

*Provisional guidance on the role of
specific antibiotics in the management of*

***Mycobacterium ulcerans* disease (Buruli ulcer)**



World Health
Organization

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Preface

Recent research and clinical experience have shown that a combination of rifampicin and an aminoglycoside (streptomycin or amikacin¹) given for 4–12 weeks with or without surgery is promising in the management of *Mycobacterium ulcerans* disease (Buruli ulcer). While the medical community awaits the results of further drug treatment trials, current and future patients may benefit from the knowledge gained to date.

This document is based on available information and expert opinion, to help health workers in affected areas to better manage patients with *M. ulcerans* disease. The implementation of this guidance will require considerable clinical judgement and close monitoring of patients to ensure the best possible treatment outcome.

¹ Because of the cost, it is recommended that amikacin should not be used in places where streptomycin is available, particularly in endemic developing countries.

1. Background

Buruli ulcer, a disease caused by *Mycobacterium ulcerans*, is largely a problem of the poor in remote rural areas and, since 1980 has emerged as an important cause of human suffering. After tuberculosis (TB) and leprosy, Buruli ulcer is the third most common mycobacterial disease. In May 2004, the Fifty-seventh World Health Assembly adopted a resolution on Buruli ulcer which called for intensified research to develop tools to diagnose, treat and prevent the disease (1).

MacCallum et al. were the first to describe *M. ulcerans* in Australia in 1948 (2). The term Buruli ulcer came from Buruli county in Uganda where large numbers of cases were described in the 1960s (3). The condition has been reported or suspected in more than 30 countries worldwide, mainly in tropical and subtropical regions, and the numbers of reported cases are growing. Africa is the worst affected region (4). Other important foci are in Australia (5, 6), French Guiana (7) and Papua New Guinea (8, 9).

More than 50% of those affected are children under the age of 15 years who live in remote rural areas and have little or no access to health services (10, 11). About 90% of patients in Africa present too late, with extensive lesions that cause severe disabilities (12). Mortality is low but disability is high: a recent study estimated that 66% of those with healed lesions have disabilities (13). The median age of this group was 12 years.

Until recently, surgery often involving extensive excision, with or without skin grafting, was the only available treatment. However, because of inadequate surgical capacities in most affected areas of endemic developing countries, access to

surgery has been very limited; moreover, where such capacities are available, the cost of surgery is far beyond the means of most of those severely affected (10). In addition, because of the need for prolonged hospitalization – averaging at least three months – limited bed capacity in hospitals where surgical treatment is possible further reduces the number of patients who can be admitted and treated. Recurrence rates after surgical treatment are variable and depend upon the experience of the doctor and the severity of the disease. In a one-year follow-up after excision of small early lesions in the Amansie West district of Ghana, Amofah et al. (14) estimated a 16% recurrence rate. Others have reported recurrence rates of 28%, mainly among late severe cases (11, 15).

Recurrences cause additional human suffering, inflate treatment costs and often frustrate successful management of the disease (16). In view of these difficulties, the need to develop drug treatment has been one of the major research priorities of the World Health Organization (WHO) since the establishment of the Buruli Ulcer Initiative in 1998 (17, 18).

2. Growing evidence on the role of specific antibiotics

Data presented at the 6th WHO Advisory Meeting on Buruli Ulcer, 10–13 March 2003, at WHO headquarters in Geneva, Switzerland (19, 20), indicated that encouraging results had been obtained with the use of a combination of rifampicin and an aminoglycoside (streptomycin or amikacin²) for the treatment of small early *M. ulcerans* lesions.

The key findings were:

- *M. ulcerans* could not be cultured from small early lesions after treatment for 4, 8 or 12 weeks;
- treatment with antibiotics for 2 weeks was insufficient as *M. ulcerans* was cultured from excised tissue specimens after 2 weeks' treatment;
- prior antibiotic treatment reduced the surface area of most lesions by more than 50%, allowing less-extensive excision;
- none of the lesions became worse while patients received antibiotic treatment, and there were no reported side-effects and no recurrences.

