

Clinical focus

Guidelines

Treatment and prevention of *Mycobacterium ulcerans* infection (Buruli ulcer) in Australia: guideline update

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Buruli ulcer (BU) is a neglected tropical disease that is increasingly common in Australia and has become an important public health issue in rural sub-Saharan Africa in the past 30 years.¹ BU is a slowly progressive destructive infection of skin and of adipose and soft tissue caused by *Mycobacterium ulcerans*, an environmental pathogen that produces a potent toxin.² It is because of progressive destruction of subcutaneous tissue that the characteristic ulcer becomes widely undermined. BU only occurs in specific endemic areas, particularly coastal Victoria, where the disease is known locally as Bairnsdale ulcer.³ The second major Australian focus is a small region between Mossman and just beyond the Daintree River, north of Cairns, Queensland (Daintree ulcer).^{4,5} Occasional cases also occur on the Capricorn coast of southern Queensland⁶ and in the Northern Territory.⁷ Typically, 0–5 cases per year occur in the Daintree region but, in 2011–2012, there was a major outbreak, with at least 75 cases identified. In Victoria, 157 cases occurred in 2011–2012. Guidelines reflecting contemporary clinical practice in the management of BU in Australia were published in 2007.⁸ This update provides guidance on the new role of antibiotics as first-line therapy; the shortened duration of antibiotic treatment and the use of all-oral antibiotic regimens; the continued importance, timing and role of surgery; the recognition and management of paradoxical reactions during antibiotic treatment; and updates on the prevention of disease (Box).

Consensus process

An update of the 2007 consensus guidelines was undertaken by selected infectious diseases physicians, plastic surgeons and general practitioners known to have experience with BU. An initial draft document based on new evidence from recent research, randomised trials, case series and increasing clinical experience was prepared by D O'Brien and P J. This draft document was then circulated to all authors for further consultation and review. The document was then peer reviewed and endorsed by the Australasian Society for Infectious Diseases. The level of evidence throughout this document is level 4/5 (observational case series/expert opinion), except where specific references are cited.

Summary

- Guidelines reflecting contemporary clinical practice in the management of Buruli ulcer (*Mycobacterium ulcerans* infection) in Australia were published in 2007.
- Management has continued to evolve, as new evidence has become available from randomised trials, case series and increasing clinical experience with oral antibiotic therapy.
- Therefore, guidelines on the diagnosis, treatment and prevention of Buruli ulcer in Australia have been updated. They include guidance on the new role of antibiotics as first-line therapy; the shortened duration of antibiotic treatment and the use of all-oral antibiotic regimens; the continued importance, timing and role of surgery; the recognition and management of paradoxical reactions during antibiotic treatment; and updates on the prevention of disease.

Key points of previous consensus guidelines

Before 2004, the treatment of BU was based on wide surgical excision and repair, as antibiotics were believed to be ineffective. However, there were examples where relapses responded to antibiotic treatment and the risk of relapse after surgery was reduced when antibiotics were combined with surgery.⁹ Formal experiments using mouse footpad models provided a scientific basis to support this practice, initially emphasising the efficacy of rifampicin combined with streptomycin or amikacin and subsequently demonstrating the efficacy of orally active agents such as moxifloxacin or clarithromycin.^{10–12} The efficacy of rifampicin combined with streptomycin in humans was first established by a small case series of patients with early lesions in Ghana that validated the evidence from the animal models.¹³

In the first Australian guidelines,⁸ we recommended surgical excision and primary closure for BU lesions. The growing confidence in antibiotics also led us to recommend adjuvant rifampicin-based antibiotic regimens for all patients who needed grafts or in whom histological examination of resection specimens showed disease at the excision margin. We emphasised that surgical intervention could be more conservative than in the past and that deep structures involved, such as tendons or nerves, should be preserved. For severe disease, we recommended intravenous amikacin in conjunction with rifampicin, in line with

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the World Health Organization recommendation to use streptomycin with rifampicin. However, amikacin is now rarely used in Australia, due to individual cases of toxicity and excellent outcomes with all-oral regimens.^{9,14-16}

In the 2007 guidelines, we also highlighted the speed and accuracy of rapid diagnosis of BU using IS2404 polymerase chain reaction (PCR) testing¹⁷ directly from ulcer swabs, and we recommended that this be the initial diagnostic test of choice.⁸ However, for non-ulcerative or pre-ulcerative lesions (oedematous, plaques or nodules),³ swabs are not appropriate specimens, as they may produce false-negative results with this test, and fine-needle aspiration¹⁸ or punch, incisional or excisional biopsy is required to obtain tissue fluid or fresh tissue. Delays in diagnosis are associated with increased morbidity from BU. Once suspected, it is important to confirm the diagnosis within a reasonable time. In this regard, PCR testing is far superior to culture, which may take up to 12 weeks.

