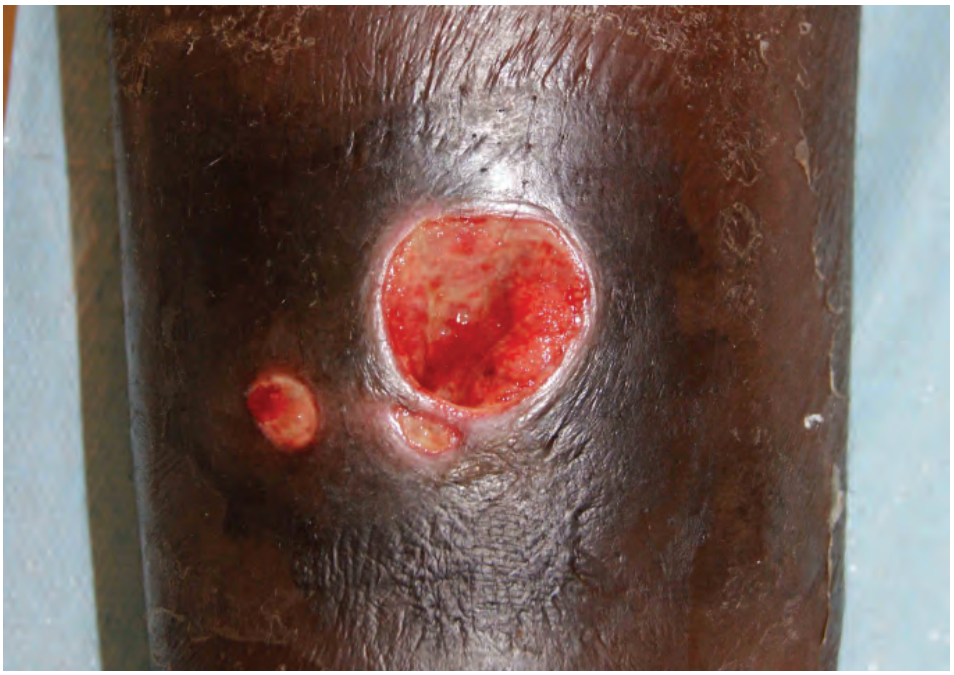


FIG. 36

SOUTH AMERICA

Fig. 37



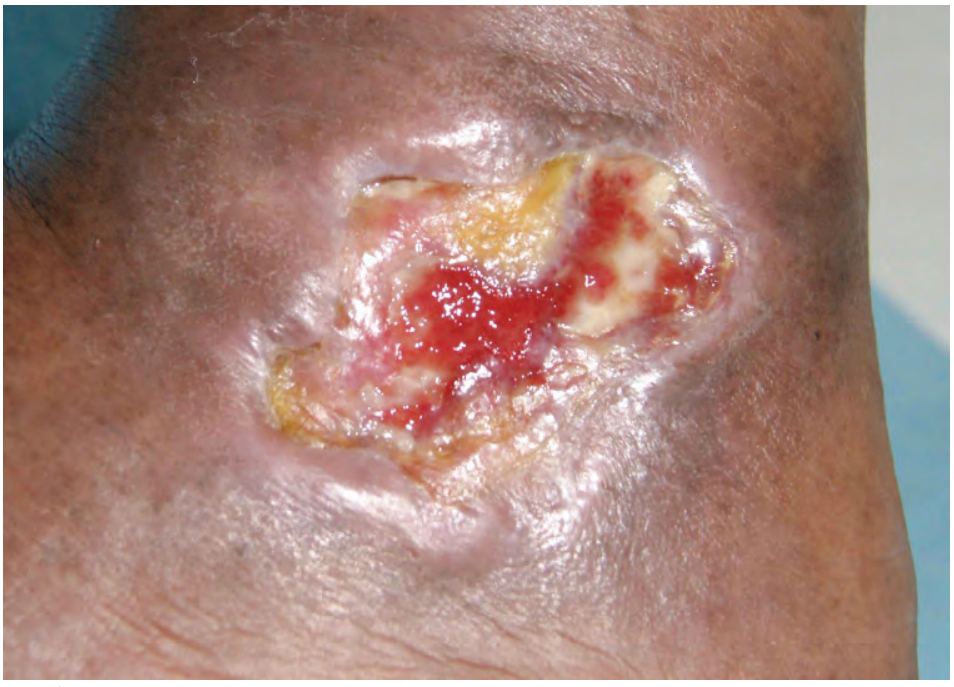
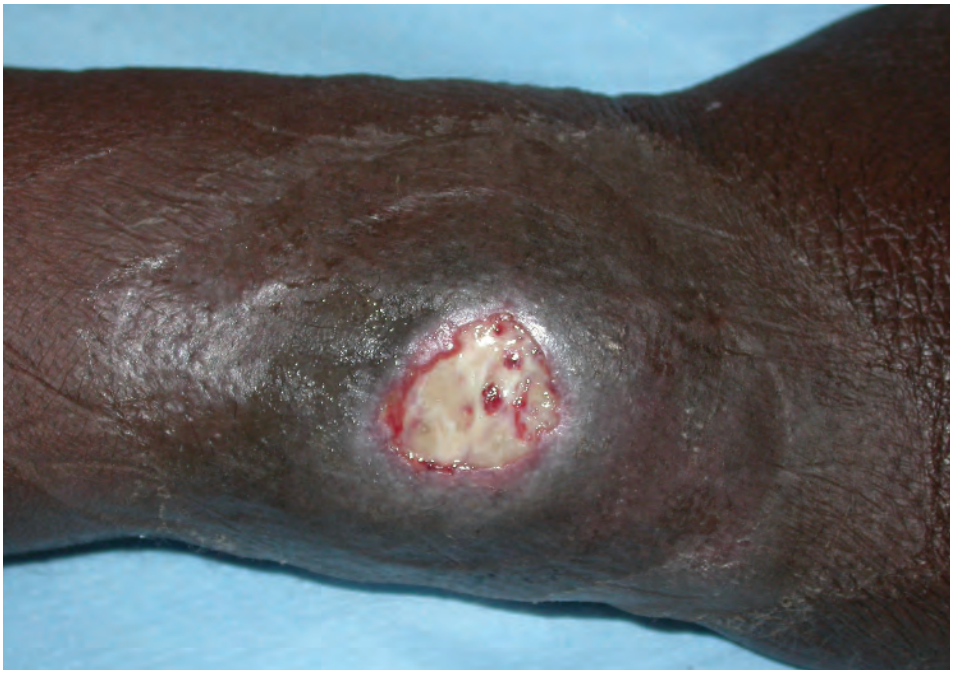