Further data were presented at the 7th WHO Advisory Group Meeting on Buruli Ulcer, 8–11 March 2004, at WHO headquarters in Geneva, Switzerland (21, 22). In a study in Benin, 88 patients were treated with a combination of rifampicin and streptomycin for a period of 4–8 weeks. In Ghana, a pilot study was conducted on 10 patients with oedematous lesions (the most aggressive form of the disease) for 2–8 weeks before surgery.

² See footnote 1.

Two main findings emerged out of the two studies:

- the lesions of about half of the patients in Benin were healed without the need for surgery and there were no deformities;
- for those who required surgery (including patients with oedematous forms), only limited excision was needed.

The Benin study also showed that patients can be treated on an ambulatory basis under direct supervision once a firm diagnosis has been made by an experienced health worker (in this case, a clinician). This ambulatory antimicrobial treatment was even possible for patients who needed surgery later.

If these results can be confirmed, detection of small early lesions and treatment with antibiotics will have a considerable impact on the control of the disease and more people will have access to effective treatment. It is also extremely important to determine the duration of antibiotic therapy necessary to achieve maximum benefit in treating the various forms of *M. ulcerans* disease.

At the International Training Workshop on the Management of Buruli Ulcer held in Yaoundé, Cameroon from 19 to 23 July 2004, participants unanimously agreed to use a combination of rifampicin and an aminoglycoside (streptomycin or amikacin) in the management of the disease, based on this provisional guidance (23).

3. Purpose of this document

While the medical community awaits the results of further drug treatment trials, patients may benefit from the knowledge gained to date. This provisional guidance is intended to help health workers in endemic areas to provide better management of *M. ulcerans* disease.

4. Important notes for health workers

- Because of the nature of the pathology of the *M. ulcerans* disease – necrosis of skin and subcutaneous tissue – surgery will be required in some cases for excision of necrotic tissue and/or skin grafting.
- To speed up healing, dead tissue should be conservatively removed. This should not be delayed because of antibiotic treatment.
- Simple debridement should be performed whenever wounds are dressed. This is painless if it does not involve live tissue. Radical debridement requires anaesthesia and is usually performed in an operating theatre.
- Any patient with **strongly suspected *M. ulcerans* disease** should be treated with the recommended combination of rifampicin and an aminoglycoside (usually streptomycin) under **direct observation** for 8 weeks (see Table 1 and Section 8).
- The two antibiotics should **always be given in combination** to prevent selection of drug-resistant mutants. Other drug

combinations are not recommended at this stage because of lack of supportive data from animal and human studies.

- For ulcers which are responding well to antibiotic therapy, perform the usual dressing and debridement during and after stopping antibiotics, and continue dressing the wound until healing is complete.
- If surgery is performed, both antibiotics should be administered about one hour before the surgical procedure to provide the best possible perioperative antibiotics coverage.
- If deemed clinically necessary, monitor patients regularly for any adverse effects (hearing, and renal- and liver-function tests).
- Other lines of management include specific or broad-spectrum antibiotics for secondary bacterial infection, physiotherapy and splints, and appropriate referrals for specialist treatment.

5. Case definitions³

5.1 Non-ulcerative forms

- **Papule**

A painless, raised skin lesion, less than 1 cm in diameter. The surrounding skin is reddened. Papules are commonly seen in Australia.

- **Nodule**

A lesion that extends from the skin into the subcutaneous tissue and is 1–2 cm in diameter. It is usually painless but may be itchy, and the surrounding skin may be discoloured compared with adjacent areas. Nodules are commonly seen in Africa.

- **Plaque**

A firm, painless, elevated, well-demarcated lesion more than 2 cm in diameter with irregular edges. The skin over the lesion is often reddened or otherwise discoloured.

- **Oedematous form**

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. There may be colour changes over the affected area and the disease may be accompanied by fever.

³ Source: (24).