New information on the management of BU

Antibiotics

Prospective studies in humans have now shown clearly that treatment with antibiotics alone, without surgery, will lead to healing of BU lesions without recurrence.^{16,19-21} Regimens tested in randomised controlled trials include rifampicin for 8 weeks combined with intramuscular streptomycin for 8 weeks or for 4 weeks followed by clarithromycin for a further 4 weeks.¹⁹ A recent observational study of 30 patients in Benin reported equivalent success with an entirely oral therapy of rifampicin plus clarithromycin daily. Fifty per cent of the patients in this study did not require surgery.²² Treatment with oral rifampicin-containing antibiotic regimens alone^{14,16} or combined with surgery¹⁵ has also been used successfully in Australia. Based on this experience, both in Africa and Victoria, Australia, the majority of cases are now managed without surgery.

A combination of two antibiotics is recommended to potentially increase treatment effectiveness and reduce the risk of antibiotic resistance. Current WHO guidelines recommend combining an injectable agent (eg, streptomycin) with oral rifampicin.²³ However, published local and overseas observational data confirms that oral rifampicin-based drug combinations are effective and well tolerated^{14-16,22} when combined with a second oral agent such as clarithromycin, moxifloxacin or ciprofloxacin. The use of all-oral regimens avoids aminoglycoside toxicity⁹ and improves patient acceptance.

We recommend rifampicin-containing combination oral antibiotic therapy for 8 weeks as first-line treatment for most patients with BU. Recommended doses are rifampicin 10 mg/kg per day up to 600 mg daily, plus any of clarithromycin 7.5 mg/kg twice daily (up to 500 mg per dose), moxifloxacin 400 mg once daily (not recommended for children) or ciprofloxacin 500 mg twice daily (not recommended for children).

According to WHO guidelines,²³ based on available published evidence, clarithromycin is the preferred oral companion drug to rifampicin. Treatment-outcome data for the use of moxifloxacin is lacking, but available data show high levels of effectiveness in vitro and in mouse

Key points and recommendations for the diagnosis, treatment and prevention of *Mycobacterium ulcerans* infection (Buruli ulcer) in Australia

Diagnosis

- Diagnosis should be confirmed via nucleic acid detection by polymerase chain reaction.
- For non-ulcerative lesions (oedematous, plaques or nodules), swab specimens may produce false-negative results, and fine-needle aspirate or biopsy is required to obtain tissue fluid or fresh tissue for diagnosis.

Use of antibiotics

- Recommended for most lesions unless contraindicated, not tolerated or declined by the patient.
- The recommended antibiotic therapy is oral rifampicin combined with either clarithromycin or a fluoroquinolone (moxifloxacin or ciprofloxacin) as a second oral agent.
- Antibiotics should be administered for 8 weeks, unless the lesion involves deeper structures (eg, bone or joint) or is associated with prednisolone therapy for a severe paradoxical reaction, when it may be prolonged up to 12 weeks.
- Antibiotics should be administered for a minimum of 4 weeks before surgery aimed at definitive wound closure.
- Paradoxical reactions occur in up to 20% of patients and do not represent failure of antibiotic treatment.
- Severe paradoxical reactions may cause significant tissue necrosis, which may be managed with oral corticosteroids (prednisolone 0.5–1.0 mg/kg daily, tapered over 4–8 weeks).

Role of surgery

- As microbiological and clinical cure is achieved with antibiotic treatment, surgery is not required for cure in addition to antibiotics.
- Surgery alone is an acceptable and effective alternative if:
 - antibiotics are declined, contraindicated or not tolerated; or
 - patient preference is for wide excision and direct closure of small lesions without antibiotics.

Note that there is a risk of relapse when surgery is performed without adjuvant antibiotics. The likelihood of relapse varies with patient characteristics, the lesion site and whether the margins of excision are clear.

- In lesions with significant skin or soft-tissue necrosis, conservative surgical debridement is indicated in combination with antibiotics to remove necrotic tissue and prepare the area for skin grafting or flap closure.
- Surgery may be required to repair large defects or to hasten the closure of a wound.