Fig. 38

FIG. 39



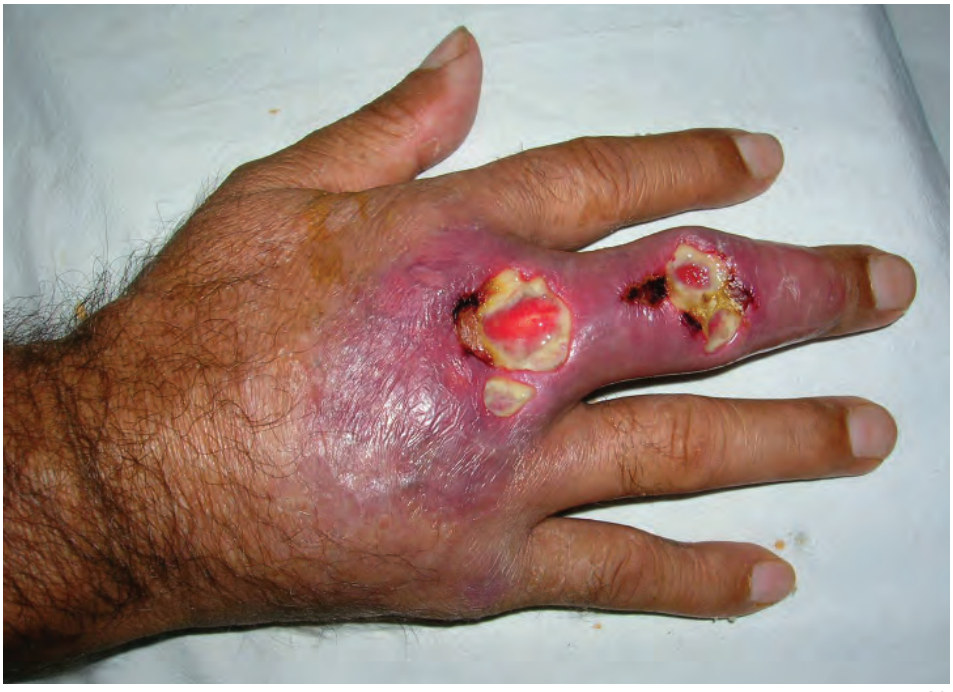
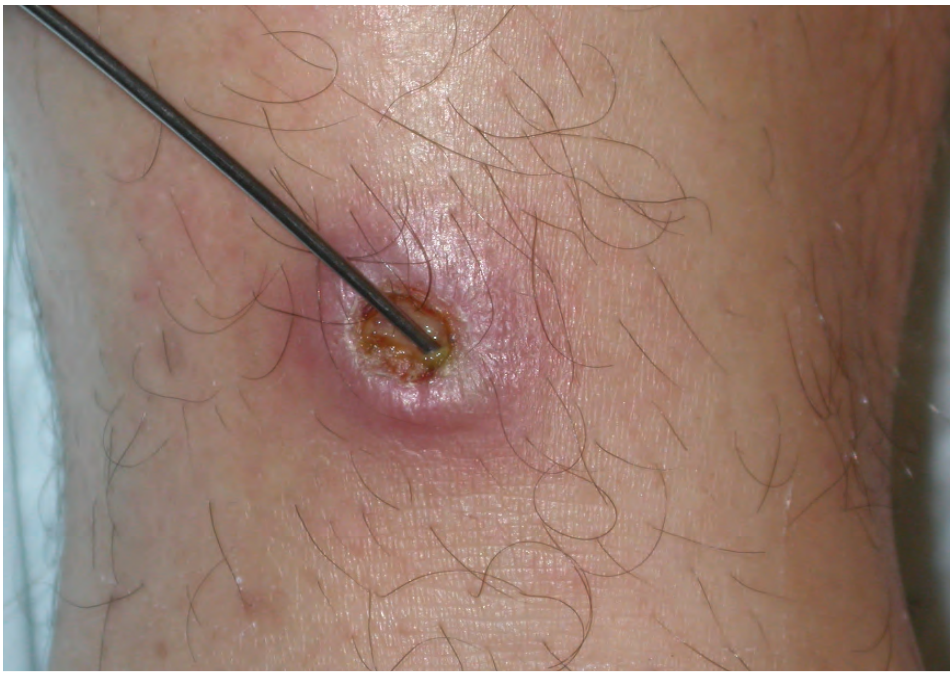


FIG. 40

Fig. 41



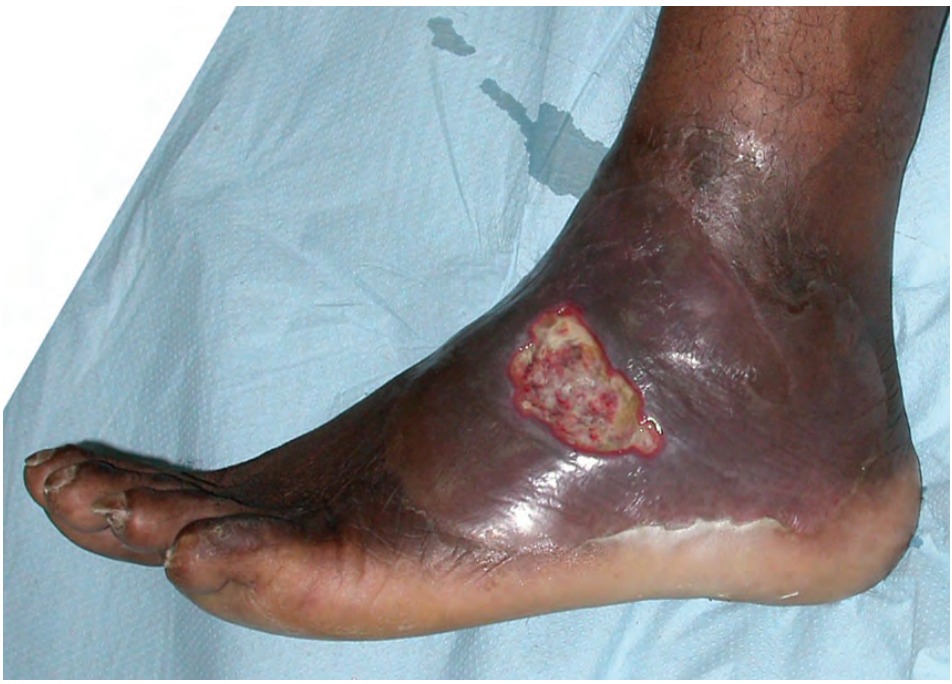
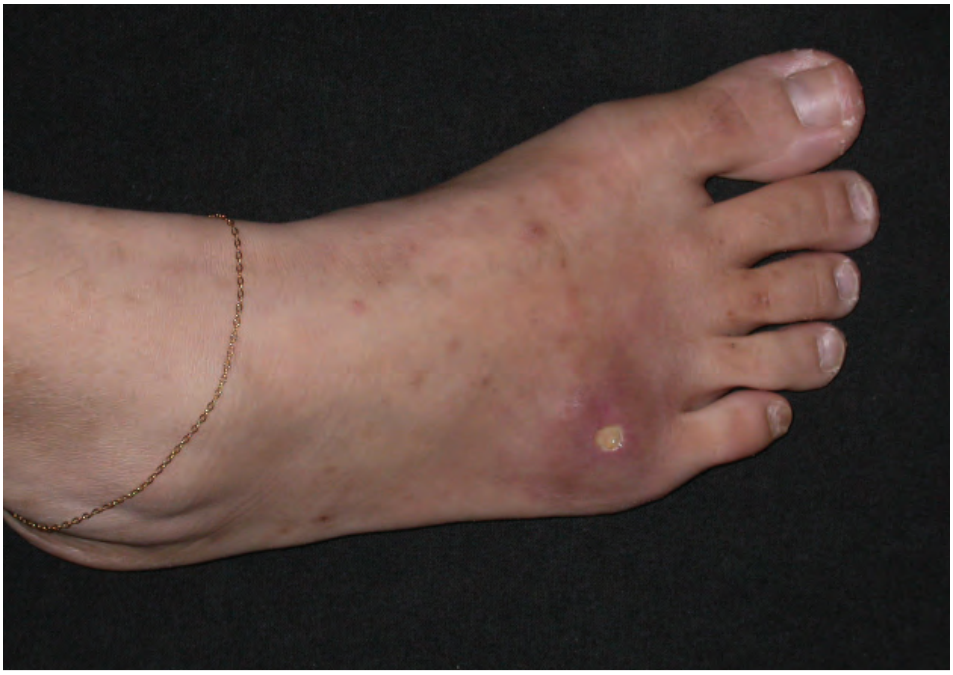