5.2 *Ulcerative forms*

When fully developed, the ulcer has undermined edges and is indurated peripherally. The floor of the ulcer may have a white, cotton wool-like appearance due to necrotic slough. The ulcer is usually painless unless there is secondary bacterial infection. When there is more than one ulcer and the ulcers are close together, they often communicate beneath intact skin.

5.3 *Disseminated or mixed forms*

Simultaneous presence of different forms of the disease including bone and joint involvement in the same patient.

5.4 *New case*

A new case is defined as a patient with no previous history of or treatment for *M. ulcerans* disease.

5.5 *Recurrent case*

A patient with previous surgical (and/or antibiotic) treatment for *M. ulcerans* who presents with another lesion or lesions at the same or different site within one year of the end of the last treatment.

6. When to suspect *M. ulcerans* disease

In a known endemic area, an experienced health worker can usually diagnose *M. ulcerans* disease on clinical grounds. The following clinico-epidemiological features are important diagnostic clues:

- most patients live in or have travelled to a known endemic area;
- most patients are children under 15 years of age;
- about 85% of lesions are on the limbs;
- lower-limb lesions are twice as common as upper-limb lesions;
- non-ulcerative lesions are almost painless or minimally painful (although ulcers may be painful in the presence of secondary bacterial infection);
- in the absence of secondary bacterial infections or other coinfections in ulcerative lesions, there are often no constitutional symptoms (such as fever);
- enlarged lymph nodes are not a feature of *M. ulcerans* disease.

7. Antibiotics administration and dosages

Usual doses are:

- rifampicin, 10 mg/kg body weight by mouth **daily** for 8 weeks;
- streptomycin, 15 mg/kg body weight by intramuscular injection **daily** for 8 weeks.

Further details are given in Table 1 and Annex 1.

Table 1: Rifampicin and streptomycin dosage according to patient body weight^a

Weight of patient (kg)	Rifampicin (300 mg/tablet) ^b		Streptomycin ^c (1 g/2 ml)	
	Dose (mg)	No. of tablets	Dose (g)	Volume (ml)
5–10	75	0.25	0.25	0.50
11–20	150	0.50	0.33	0.70
21–30	300	1.00	0.50	1.00
31–39	300	1.00	0.50	1.00
40–54	450	1.50	0.75	1.50
>54	600	2.00	1.00	2.00

^a Adapted from (25).

^b Syrup form may be used for children.

^c Contraindicated during pregnancy.

¹ Source: (24).

8. Treatment

For the purposes of this guidance, patients are divided into three categories of treatment according to the size of the lesion and other complications (see Table 2). Although the optimal duration of therapy is yet to be determined, based on available data, antibiotic treatment is recommended for 8 weeks. If a lesion deteriorates (enlarges) during antibiotic treatment, review the initial clinical diagnosis. The lesion should be excised and tissue samples sent for histological diagnosis if possible. If a patient develops adverse effects (see Table 3), review antibiotic treatment. If surgery is combined with antibiotic therapy, the aim is to use minimal surgery to excise necrotic tissue when antibiotics have arrested progress of the disease. The timing of these tissue-conserving interventions is at the discretion of the health worker (in this case, a clinician). Small early lesions are a special case when there are facilities to excise the whole lesion immediately. If small early lesions are immediately excised, it is not known for how long antibiotics need to be administered after surgery in order to prevent recurrence, but 4 weeks is recommended currently.

Note. The three categories of treatment are only guidance for management and do not cover every clinical presentation. Therefore clinical judgment will be needed for other presentations and their treatment options. For example, ulcerative plaque or oedematous forms, irrespective of the size of the ulcer, should be treated as in category II, i.e. at least 4 weeks of antibiotics before and after surgery (total duration 8 weeks) with the aim of reducing the extent of excision. Bone and joint involvement should be given priority over other forms of the disease. For cosmetic reasons, lesions on the face should be treated sufficiently with antibiotics before any surgical intervention is attempted.