Prevention

- During outbreaks, people living in endemic areas are likely to reduce their risk of exposure by wearing protective clothing, avoiding biting insects, washing areas of skin or wounds exposed to soil and using insect repellents.
- In endemic areas in south-eastern Victoria, where there is evidence supporting mosquito transmission, local authorities should consider enhanced mosquito-control strategies.

models.^{11,12} The use of ciprofloxacin is based on published in vitro evidence of its activity against *M. ulcerans*,^{24,25} and on clinical experience with its use in combination with rifampicin by clinicians from Barwon Health in Victoria.^{15,16,26} However, its use has not been studied in controlled clinical trials and it is not currently one of the oral drugs recommended by the WHO.²³

If rifampicin is contraindicated or not tolerated, we recommend clarithromycin combined with a fluoroquinolone antibiotic, based on data showing effectiveness in mouse models.¹¹ In pregnancy, the combination of rifampicin and clarithromycin is recommended.²³

As discussed in the 2007 consensus guidelines,⁸ the use of antibiotics for the treatment of *M. ulcerans* is off-label. The usual precautions should be taken whenever new drugs are prescribed, and the full product information should always be consulted. Fluoroquinolones are not generally recommended in prepubertal children, as studies in animal models have demonstrated arthropathy.²⁷ However, there is limited evidence from human studies that

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doi:10.5694/mja13.11331

short courses of ciprofloxacin may be safe in children.²⁸ Patients should be warned about the small risk of drug-related hepatitis associated with combinations that include rifampicin, and liver function should be monitored periodically. There is a small risk of tendinitis associated with quinolone use, and an alternative agent should be found if tendon stiffness develops during treatment. Because clarithromycin and fluoroquinolones can prolong the cardiac QT interval, this should be monitored by electrocardiograms at baseline and after 2 weeks of treatment, especially if these antibiotics are combined.

Lesions can be associated with significant necrosis, and healing of BU lesions is slow and known to continue for up to 12 months after completion of the recommended 8-week antibiotic regimen if skin defects are large, particularly when the diagnosis of BU has been delayed.¹⁹ Patients need to be educated that ulcers are often not healed when antibiotic therapy is ceased. Prolonged wound healing may also lead to significant expense and inconvenience from regular dressings and medical reviews, which can be disabling and may lead to time off work or school, resulting in both patient and health care provider dissatisfaction.

Surgery

While routine extensive curative surgery with wide margins is not required to sterilise infection and is now infrequently recommended, there is still a significant role for surgery in the management of BU.²⁹

Indications for surgery include:

- Debridement of necrotic tissue consistent with established surgical principles aimed at improving the rate of wound healing and preventing deformity or scarring in lesions with significant skin or soft-tissue necrosis. The extent of such surgery should be as conservative as practicable and, at times, may need to be repeated to remove newly recognised areas of necrosis or liquefied subcutaneous fat.
- When antibiotics are not tolerated, contraindicated or declined, curative excisional surgery can be attempted without antibiotics, or with a shorter duration of antibiotics in cases of intolerance. The excision should be performed with wide margins through uninvolved tissue. However, there is a risk of disease relapse, either locally or distantly, which is greater if histological margins of the excised specimen include visible bacteria or active inflammation, the patient is immunosuppressed, or the lesion had been present for ≥ 75 days before diagnosis.³⁰
- In some cases of advanced disease, surgery is required to repair large defects or to hasten the closure of a wound in order to lessen the expense and inconvenience of prolonged dressings, allow a faster return to normal daily activities, and increase patient and health care provider satisfaction with treatment. We recommend that antibiotics be given for at least 4 weeks, and generally for 8 weeks, before definitive repair to arrest disease progression and reduce inflammation. In our experience, this practice reduces the extent of the excision and often allows direct closure, although if an extensive residual skin defect remains, grafting or the use of vascularised tissue flaps may be necessary. The risk of bacteriological relapse is negligible in patients who have completed 8 weeks of antibiotics.¹⁵

- Patients with small early lesions may elect to be managed with wide curative excision and direct closure, to avoid prolonged daily antibiotic treatment and to achieve more rapid wound closure.
- Delayed scar revision may be useful to reduce deformity and morbidity from BU disease.