Fig. 42

FIG. 43



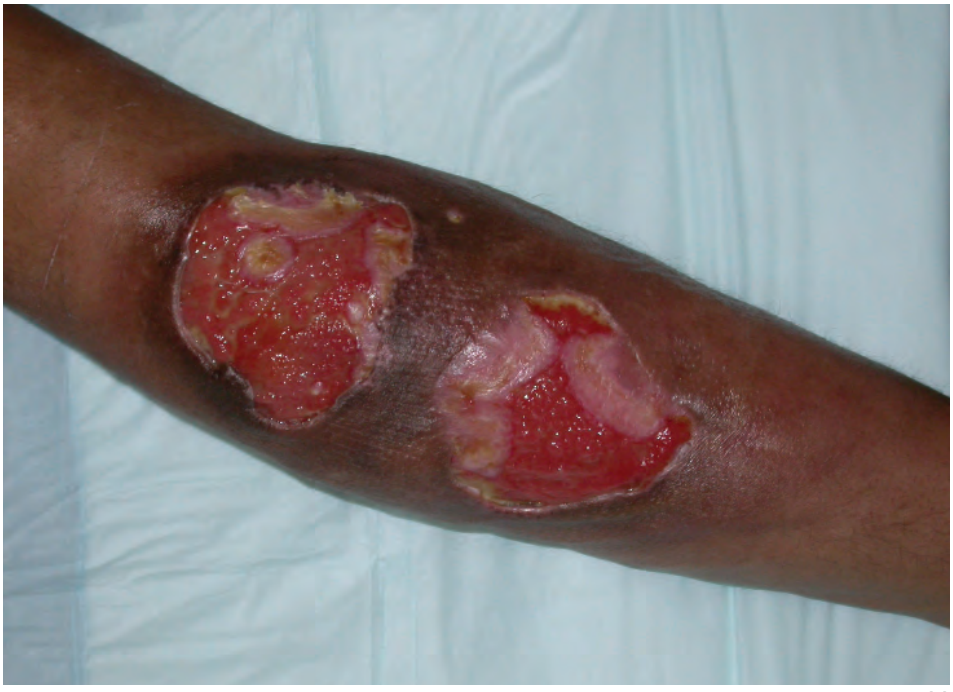


FIG. 44

5. CASE DEFINITIONS

Standardized case definitions allows proper patient registration and case notification; selection of appropriate standard treatment regimens; standardization of data collection; evaluation of the proportions of clinical forms, categories and treatment outcomes; accurate monitoring of trends and evaluation of the effectiveness of Buruli ulcer programmes within and across districts and countries.

Buruli ulcer case definitions refer to the patient, clinical forms and categories.

THE PATIENT

A ***new case*** is defined as a person presenting with a Buruli ulcer lesion who has not previously received antibiotic treatment for Buruli ulcer.

A ***recurrent case*** is defined as a patient who has previously received antibiotics for Buruli ulcer, who presents with a lesion at another site or lesions at the same site within 1 year of the end of the last antibiotic treatment.

The breakdown of old Buruli ulcer scars does not constitute recurrence.

Paradoxical reactions are a recently recognized phenomenon, and some cases previously classified as recurrent lesions may have been due to paradoxical reactions (37,41). Such reactions occur during or long after antibiotic treatment, with new inflammatory disease (presenting as a nodule/swelling, plaque or oedema) leading to extension of the existing ulcer or a new lesion on a different part of the body, usually with pus formation and pain. These are sometimes seen on parts of the body where there was no evidence of disease before antibiotic treatment, perhaps as a result of subclinical infection. Cultures of tissue or pus are usually sterile, although acid-fast bacilli can still be seen and polymerase chain reaction (PCR) for ***M. ulcerans IS2404*** remains positive. Histopathological examination of the lesion demonstrates an intense immunological reaction within and around the lesion.

CLINICAL FORMS

Buruli ulcer presents in two different forms: non-ulcerative and ulcerative.

CLINICAL FORMS

	Non-ulcerative	Ulcerative
Africa	26%	74%
Australia	13%	87%
Japan	6%	94%

A ***papule*** is a painless, raised skin lesion < 1 cm in diameter. The surrounding skin is reddened. Papules are commonly seen in Australia and may be confused with an insect bite.

A ***nodule*** is a lesion < 3 cm in diameter that extends from the skin into the subcutaneous tissue. It is usually firm and painless but may be itchy, and the surrounding skin may be discoloured in comparison with adjacent areas. Nodules are commonly seen in Africa.

A ***plaque*** is a firm, painless, elevated, lesion > 3 cm in diameter with ill-defined edges. The skin over the lesion may be reddened or otherwise discoloured.

The ***oedematous form*** is a diffuse, extensive, usually non-pitting swelling. The affected area has ill-defined margins, is firm and painless and involves part or all of a limb or other part of the body. The colour of the skin may be changed over the affected area. The disease may be accompanied by low-grade fever.

All the above forms may progress to ulcers after a variable time (as short as 4 weeks). Some of the largest ulcers follow from the oedematous form. Oedema may also develop around an already formed ulcer, leading to rapid extension.

When fully developed, Buruli ulcer is a painless, deep ulcer extending into the subcutaneous fatty tissue. It has undermined edges where the overlying skin may be necrotic. The floor of the ulcer may have a white, cotton wool-like appearance due to necrotic slough. Untreated ulcers are painless, unless there is secondary bacterial infection. When there is more than one ulcer and the ulcers are close together, they often communicate beneath normal looking skin and could extend over a considerable distance.

Osteomyelitis is a complication of severe cases, with an estimated frequency of 10% of such cases in Benin. It usually results from contiguous spread of infection from overlying non-ulcerative or ulcerative disease, especially on the forearm or lower leg. Some cases may be the consequence of haematogenous spread of ***M. ulcerans***, and joints and small bones are often involved. Usually, an old retractile stellate scar is found on another part of the patient's body. A diagnosis of osteomyelitis is made by radiology. When osteomyelitis occurs at a site distant from the Buruli ulcer, it should not be assumed to be caused by ***M. ulcerans***. Even when it is at the same site, it could be caused by a different organism, especially when the ulcer is of long duration, and a sample for biological confirmation (direct smear examination, PCR or culture) should be obtained.

CATEGORIES OF DISEASE

In addition to the standard classification of the disease into non-ulcerative and ulcerative forms, WHO has introduced an additional classification, based on lesion size, for two reasons: (i) small lesions are more likely to heal with antibiotic treatment alone; and (ii) small lesions reflect the impact of health promotion of early diagnosis and can therefore be used to monitor progress.

The following table shows the distribution of categories of lesions in different regions.