Table 2: Categories and aims of treatment, level of health-care system and diagnosis required

Cat.	Form of disease	Treatment	Primary aim	Secondary aim	Level of health-care system	Diagnosis
I	Small early lesions (e.g. nodules/papules/plaques & ulcers less than 5 cm in diameter)	For papules & nodules, if immediate excision & suturing is possible, start antibiotics at least 24 hours before surgery & continue for a total of 4 weeks Otherwise treat all lesions in this category with antibiotics for 8 weeks	Cure without surgery except for simple removal of dead tissue	Reduce/prevent recurrence	Community, health centres & district hospitals (see Section 13.6)	Strong clinical diagnosis & laboratory
II	Non-ulcerative & ulcerative plaque & oedematous forms Large ulcerative lesions more than 5 cm in diameter Lesions in the head & neck region particularly face	Treat with antibiotics for at least 4 weeks, then surgery (if necessary), followed by another 4 weeks of antibiotics	Reduce the extent of surgical excision	Reduce/prevent recurrence	District & tertiary hospitals (see Section 13.6)	Strong clinical diagnosis & laboratory
III	Disseminated/mixed forms such as osteitis, osteomyelitis, joint involvement	Treat for at least 1 week before surgery & continue for a total of 8 weeks	Reduce <i>M. ulcerans</i> infection & dissemination before and after surgery	Reduce/prevent recurrence Reduce the extent of surgical excision	District & tertiary hospitals	Strong clinical diagnosis & laboratory

Table 3: Symptom-based approach to identifying and managing the side-effects of rifampicin and streptomycin treatment^{a, b}

Common side-effects	Drug probably responsible	Management
Anorexia, nausea, abdominal pains	Rifampicin	Continue treatment, give drugs with small meals or at night before going to bed
Jaundice and hepatitis (with other causes excluded)	Rifampicin	Stop treatment
Shock, purpura, acute renal failure ^c	Rifampicin	Stop treatment
Hearing impairment (with absence of wax confirmed by auroscopy)	Streptomycin	Stop treatment
Dizziness with vertigo and nystagmus	Streptomycin	Stop treatment

^a Source: (25).

^b It must be emphasized that evidence from studies suggests that side-effects are rare. However, close monitoring of patients and strict observation of this guidance are necessary.

^c These side-effects occur principally when rifampicin intake is intermittent and dose exceeds 10 mg/kg.

9. Documenting *M. ulcerans* disease and monitoring response during and after treatment

The forms for recording treatment and follow-up can be found in Annexes 2–4.

9.1 *New cases*

Role of the health worker

Health workers who prescribe the antibiotic combination for the management of *M. ulcerans* disease should carefully document all clinical decisions, procedures, clinical improvement and any adverse effects.

Role of the laboratory

Depending on the laboratory facilities available in the particular area or country, any of the following or a combination may be used:

- direct smear examination,
- culture,
- polymerase chain reaction (PCR),
- histopathology.

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. Specimens (swabs or tissue fragments) should also be taken at the end of antibiotic treatment (if the lesion has not healed or surgery is indicated) to analyse the response to the treatment.

For non-ulcerative lesions, before the start of antibiotic treatment, a small punch biopsy (3 mm diameter) should be taken if possible from the estimated centre of the lesion for microbiological (direct smear examination, culture and PCR) and histopathological analyses. During or at the end of antibiotic treatment, if surgery becomes necessary, specimens should again be taken for laboratory analyses.

Measurements

Where possible and practical, documentation of the response to treatment should include serial tracing of lesions and measurement of the size of lesions at regular intervals, possibly weekly. For oedematous lesions, the circumference of the limb should be measured at three fixed points at weekly intervals. For purposes of comparison, measure the unaffected limb at the same points at the start of and throughout the treatment.

Photography

Photography is a powerful and convincing way of recording the disease and the results of antibiotic and surgical treatments. For oedematous lesions on the limbs, the photographs should be taken in a position so that the affected and the unaffected limbs can be compared. For all forms of the disease, it is also important that consecutive photographs should be taken from an equidistant position to permit reasonable comparison.