Paradoxical reactions

About one in five patients treated with antibiotics develop worsening of the appearance of their BU lesion due to the development of a paradoxical reaction, also known as an immune reconstitution inflammatory reaction.^{31,32} Clinically, this presents as a deterioration in the clinical appearance of the lesion after initial improvement, with increasing induration, pain, wound discharge and occasionally new ulceration. New lesions may also appear during or after the completion of antibiotic treatment, either locally or on a distant body site.^{32,33} This syndrome is often thought by clinicians to be caused by antibiotic failure and may trigger unnecessary surgical intervention or change in the antibiotic regimen. Histopathology of tissue excised from these reactions reveals an intense immune reaction, often with multinucleated giant cells, with few or sparse acid-fast bacilli visible.³⁴ The mycobacteria in the lesions appear to be non-viable and thus mycobacterial cultures are usually negative, but PCR and acid-fast bacilli staining will remain positive in the majority of cases (59% and 88% of cases, respectively).³² The pathogenesis of paradoxical reactions is thought to be explained by the reversal of intense local immunosuppression mediated by mycolactone, a potent necrotising and immunosuppressive toxin produced by viable *M. ulcerans* cells that is responsible for most of the clinical manifestations of BU.² This leads to the development of an intense immunological reaction presumably against persisting dead or viable mycobacteria. Risk factors associated with paradoxical reactions in Australian patients include oedematous BU lesions, patient's age ≥ 60 years and the use of amikacin in the initial antibiotic regimen.³²

Initial management of clinically suspected paradoxical reactions is to exclude antibiotic failure, usually due to poor adherence which should be corrected if suboptimal. Antibiotic failure can be distinguished by histopathological examination of a tissue biopsy specimen, which will show features typical of untreated BU compared with the intense local inflammation in the case of a paradoxical reaction.³⁴ However, true antibiotic failure during treatment in adherent patients is very rare in our experience. If a paradoxical reaction is considered likely, the antibiotic regimen should be continued at the same dose and duration as for mild to moderate reactions.³² For severe and destructive paradoxical reactions, we recommend oral prednisolone 0.5–1.0 mg/kg daily tapered over 4–8 weeks, and in these cases antibiotics may be extended to 12 weeks' total duration.^{35,36} Fluctuant lesions may require aspiration or drainage, and some severe reactions may need to be managed with limited surgical debridement.³²

Heat therapy

There are several unpublished anecdotal reports of success with heat therapy which was employed before the effective-

ness of antibiotics was recognised. The scientific basis for the use of heat is optimal in vitro growth of *M. ulcerans* at 28–32°C and no growth at higher temperatures. Various devices have been used including servo-controlled electric heating coils and hot-air delivery systems similar to those used to reheat patients after prolonged anaesthesia. A German group working in Cameroon has reported success using heat alone in selected cases that was delivered by low-cost and less cumbersome sodium acetate trihydrate heat blocks.³⁷ A larger prospective cohort study to validate this observation is currently underway. Adjuvant heat therapy could be considered in extensive lesions where antibiotics are not tolerated or contraindicated, and curative surgery by excision and primary closure is unlikely to produce an optimal outcome for the patient or is not possible. Data on the necessary timing and duration of heat therapy is being obtained from an observational study in Cameroon, but 4–6 hours per day for 4–8 weeks is currently recommended by Australian clinicians.

Transmission and prevention

Despite considerable efforts in Australia and elsewhere, the environmental reservoir and mode of transmission of *M. ulcerans* remain obscure, making it difficult to recommend prevention strategies. However, the geographically restricted epidemiology of *M. ulcerans* transmission is highly characteristic of BU. Risk is negligible outside endemic areas. There is no evidence that direct person-to-person transmission is an important source of new cases. In Victoria, but not elsewhere so far, there is evidence that mosquitoes and possibly other biting insects may transmit the infection.^{38–40} There is also new evidence that BU in Victoria may be a zoonosis transmitted from possums to humans by mosquitoes.⁴¹ Case-control studies performed in Victoria and Africa, respectively, have shown reduced risk in patients who reported regular use of insect repellent³⁹ or bed nets for sleeping.^{42,43} Contact with contaminated soil may also play a role. Hence, during outbreaks in Australia, use of protective clothing, avoidance of biting insects, use of insect repellents, cleaning of skin or wounds after soil exposure, and mosquito control are logical preventive strategies that should be considered by individuals and public health authorities.

Competing interests: No relevant disclosures.

Provenance: Not commissioned; externally peer reviewed.

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