CATEGORY

	Category I	Category II	Category III
Africa	32%	35%	33%
Australia	90%	5%	5%
Japan	81%	19%	0%

The three categories of lesion are:

Category I: a single lesion < 5 cm in diameter. Most category I lesions heal completely with antibiotic treatment.

Category II: a single lesion measuring 5–15 cm in diameter. Some category II lesions heal completely with antibiotic treatment.

Category III: a single lesion > 15 cm in diameter, multiple lesions, lesion(s) at a critical site (eye, breast, genitalia) and osteomyelitis. Category III ulcers are usually managed, in addition to antibiotics, by surgery (debridement and skin grafting) to achieve an acceptable rate of healing, but the optimal timing is not yet known. Multiple small lesions and lesions at critical sites may heal with antibiotics alone, and careful consideration should be given to avoiding surgery. Treatment indications may differ according to the sub-category:

- 3a: a single lesion > 15 cm in diameter and osteomyelitis (complete antibiotics before surgery);
- 3b: lesions at critical sites (complete antibiotics and carefully avoid surgery if possible); and
- 3c: small multiple lesions (complete antibiotics, if possible, before considering surgery).

6. DOCUMENTATION

The standard patient recording forms are BU 01 (***Annex 3***), BU 02 (***Annex 4***) and BU 03 (***Annex 5***). Additional forms may be adapted from those in annexes 2 and 6.

ROLE OF THE HEALTH WORKER

Health workers who prescribe and administer the antibiotic combination for the management of Buruli ulcer should carefully document all clinical decisions, diagnostic procedures, clinical evaluation and adverse effects:

1. Take a history and carry out a general physical examination.
2. Fill out the BU 01 and BU 02 forms and the patient treatment card (***Annex 2***).
3. Determine any limitation of movement by comparing the affected and unaffected sides.
4. Obtain samples for diagnostic confirmation and complete the BU 03 laboratory form.
5. Check for any contraindications and prescribe appropriate antibiotics.
6. Inform the patient or guardian about the duration of treatment, compliance, side-effects, response to treatment, prevention of disability, wound care and nutrition.
7. Enquire about any social problems that may influence the patient's full compliance with the treatment and help find solutions.
8. Follow-up of the treatment of the patient:
   - daily administration of antibiotics,
   - regular wound dressing,
   - periodic photographs of the lesion,
   - regular movement and use of affected body part,
   - monitor side-effects, and
   - assess clinical improvement or worsening (secondary infection, movement limitation) and note all new events on the back of the BU 01 form.

ROLE OF THE LABORATORY

Depending on the laboratory facilities available in the area or country, any of the following or a combination may be used: direct smear examination, PCR, histopathology and culture (not for diagnosis and treatment).

For ulcerative lesions, for example, at the start of antibiotic treatment, swabs should be taken from the undermined edges of the ulcer for direct smear examination, culture and PCR. Swabs should also be taken at the end of antibiotic treatment (if the lesion has not healed or surgery is indicated) to allow analysis of the response to treatment.

For non-ulcerative lesions, before the start of antibiotic treatment, a fine-needle aspirate should be taken from the estimated centre of the lesion for microbiological analyses (direct smear examination, PCR and culture). Other procedures that can be used to obtain specimens include punch and surgical biopsy, if histopathological analysis is strongly required. A guideline for obtaining specimens for laboratory confirmation is available (***42***).

MEASUREMENTS

Where possible and practical, documentation of the response to treatment should include serial tracing of lesions and measurement of the lesions at regular intervals, possibly weekly. Tracings may be done on acetate sheets. This is easily applicable in Category I and some Category II lesions (≤ 10 cm cross-sectional diameter). For oedematous lesions, the circumference of the limb should be measured at three fixed points at weekly intervals. For purposes of comparison, the unaffected limb should be measured at the same places at the start of and throughout treatment.

Serial measurements of lesion sizes may be made by digital photography or other equipment (*43*). Photography is a useful way of recording disease and treatment outcomes after antibiotic and surgical treatments. For oedematous lesions on the limbs, the photographs should be taken so that the affected and the unaffected limbs can be compared. For all forms of the disease, it is important that consecutive photographs be taken from an equidistant position to permit reasonable comparison.

PATIENT INFORMATION AND COMPLIANCE

This document does not constitute a research protocol; however, as part of good medical practice, health workers should explain treatments and all procedures to patients and their relatives. In particular, the importance of laboratory confirmation and of sample collection, the role of antibiotic treatment in Buruli ulcer and the importance of compliance, the possibility of debridement and skin grafting to speed healing in cases of large lesions should be explained to the patient to avoid 'high expectations of rapid cure'. This will ensure that patients and their relatives understand the conditions and thereby comply with treatment.

FOLLOW-UP AFTER ANTIBIOTIC TREATMENT

After patients have completed antibiotic treatment, they should be followed up for at least 10 months (i.e. for at least 12 months after the start of treatment) to confirm cure, assess possible complications and observe any recurrences. The form in annex 6 may be used to document follow-up visits.

REPORTING OF EXPERIENCES

All health workers are encouraged to carefully document their experiences so that they can be published or presented at meetings to support future revisions of this guidance.

7. IMPLEMENTATION OF THIS GUIDANCE

Collaboration with tuberculosis programmes at all levels is recommended, particularly in areas such as coordination of drug procurement, use of laboratory facilities and networks and monitoring for potential antibiotic resistance. Collaboration with HIV / AIDS programmes at all levels is important in the management of Buruli ulcer patients who may be co-infected with HIV. Collaboration with academic and research laboratories is essential for laboratory confirmation of Buruli ulcer cases.

Training and retraining of health workers on the correct, consistent use of the guidance is essential.

Patients, family members and communities should be involved in early detection and treatment of cases.

This guidance should be implemented in endemic areas, where the disease may be reliably diagnosed and where treatment in accordance with the guidance is possible. To avoid or minimize wasteful antibiotic treatment of patients who do not have Buruli ulcer, at least a strong clinical diagnosis is essential before treatment is started. Furthermore, efforts should be made to collect samples for laboratory confirmation, as recommended by WHO.

National Buruli ulcer control programmes should ensure that the health facilities in which this guidance is implemented have: (i) an uninterrupted supply of the antibiotics; (ii) the necessary recording forms (***Annexes 2–6***); (iii) a digital camera; (iv) specimen containers and (v) transport.

To reduce pressure on limited numbers of hospital beds, patients with small early lesions who do not need hospitalization and those with larger lesions who are well enough to take antibiotics at home may be given a 2-week course of antibiotics under direct observation in a health-care facility close to their homes. After the 2 weeks, the patients should return to the hospital for reassessment: provided that there is evidence of improvement, the antibiotics should be given for a further 2 weeks. This regimen should continue until the patient has completed the 8-week course.

If the patient is not hospitalized, it is important to ensure appropriate dressing of ulcers at a decentralized health centre. All patients treated with antibiotics should be registered, and the following information should be recorded: name, age, sex, address (city, town or village), the results of at least one confirmatory laboratory examination, date treatment started, date treatment ended, measures of response to treatment (including reduction of swelling around the lesion), limitations of movement, adverse effects and whether surgery was performed (***Annex 3***).

Close monitoring is needed at all levels (community, district, regional, national and WHO) to ensure effective implementation of this guidance.