9.2 Recurrent cases

These should be noted and documented in the same way as new cases.

10. Patient information and compliance

This document is not a research protocol. However, as part of good medical practice, health workers should explain treatments and all procedures to patients and/or their relatives. This will ensure that patients and their relatives understand the condition and thereby enhance compliance with treatment.

11. Follow-up after antibiotic treatment

After completing antibiotic treatment, patients 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 4 may be used to document follow-up visits.

12. Reporting of experiences

All health workers are encouraged to document their experiences so that they can be published and/or presented at meetings. Good documentation should provide sufficient information to allow a definitive policy on the use of antibiotics to be formulated.

13. Implementation of this guidance

13.1 Close collaboration with TB programmes at all levels is recommended, particularly in areas such as coordination of drug procurement, use of TB laboratory facilities and networks, and monitoring for potential antibiotic resistance.

13.2 Before implementation of this guidance, national control programmes should organize workshops to train health workers on the correct and consistent use of the guidance.

13.3 The initial implementation of this guidance should be in endemic areas where the disease may be reliably diagnosed and where treatment in accordance with the guidance should be possible. To avoid or minimize wasteful treatment of patients who do not have *M. ulcerans* disease, at least a **strong clinical diagnosis** is essential before antibiotic treatment is started.

13.4 National control programmes should ensure that the health facilities where this guidance is implemented have the following: (i) continuous uninterrupted supply of the antibiotics; (ii) the necessary recording forms (Annexes 2–4); (iii) a camera (preferably digital); and (iv) specimen containers (containing transport media for microbiological analyses and 10% formalin for histopathology analysis) for collection and timely transport of specimens to designated local laboratories or reference laboratories abroad.

13.5 National control programmes should develop simple patient treatment cards and health facility registers to support the implementation of this guidance. Examples that may be adapted to suit the needs of particular programmes are given in Annexes 2, 3 and 4.

13.6 To reduce the pressure on limited numbers of hospital beds, patients with small early lesions not needing hospitalization and those with larger lesions who are well enough to take antibiotics at home while awaiting definitive surgery 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, 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 course of antibiotic treatment or is ready for surgery.

It should be understood that compliance with the prescribed treatment (e.g. the regular daily oral intake of rifampicin at the standard dose and sterile intramuscular injections of the standard dose of streptomycin) is crucial.

13.7 If the patient is not hospitalized, it is important to ensure the appropriate dressing of ulcers.

13.8 All patients treated with antibiotics should be registered and the following information should be recorded: name, age, sex, address (city/town/village), date treatment started, date treatment ended, measurements of response to treatment (including reduction of swelling around the lesion), adverse effects and whether or not surgery was performed (see Annex 3).

14. Monitoring

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

15. Important issues to consider

15.1 What treatment should be given for recurrence?

It is assumed the initial diagnosis of *M. ulcerans* disease was correct. In the case of a recurrence at the original site when antibiotics were given for 8 weeks, if possible, samples (preferably punch biopsy) should be taken for culture before restarting rifampicin and streptomycin treatment, since some lesions may be caused by an immune response to dead organisms and they may be sterile. Antibiotics should then be administered for 4 weeks and surgery undertaken to excise the lesion at the optimum time.

If antibiotics were given for less than 8 weeks in the first course, a longer period of treatment should be considered for the recurrence, but should not exceed 12 weeks.

15.2 If severe side-effects develop with these antibiotics, what alternative antibiotics should be used?

Since, at present, there are no alternative drugs of proven value, stop treatment if severe side-effects develop, e.g. shock or jaundice resulting from rifampicin, and severe dizziness or hearing impairment resulting from streptomycin. There is an increased risk from streptomycin if the duration of treatment is more than 90 days; remember that aminoglycoside toxicity is cumulative and thus special attention should be given to patients who have previously been treated with an aminoglycoside, whichever aminoglycoside was used, the duration and reason for its use. Operate and send specimens to the

laboratory. If hearing impairment is conductive, and not sensorineural, treat the cause and continue antibiotic treatment. Good evaluation of patients is vital.

15.3 *What about streptomycin for children?*

At present, there is no alternative aminoglycoside for the treatment of *M. ulcerans* disease in children. Close clinical monitoring of adverse effects is therefore essential. Painful daily injections of streptomycin are a problem for children, so efforts should be made to give successive injections at different sites. Small-bore needle should be used.

15.4 *What about streptomycin for pregnant women?*

The use of streptomycin is contraindicated during pregnancy and surgery should therefore be the first line of treatment for pregnant women. Pregnancy should be ruled out before antibiotic treatment of women of reproductive age is started.

15.5 *What about coinfection with other mycobacteria (TB and leprosy)?*

Coinfection is uncommon, but any patient with *M. ulcerans* disease who is coinfecting with the mycobacteria causing either TB or leprosy, the standard treatment for TB or leprosy should be continued. The rifampicin and streptomycin components of the regimen should be given daily for the duration of treatment of *M. ulcerans* disease after which the standard treatment regimens for TB or leprosy should be continued.

16. Provision of antibiotics

16.1 In the initial phase of implementation of this guidance, WHO will provide the necessary antibiotics to interested endemic countries, in response to requests from national control programmes made via the WHO country offices. Governments of affected countries, nongovernmental organizations and other donors are encouraged to provide these antibiotics as well.

16.2 The request from national control programmes should contain the following information:

- estimated number of patients (adults and children) to be treated in the endemic area in a given period;
- name of the district and the hospital where drugs will be kept and administered;
- a signed commitment from the national programme, district(s) and hospital(s) to implement and monitor consistent use of this guidance.

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Annex I

Information on rifampicin, streptomycin and amikacin⁴

A1.1 Rifampicin

• General information

Group: antimycobacterial agent

Capsule or tablet: 150 mg, 300 mg

Rifampicin, a semisynthetic derivative of rifamycin obtained from *Streptomyces mediterranei*, is a complex macrocyclic antibiotic that inhibits ribonucleic acid synthesis in a broad range of microbial pathogens. Rifampicin is lipid soluble. Following oral administration, it is rapidly absorbed and distributed throughout the cellular tissues and body fluids. A single dose of 600 mg produces a peak serum concentration of about 10 µg/ml in 2–4 hours, which subsequently decays with a half-life of 2–3 hours. It is extensively recycled in the enterohepatic circulation, and metabolites formed by deacetylation in the liver are eventually excreted in the faeces. Since resistance readily develops, rifampicin must always be administered in combination with other effective antimycobacterial agents.

• Clinical information

Uses

Rifampicin is a component of all TB and leprosy chemotherapeutic regimens currently recommended by WHO.

⁴ Adapted from (25).

Administration and dosage

Rifampicin should preferably be given at least 30 minutes before meals, since absorption is reduced when it is taken with food. This may not, however, be clinically significant, and food can reduce intolerance to drugs. Adults and children: 10 mg/kg (8–12 mg/kg) daily, maximum 600 mg daily.

Contraindications

Known hypersensitivity to rifamycins. Hepatic dysfunction.

Precautions

Serious immunological reactions resulting in renal impairment, haemolysis or thrombocytopenia are on record in patients who resume taking rifampicin after a prolonged lapse of treatment. In this rare situation, it should be immediately and definitively withdrawn. Careful monitoring of liver function is required in the elderly and in patients who are alcohol dependent or have hepatic disease. Patients should be warned that treatment may produce reddish coloration of urine, tears, saliva and sputum, and that contact lenses may be irreversibly stained.

Side-effects

Rifampicin is well tolerated by most patients at currently recommended doses, although gastrointestinal intolerance can be unacceptably severe. Other adverse effects (fever, influenza-like syndrome and thrombocytopenia) are more likely to occur with intermittent administration, and skin rashes are just as likely. Moderate rises in serum concentrations of bilirubin and transaminases, which are common at the outset of treatment, are often transient and without clinical significance. However, dose-related hepatitis can occur, which is potentially fatal. It is consequently important not to exceed the maximum total daily dose of 600 mg.