PROVISION OF ANTIBIOTICS

Coordinated procurement of the drugs is encouraged. Currently, WHO and partners provide the antibiotics to countries on request from national control programmes.. Governments of affected countries, nongovernmental organizations and other donors are also encouraged to provide these antibiotics to ensure that there is an uninterrupted supply.

8. ANTIBIOTIC TREATMENT IN SPECIAL SITUATIONS

WHAT TREATMENT SHOULD BE GIVEN FOR RECURRENCE OR PARADOXICAL REACTION?

Recurrence is rare after a full 8-week course of antibiotics has been completed. If antibiotics were given for fewer than 8 weeks in the first course or poor adherence is suspected, further antibiotic treatment or surgery should be considered. The duration of a second course of antibiotics depends on the situation, but care must be taken not to give streptomycin for more than 90 days in total.

Paradoxical reactions usually resolve without further antibiotic treatment. Clinicians should not therefore rush to restart or extend antibiotic treatment. These reactions can be managed conservatively with drainage of pus and routine dressings. Samples should be taken for culture and histopathology. Underlying osteomyelitis should be eliminated. If the lesion due to a paradoxical reaction does not appear to be improving within 6 weeks of conservative treatment, surgery should be considered and samples taken for microbiological and histopathological analyses to look for progressive active infection as an alternative diagnosis. If this reaction occurs during the course of antibiotic treatment, however, the full course of 8 weeks should be completed.

IF SEVERE SIDE-EFFECTS DEVELOP WITH THESE ANTIBIOTICS, WHAT ALTERNATIVE ANTIBIOTICS SHOULD BE USED?

Severe side-effects are uncommon with the recommended antibiotics. Stop treatment if severe side-effects develop, such as shock or jaundice resulting from rifampicin or severe dizziness or hearing or renal impairment resulting from streptomycin (*Table 2*). Streptomycin is particularly risky if treatment lasts for more than 90 days; aminoglycoside toxicity is cumulative, and special attention should be given to patients who have previously been treated with any aminoglycoside. If hearing impairment is found to be conductive, not sensori-neural, treat the cause and continue antibiotic treatment. Occasionally, patients develop a generalized skin rash.

In the case of severe rifampicin toxicity, there is no alternative drug regimen of proven value. If clarithromycin is available, consider treatment with streptomycin plus clarithromycin for 8 weeks. Surgical excision with antibiotic cover for 4 weeks is an alternative.

In cases of severe streptomycin toxicity, rifampicin may be combined with clarithromycin or moxifloxacin (adults only) for 8 weeks, if it is available. The efficacy of these two regimens have not been established, but it has been used extensively in clinical practice in Australia and French Guiana, with high cure rates.

WHAT ABOUT CHILDREN?

Painful daily injections of streptomycin are a concern for children. Good clinical experience and limited observational data suggest that rifampicin and clarithromycin may be an alternative regimen for children, although it has not been formally tested.

CAN STREPTOMYCIN BE USED FOR PREGNANT WOMEN?

The use of streptomycin is contraindicated during pregnancy. In routine practice, pregnancy should be ruled out before streptomycin is prescribed for women of reproductive age. Rifampicin combined with clarithromycin may be used in pregnant women.

WHAT ABOUT CO-INFECTION WITH OTHER MYCOBACTERIA (TUBERCULOSIS AND LEPROSY)?

Co-infection with the mycobacteria that cause either tuberculosis or leprosy is uncommon. Any patient with Buruli ulcer who is co-infected should continue to receive the standard treatment for tuberculosis or leprosy, but the rifampicin and streptomycin (or other antibiotic) components of the regimen should be given daily for 8 weeks, after which the standard treatment regimens for tuberculosis or leprosy should be continued.

WHAT ABOUT PATIENTS WITH HIV INFECTION?

Buruli ulcer and HIV co-infection is an emerging area and complicates clinical management. The first case of Buruli and HIV co-infection was reported from Democratic Republic of the Congo in 1992.[2] A study conducted in Benin from 2002–2003 found that HIV prevalence among patients with Buruli ulcer was higher (2.6%, 11/426) than among controls (0.3%, 2/613).[3] In Benin, 6 (3.6%) out of 156 patients treated at Pobè Buruli Ulcer Treatment Center in 2006 were positive for HIV, and in 2010, 2 (1.5%) out of 135 patients were HIV positive. In Cameroon, an HIV prevalence of 33% has been reported among adult Buruli ulcer patients (compared to 5% in the general population).[4]

HIV weakens the immune system and tends to make Buruli ulcer progress more aggressive[5] and could possibly affect the response to antibiotic treatment. Co-infected patients are often adults (>15 years old) who present with multifocal lesions and osteomyelitis. Although further studies are required to improve our understanding of this issue, the management of BU/HIV co-infection may follow the guidelines for managing TB/HIV co-infection. First, HIV counselling and testing should be offered for all patients presenting with BU. Second, co-infected patients should be screened for tuberculosis. Thirdly, as for TB, co-infected patients may receive early antiretroviral treatment to ensure a better response to treatment irrespective of CD4 count. Due to the interaction between rifampicin and some ARVs, the NNRTI component of the ART regimen should be changed from NVP to EFV, and if protease inhibitors are being used the TB/HIV guidelines[6] should be consulted for suggested management.

WHAT ABOUT OSTEOMYELITIS?

The first line of treatment should be with rifampicin and streptomycin for 8 weeks. Surgery is usually required to remove nonviable bone and to hasten healing. The response to treatment can be monitored radiologically.

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ANNEXES

ANNEX 1:
INFORMATION ON RIFAMPICIN, STREPTOMYCIN, CLARITHROMYCIN AND MOXIFLOXACIN

RIFAMPICIN (1)

GENERAL INFORMATION

Group: antimycobacterial agent

Capsule or tablet: 150 mg, 300 mg

Rifampicin is a semisynthetic derivative of rifamycin. It is a complex macrocyclic antibiotic that inhibits ribonucleic acid synthesis in a broad range of microbial pathogens. It has bactericidal action and a potent sterilizing effect against tubercle bacilli in both cellular and extracellular locations.

Rifampicin is lipid-soluble. After oral administration, it is rapidly absorbed and distributed throughout the cellular tissues and body fluids; if the meninges are inflamed, significant amounts enter the cerebrospinal fluid. A single dose of 600 mg produces a peak serum concentration of about 10 µg/ml in 2–4 h, which subsequently decays, with a half-life of 2–3 h. It is extensively recycled in the enterohepatic circulation, and metabolites formed by deacetylation in the liver are eventually excreted in the faeces.

As resistance develops readily, rifampicin must always be administered in combination with other effective antimycobacterial agents.

CLINICAL INFORMATION

Uses

Rifampicin is a component of all chemotherapeutic regimens currently recommended by WHO against mycobacterial infections (tuberculosis, leprosy, Buruli ulcer).

Administration and dosage

Rifampicin should be taken at least 30 min before a meal, as absorption is reduced when it is taken with food. This may not, however, be clinically significant, and food can reduce intolerance to drugs. Rifampicin is also available for intravenous administration for critically ill patients

Adults: 10 mg/kg body weight (8–12 mg/kg) daily or 3 times weekly, maximum 600 mg

Contraindications

Known hypersensitivity to rifamycins and active, unstable hepatic disease (with jaundice) (3).

Precautions

Serious immunological reactions resulting in renal impairment, haemolysis or thrombocytopenia have been recorded in patients who take rifampicin after a prolonged lapse of treatment. In this rare situation, rifampicin should be immediately and permanently withdrawn. Clinical monitoring (and liver function tests, if possible) should be performed during treatment of all patients with pre-existing liver disease, who are at increased risk for further liver damage. Patients should be

warned that treatment may cause reddish coloration of all body secretions (urine, tears, saliva, sweat, semen and sputum), and that contact lenses and clothing may be irreversibly stained.

Use in pregnancy

Vitamin K should be administered at birth to the infant of a mother taking rifampicin because of the risk for postnatal haemorrhage.

Adverse effects

Rifampicin is well tolerated by most patients at currently recommended doses but may cause gastrointestinal reactions (abdominal pain, nausea, vomiting) and pruritus with or without rash. Other adverse effects (fever, influenza-like syndrome and thrombocytopenia) are more likely to occur with intermittent administration. Exfoliative dermatitis is more frequent in HIV-positive tuberculosis patients. Temporary oliguria, dyspnoea and haemolytic anaemia have also been reported in patients taking the drug three times weekly; these reactions usually subside if the regimen is changed to daily dosage.

Moderate rises in serum concentrations of bilirubin and transaminases, which are common at the outset of treatment, are often transient and without clinical significance. Dose-related hepatitis can occur and is potentially fatal; it is therefore important not to exceed the maximum recommended daily dose of 600 mg.

Drug interactions

Rifampicin induces hepatic enzymes, and may increase the dosage requirements of drugs metabolized in the liver , including:

- anti-infective agents, including certain antiretroviral drugs (3), mefloquine, azole antifungal agents, clarithromycin, erythromycin, doxycycline, atovaquone, chloramphenicol;
- hormone therapy, including ethinyloestradiol, norethindrone, tamoxifen, laevothyroxine;
- methadone;
- warfarin;
- cyclosporine;
- corticosteroids;
- anticonvulsants (including phenytoin);
- cardiovascular agents, including digoxin (in patients with renal insufficiency), digitoxin, verapamil, nifedipine, diltiazem, propranolol, metoprorol, enalapril, losartan, quinidine, mexiletine, tocainide, propafenone;
- theophylline;
- sulfonylurea hypoglycaemic agents;
- hypolipidaemic agents, including simvastatin and fluvastatin; and
- nortriptyline, haloperidol, quetiapine, benzodiazepines (including diazepam, triazolam), zolpidem, buspirone.

As rifampicin reduces the effectiveness of oral contraceptives, women should be advised to choose between one of two options for contraception: After consultation with a clinician, the patient may use an oral contraceptive pill containing a higher dose of oestrogen (50 µg); alternatively, a nonhormonal method of contraception may be used throughout rifampicin treatment and for at least 1 month subsequently.

Current antiretroviral drugs (non-nucleoside reverse transcriptase inhibitors and protease inhibitors) interact with rifampicin, which may reduce the effectiveness of the antiretroviral drugs, cause treatment of tuberculosis to be ineffective or increase risk of drug toxicity.

Biliary excretion of radiocontrast media and sulfobromophthalein sodium may be reduced and microbiological assays for folic acid and vitamin B12 disturbed.

Overdosage

Gastric lavage may be of value if undertaken within a few hours of ingestion. Very large doses of rifampicin may depress central nervous function. There is no specific antidote, and treatment is supportive.

Storage

Capsules and tablets should be kept in tightly closed containers, protected from light.

STREPTOMYCIN (2)

GENERAL INFORMATION

Group: antimycobacterial agent

Injection (powder for solution): 1 g (as sulfate) in vial

Streptomycin is not absorbed from the gastrointestinal tract, but, after intramuscular administration, it diffuses readily into the extracellular component of most body tissues and attains bactericidal concentrations, particularly in tuberculous cavities. Little normally enters the cerebrospinal fluid, although penetration increases when the meninges are inflamed. The plasma half-life, which is normally 2–3 h, is considerably extended in the newborn, the elderly and patients with severe renal impairment. Streptomycin is excreted unchanged in the urine.

CLINICAL INFORMATION

Uses

Streptomycin is a component of several chemotherapeutic regimens currently recommended by WHO against tuberculosis. It is an aminoglycoside antibiotic derived from Streptomyces griseus used in the treatment of tuberculosis and sensitive Gram-negative infections.

Administration and dosage

Streptomycin must be administered by deep intramuscular injection. Syringes and needles should be adequately sterilized to exclude any risk of transmitting viral pathogens. It is also available for intravenous administration

Adults: 15 mg/kg body weight (12–18 mg/kg) daily or two or three times weekly; maximum daily dose is 1000 mg.

Patients aged over 60 years may not tolerate more than 500–750 mg daily, so some guidelines recommend reducing the dose to 10 mg/kg per day for patients in this age group. Patients weighing less than 50 kg may not tolerate doses above 500–750 mg daily.

Contraindications

Known hypersensitivity; auditory nerve impairment; myasthenia gravis; pregnancy.

Precautions

Hypersensitivity reactions are rare. If they do occur (usually during the first weeks of treatment), streptomycin should be withdrawn immediately. Once fever and skin rash have resolved, desensitization may be attempted.

Both the elderly and patients with renal impairment are vulnerable to dose-related toxic effects resulting from accumulation. Streptomycin should be used with caution in patients with renal insufficiency, because of the increased risks for nephrotoxicity and ototoxicity. The dose should be maintained at 12-15 mg/kg but at a reduced frequency of two to three times per week (4). When possible, serum levels should be monitored periodically and the dosage adjusted appropriately to ensure that plasma concentrations, measured when the next dose is due, do not exceed 4 µg/ml.

Protective gloves should be worn when injecting streptomycin, to avoid sensitization dermatitis.

Use in pregnancy

Streptomycin should not be used in pregnancy: it crosses the placenta and can cause auditory nerve impairment and nephrotoxicity in the fetus. Pregnancy should be ruled out before antibiotic treatment is started for women of reproductive age.

Adverse effects

Streptomycin injections are painful. Rash, induration or sterile abscesses can form at injection sites. Numbness and tingling around the mouth occur immediately after injection. Cutaneous hypersensitivity reactions can occur.

Impairment of vestibular function is uncommon with currently recommended doses. Hearing loss is less common than vertigo. Manifestations of damage to the eighth cranial (auditory) nerve include ringing in the ears, ataxia, vertigo and deafness; damage usually occurs during the first 2 months of treatment but is reversible if the dosage is reduced or the drug is stopped .

Streptomycin is less nephrotoxic than other aminoglycoside antibiotics. If urinary output falls, albuminuria occurs or tubular casts are detected in the urine, streptomycin should be stopped and renal function should be evaluated. Haemolytic anaemia, aplastic anaemia, agranulocytosis, thrombocytopenia and lupoid reactions are rare adverse effects.

Drug interactions

Other ototoxic or nephrotoxic drugs should not be administered to patients receiving streptomycin. These include other aminoglycoside antibiotics, amphotericin B, cefalosporins, etacrynic acid, cyclosporin, cisplatin, furosemide and vancomycin. Streptomycin may potentiate the effect of neuromuscular blocking agents administered during anaesthesia.