Drug interactions

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

include corticosteroids, steroid contraceptives, oral hypoglycaemic agents, oral anticoagulants, phenytoin, cimetidine, cyclosporin and digitalis glycosides. Since rifampicin reduces the effectiveness of oral contraceptives, women should be advised to choose between one of the following two options for contraception. Firstly, following consultation with a clinician, the patient may use an oral contraceptive pill containing a higher dose of estrogen (50 µg). Alternatively, a non-hormonal method of contraception may be used throughout rifampicin treatment and for at least one month subsequently. 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.

A1.2 Streptomycin

• General information

Group: antimycobacterial agent

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

Streptomycin, an aminoglycoside antibiotic derived from *Streptomyces griseus*, is used in the treatment of TB and susceptible Gram-negative infections. After intramuscular

administration, streptomycin diffuses readily into the extracellular component of most body tissues. In adults, a single injection of 1 g (15 mg/kg) produces a peak serum concentration of about 30–40 µg/ml in 1–2 hours. The plasma half-life, which is normally 2–3 hours, 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 TB chemotherapeutic regimens currently recommended by WHO.

Administration and dosage

Streptomycin must be administered by deep intramuscular injection. The dose for adults and children is 15 mg/kg body weight daily. Syringes and needles should be adequately sterilized to exclude any risk of transmitting viral pathogens.

Drug interactions

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

Side-effects

Severe nausea, vomiting, dizziness, rash and fever. Loss of hearing has been reported following long-term use. Streptomycin should not be used in patients with kidney impairment because it increases the risk of severe toxic reactions. Symptoms subside and recovery is usually complete after treatment is stopped. Roaring noises or ringing in the ears are signs that

treatment with streptomycin should be stopped. Ototoxicity, deafness, vertigo or reversible nephrotoxicity may occur.

Overdosage

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

Storage

Solutions retain their potency for 48 hours 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.

A1.3 Amikacin

• General information

Amikacin is an aminoglycoside bactericidal agent, obtained from *Streptomyces*. Its bactericidal effect and adverse reactions are very similar to those of other aminoglycosides.

• Clinical information

Presentation and dosage

Amikacin is presented as a sterile white powder for intramuscular injection in sealed vials containing the equivalent of 250 mg, 500 mg or 1 g of drug. The drug should be dissolved in 2 ml of 0.9% sodium chloride or water for injection. The optimal dose is 15 mg/kg body weight, usually 750 mg to 1 g in total, given daily by deep intramuscular injection or intravenously. Rotation of injection sites avoids local discomfort.

Side-effects

Side-effects are similar to those associated with streptomycin. Ototoxicity, deafness, vertigo or reversible nephrotoxicity may occur.

Precautions

In patients with impaired renal function, the daily dosage should be reduced and/or the intervals between doses increased, to avoid accumulation of the drug. In these patients, renal function should be monitored regularly during antibiotic treatment. This drug should not be used in pregnant women except as a last resort.

Annex 2

Treatment cards for inpatient and outpatient use

Patient treatment card

Rifampicin and streptomycin (or amikacin) treatment for *M. ulcerans* disease (Buruli ulcer)

Name of patient: _____

Treatment category: _____

Address (city/town/village): _____

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

Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8
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	25	33	40	47	54
6	13	20	27	34	41	48	55
7	14	21	28	35	42	49	56

The health worker should cross out each day to indicate that the patient has taken both drugs.

Annex 4: Follow-up form after antibiotic treatment

Date _____	1st month		2nd month		3rd month		4th month		5th month		6th month		7th month		8th month		9th month		10th month		
	yes	no	yes	no	yes	no	yes	no	yes	no	yes	no	yes	no	yes	no	yes	no	yes	no	
Visit of patient																					
Scar (stable/head)																					
Deformity																					
Recurrence																					
Any other complications																					
Photographs taken																					



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