Overdosage

Haemodialysis can be beneficial. There is no specific antidote, and treatment is supportive.

Storage

Solutions retain their potency for 48 h after reconstitution at room temperature and for up to 14 days when refrigerated. Powder for injection should be stored in tightly closed containers, protected from light.

CLARITHROMYCIN (3)

GENERAL INFORMATION

Group: Macrolide antibiotic

Capsule or tablet: 500 mg immediate-release tablets or 500 mg extended-release capsules

Clarithromycin is a macrolide antibiotic that acts by binding to subunit 50S of the bacterial ribosome and thus inhibiting the translation of bacterial peptides. Clarithromycin has a fairly rapid first-pass hepatic metabolism, where it is converted to 14-OH clarithromycin. The 14-hydroxy metabolite is much less active against ***M. ulcerans*** than the parent compound, and co-administration with rifampicin increased the conversion to 14-OH clarithromycin, while blood concentrations of rifampicin are slightly increased. The half-life is 7 h for 14-OH clarithromycin and 5 h for clarithromycin. The main routes of elimination of clarithromycin and its metabolites are urinary and biliary excretion. Of all the drugs in its class, clarithromycin and its metabolites have the best bioavailability (50%), so that they can be taken orally.

CLINICAL INFORMATION

Uses

Clarithromycin is a commonly used antibiotic for the treatment of community acquired infections in adults and children. It is also used to treat mycobacterial infections.

Administration and dosage

Adults: immediate-release tablets, 7.5 mg/kg twice daily; extended-release capsules, 15 mg/kg once daily.

Children < 20 kg body weight: immediate-release tablets or paediatric suspension, 7.5 mg/kg once or twice daily.

Contraindications

Known hypersensitivity to macrolide antibiotics. Caution should be used for patients predisposed to QT interval prolongation or severe hepatic or renal dysfunction.

Use in pregnancy

Clarithromycin should not be used in pregnant women except under clinical circumstances in which no alternative therapy is appropriate.

Side-effects

Mild gastrointestinal intolerance is common, with nausea, diarrhoea, vomiting or abdominal discomfort. Less common side-effects include headaches, extreme irritability, dizziness, motion sickness, rashes, facial swelling, altered senses of smell and taste; it may aggravate or cause QTc prolongation.

MOXIFLOXACIN (4)

GENERAL INFORMATION

Group: Fourth-generation fluoroquinolone antibiotic

Capsule or tablet: 400 mg

Moxifloxacin, a synthetic fourth-generation fluoroquinolone antibiotic, is bactericidal against an extensive range of Gram-positive, Gram-negative, atypical and anaerobic pathogens. In vitro, it inhibits both type II topoisomerases (DNA gyrase and topoisomerase IV), which are required for DNA replication, transcription and repair. Moxifloxacin shows a concentration-dependent killing rate. Unlike other fluoroquinolones, it contains a methoxy-group at the C8 position, which lowers selection of resistant mutants of Gram-positive bacteria. Specific point mutations on the bacteria can alter enzymatic sites and reduce the binding of antimicrobial agents, but resistance to moxifloxacin requires multiple mutations and therefore develops less rapidly.

CLINICAL INFORMATION

Uses

Moxifloxacin is used to treat a variety of bacterial infections, including tuberculosis.

Administration and dosage

The recommended dose is 400 mg once daily for all indications. No dosage adjustments are necessary by gender, for elderly populations, adults with low body weight, mild or moderate hepatic insufficiency (Child Pugh Class A and B), renal impairment or patients on chronic dialysis.

Moxifloxacin tablets should be swallowed whole with adequate liquid and can be given with or without food. Antacids, antiretroviral drugs and other preparations containing magnesium, aluminium, sucralfate, iron or zinc should be taken 4 h before or 2 h after a moxifloxacin dose.

Contraindications

Below 18 years of age; pregnant or lactating; known hypersensitivity to moxifloxacin, other quinolones or any of the excipients; severe hepatic insufficiency (Child Pugh Class C).

Precautions

Changes in cardiac electrophysiology (QT prolongation) have been recorded. Avoid use in patients known to have a prolonged QT interval, uncorrected hypokalaemia or receiving class IA or III antiarrhythmic agents. Use with caution for patients receiving drugs that prolong the QT interval or with liver cirrhosis, proarrhythmic conditions, central nervous system disorders or myasthenia gravis.

Cases of fulminant hepatitis have been reported. Patients should be advised to contact their doctor immediately before continuing treatment if symptoms of liver failure occur. Cases of bullous skin reactions (Stevens-Johnson syndrome, toxic epidermal necrolysis) have also been reported. Patients should be advised to contact their doctor immediately before continuing treatment if skin or mucosal reactions occur. Patients should be warned that tendon inflammation and rupture may occur, especially in the elderly. There is also a risk for photosensitivity.

Drug interactions

Concomitant ingestion of moxifloxacin with antacids, minerals and multi-vitamins may reduce absorption. Cases of increased anticoagulant activity have been reported in patients receiving these drugs. Careful monitoring should be conducted and, if necessary, the anticoagulant dosage adjusted.

Side-effects

Common (1–3%) side-effects include mycotic superinfections, headache, dizziness, QT prolongation in patients with hypokalaemia, nausea (< 10%), vomiting, gastrointestinal and abdominal pains, diarrhoea (< 10%), increased levels of transaminases, photosensitivity, tendonitis and injection-site reactions.

Rare but potentially life-threatening adverse reactions reported include hypersensitivity reactions, disturbed coordination, cardiac arrest (in patients with severe underlying proarrhythmic conditions), antibiotic-associated colitis, fulminant hepatitis potentially leading to liver failure and bullous skin reactions.

Overdosage

There is no specific antidote, and treatment is supportive. The stomach should be emptied and adequate hydration maintained. Electrocardiograph monitoring is recommended because of possible QT interval prolongation. Administration of activated charcoal may prevent an excessive increase in systemic exposure to moxifloxacin. Adverse clinical signs included central nervous system and gastrointestinal effects, such as decreased activity, somnolence, tremor, convulsions, vomiting and diarrhoea.

Storage

Store tablets at 25 °C, with excursions permitted to 15–30 °C. Avoid high humidity.

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ANNEX 2: TREATMENT CARDS FOR INPATIENT AND OUTPATIENT USE

Antibiotic treatment for *M. ulcerans* disease (Buruli ulcer)

Patient treatment card (to be kept by the patient)

Name of patient: _____; Age: _____; Sex: _____

Address (city/town/village): _____

Treatment centre: _____: Name of health worker in charge: _____

Treatment category: _____;

Antibiotics prescribed (dosage) : _____ (_____)/_____(_____)

Treatment start date (dd/mm/yyyy): _____

Date of completion of antibiotic treatment (dd/mm/yyyy): _____Date of wound healing/discharge (dd/mm/yyyy): _____

	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Status after completion of antibiotic treatment (healed/not healed)
Size of lesion, cm (length x width)									
	Day 1	Day 8	Day 15	Day 22	Day 29	Day 36	Day 43	Day 50	
	2	9	16	23	30	37	44	51	
	3	10	17	24	31	38	45	52	
	4	11	18	25	32	39	46	53	
	5	12	19	26	33	40	47	54	
	6	13	20	27	34	41	48	55	
	7	14	21	28	35	42	49	56	

ANNEX 3: BURULI ULCER CLINICAL AND TREATMENT FORM – NEW CASE (BU 01)

Buruli ulcer clinical and treatment form – new case **BU 01**

Health facility : _____
Name of health worker treating patient: _____

Date of clinical diagnosis or admission (dd/mm/yy) : ____/____/____
Date of complete healing (dd/mm/yy) : ____/____/____

Name of patient: _____ ID#: _____ __
Address (village or town) : _____ District : _____
Province/Region/State:_____ Country: _____

Age (years): _____ Sex: ☐ Male ☐ Female
Weight (kg): _____ Profession:_____

CLINICAL HISTORY AT DIAGNOSIS

Duration of illness before seeking are (weeks) : _____
Use of traditional treatment: ☐ Yes ☐ No
Limitation of movement at any joint: ☐ Yes ☐ No
Previous treatment with streptomycin: ☐ Yes (duration in days : ___) ☐ No

REFERRED BY :

☐ Self-referral ☐ Former patient
☐ Family member ☐ Schoolteacher
☐ Health worker ☐ Other (specify) :
☐ Village health worker _____

CLINICAL FORMS

☐ Nodule (N) ☐ Plaque (Q)
☐ Oedema (E) ☐ Ulcer (U)
☐ Osteomyelitis (O) ☐ Papule (P)

CATEGORIES

☐ **Category I** : A single lesion ≤ 5 cm in diameter
☐ **Category II** : A single lesion 5–15 cm in diameter
☐ **Category III** : A single lesion >15 cm in diameter, multiple lesions, lesions at critical sites, osteomyelitis

LOCATION OF LESION(S)

☐ Upper limb (UL) ☐ Abdomen (AB) ☐ Buttocks and perineum (BP)
☐ Lower limb (LL) ☐ Back (BK) ☐ Thorax (TH) ☐ Head and neck (HN)

CRITICAL SITES

☐ Eye ☐ Breast ☐ Genitalia

LABORATORY CONFIRMATION

Specimen(s) collected: ☐ **Yes** ☐ **No -** Date first specimen(s) taken: ___/___/___

Specimen(s) type(s): ☐ Swab ☐ Fine needle aspiration (FNA) ☐ Biopsy

Results				
☐ ZN :	☐ *Positive*	☐ *Negative*	☐ *Positive*	☐ *Negative*
☐ PCR :	☐ *Positive*	☐ *Negative*	☐ *Positive*	☐ *Negative*
☐ Histo :	☐ *Positive*	☐ *Negative*	☐ *Positive*	☐ *Negative*

TREATMENT TYPE (Tick all applicable): ☐ Dressings ☐ Antibiotics ☐ Surgery (date:_____/_____/____ ☐ POD (prevention of disability)

DOSAGES **Rifampicin:** _____ **(mg)** **Streptomycin :**_____ **(g)** **Other (name) :** _____ **:** _____ **(mg)**

Cross out each day (X) after administering the antibiotics ; if antibiotics are not taken, indicate with the symbol Ø

Month \ Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	Total Doses

TREATMENT OUTCOME

☐ 1a: Antibiotic treatment completed ☐ 2a: Healed without surgery ☐ 3a: Healed without limitation of movement at any joint ☐ 4: Referred for further treatment
☐ 1b: Antibiotic treatment **not** completed ☐ 2b: Healed with surgery ☐ 3b: Healed with limitation of movement at any joint ☐ 5: Lost to follow-up ☐ Died

Buruli ulcer clinical and treatment form – new case **BU 01**

DOSAGE GUIDE						
Weight of patient (kg)	Rifampicin (300 mg/tablet)		Streptomycin (1 g/2 ml)		Other: _____	
	Dose (mg)	Number of tablets	Dose (g)	Volume (ml)	Dose (mg)	Number of tablets
5 – 10	75	0.25	0.25	0.50		
11 – 20	150	0.50	0.33	0.70		
21 – 39	300	1.00	0.50	1.00		
40 – 54	450	1.50	0.75	1.50		
>54	600	2.00	1.00	2.00		
If streptomycin is contraindicated (e.g. pregnancy, previous treatment with streptomycin), please contact the national programme manager or a designated referral treatment centre.						

FOLLOW-UP APPOINTMENTS AFTER TREATMENT	
DATE (dd/mm/yy)	**COMMENTS**
___/___/___	
___/___/___	
___/___/___	
___/___/___	
___/___/___	
___/___/___	
___/___/___	
___/___/___	
___/___/___	
___/___/___	

ANNEX 4:
BURULI ULCER - NEW CASE REGISTER (BU 02)

BURULI ULCER - NEW CASE REGISTER (BU 02)

Month: _____ 200__

Name of health facility: _____ District: _____ Region: _____

No	Date (dd/mm/yy)	Name (first/family)	Age	Sex	Address (village/ town)	District	Patient classification		Clinical form(s)	Location of lesion(s)	Cat.*	Limitation of joint movement (Yes/No)	Specimens collected (Yes/No)	Antibiotic treatment (Yes/No)
							New	Rec.						
1														
2														
3														
4														
5														
6														
7														
8														
9														
10														
11														
12														
13														
14														
15														

***Category I**: A single lesion ≤ 5 cm in diameter; **Category II**: A single lesion 5 - 15 cm in diameter;
Category III: A single lesion >15 cm in diameter, multiple lesions, lesions at critical sites, osteomyelitis

ANNEX 5:
REQUEST FOR LABORATORY CONFIRMATION OF A BURULI ULCER CASE (BU 03)

I. GENERAL INFORMATION

Name of treatment facility:_____

Name of health worker requesting examination:_____

Name of patient: _____ ID#:_____

Age (yrs):_____ Sex: ☐ M ☐ F

Address (village or town): _____ District: _____

Classification: ☐ New ☐ Recurrent

Clinical form: ☐ Nodule (N) ☐ Plaque (Q) ☐ Oedema (E) ☐ Ulcer (U) ☐ Osteomyelitis (O)

Date of specimen collection (dd/mm/yy): ___/___/___

Type of specimen: ☐ Swab ☐ Fine needle aspiration (FNA) ☐ Biopsy

II. REASONS FOR REQUESTING LABORATORY CONFIRMATION

Type of examination(s)	☐ ZN	☐ PCR	☐ Culture	☐ Histopathology

Reasons

☐ Diagnosis of a new case

☐ *Follow-up of a patient during antibiotic treatment (weeks of antibiotic treatment: _____)

☐ Diagnosis of a recurrent case (end of last antibiotic treatment (date or month: _____)

☐ Follow-up of a patient after antibiotic treatment

III. RESULTS

	ZN	PCR	Culture	Histopathology
Date (dd/mm/yy): ___/___/___				
Date (dd/mm/yy): ___/___/___				

Comments:_____

_____

Name of laboratory scientist providing the results:_____

Name of laboratory:_____

Date:_____

* May include patients who do not respond to treatment as expected

ANNEX 6:
FOLLOW-UP FORM AFTER ANTIBIOTIC TREATMENT

	Patient visit after completion of antibiotic treatment										
Month	1st	2nd	3rd	4th	5th	6th	7th	8th	9th	10th
	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No
Date	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__
Wound healed										
Scar										
Contracture										
Deformity										
Any other complication										
Photographs taken										

This form can be printed on the back of the patient treatment card.