Consensus recommendations for the diagnosis, treatment and control of *Mycobacterium ulcerans* infection (Bairnsdale or Buruli ulcer) in Victoria, Australia

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ABSTRACT

- *Mycobacterium ulcerans* causes slowly progressive, destructive skin and soft tissue infections, known as Bairnsdale or Buruli ulcer (BU).
- Forty-six delegates with experience in the management of BU attended a 1-day conference in Melbourne on 10 February 2006, with the aim of developing a consensus approach to the diagnosis, treatment and control of BU. An initial draft document was extended and improved during a facilitated round table discussion.
- BU is an environmental infection that occurs in specific locations. The main risk factor for infection is contact with an endemic area.
- Prompt cleaning of abrasions sustained outdoors, wearing protective clothing, and avoiding mosquito bites may reduce an individual's risk of infection.
- BU can be rapidly and accurately diagnosed by polymerase chain reaction testing of ulcer swabs or biopsies.
- Best outcomes are obtained when the diagnosis is made early. To aid early diagnosis, health authorities should keep local populations informed of new outbreaks.
- BU is best treated with surgical excision, which, if possible, should include a small rim of healthy tissue. For small lesions this may be all that is required. However, there is a role for antibiotics for more extensive disease, and their use may allow more conservative surgery.

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Bairnsdale or Buruli ulcer (BU) had been a rare disease in Victoria, but its incidence has risen markedly since 1990. Clinicians are increasingly called upon to diagnose and treat BU, but there is little information on the best approach. These guidelines reflect contemporary clinical practice in Victoria. They may not be applicable in countries with less developed health infrastructure. Existing guidelines, approved by the World Health Organization, are recommended for such areas.[1]

Consensus process

In late 2004, the Victorian Department of Human Services called for targeted research on BU. The development of consensus guidelines was one component of the successful grant application.

Plastic surgeons, general practitioners, laboratory scientists, pathologists, infectious diseases physicians and public health experts known to have experience with BU were invited to participate. Of 85 invitees, 46 attended the conference on 10 February 2006.

Before the conference, participants received a draft document written by the conference conveners. In the morning, 10 speakers reviewed the published literature and presented and discussed recent cases. In the afternoon, the draft document was systematically reviewed, extended and improved through interactive round table discussion, with the help of a professional facilitator. The next draft was circulated to all participants after the conference, and final comments and suggestions were incorporated. The penultimate document underwent peer review and was edited for publication. The level of evidence throughout this document is level 4/5 (observational case series/expert opinion), except where specific references are cited.

Epidemiology

Mycobacterium ulcerans was discovered in 1948 by Australian scientists who were investigating a cluster of patients with unusual skin ulcers in the Bairnsdale region of eastern Victoria.[2] *M. ulcerans* is related to the causative agents of tuberculosis and leprosy, but is transmitted from the environment rather than from person to person.[3] The major virulence factor is a lipid toxin, mycolactone, which causes necrosis of fat and subcutaneous tissue.[4]

M. ulcerans infection is not fatal, but can result in significant morbidity and is expensive to treat.[5,6] It has been reported in more than 30 countries, and is currently a significant public health problem in sub-Saharan Africa (Buruli ulcer).[3] In Australia, there are active foci in coastal Victoria (Bairnsdale ulcer),[7] Far North Queensland (Daintree ulcer),[8] and near Rockhampton.[9] Single cases also occur elsewhere in the Wet Tropics. The reason for this patchy distribution is unknown, but molecular typing has shown differences between strains isolated from patients in different regions.[10]

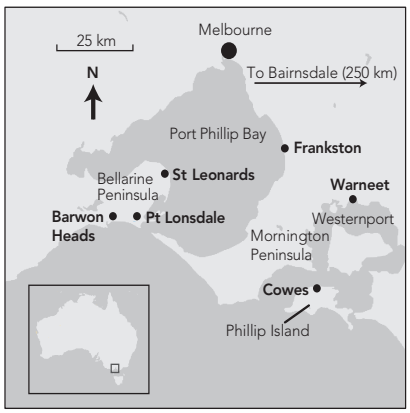
BU continues to occur in low numbers in the Bairnsdale/Gippsland Lakes area. In 1980, a new focus was noted near Tooradin and Warneet (Box 1) on Westernport,[7] and this was followed by significant outbreaks at East Cowes on Phillip Island (1992–1995),[7,11,12] Frankston and Langwarrin (1990–1998),[7] St Leonards (1998–2001), Point Lonsdale (since 2002)[13] and Barwon Heads and Ocean Grove (since 2005). There are also frequent single cases from other parts of the Mornington and Bellarine Peninsulas.

The incidence of BU in Victoria has increased sharply in recent years (Box 2). It is unlikely that this increase is due to improved diagnosis, as there has been considerable publicity since 1994, and all diagnostic polymerase chain reaction (PCR) assays have been available at a single institution since 1995.[14] BU was made formally notifiable in Victoria from January 2004. Although the incidence in Victoria is currently only 1.4 per 100 000 overall, it is estimated that up to 6% of the permanent population of East

* A group convened at the Consensus Conference, Melbourne, 10 February 2006 (see Appendix).

Cowes (1992–1995)[15] and 1% of the permanent population of Point Lonsdale have required treatment. Visitors to endemic areas are also at risk, and brief contact may be sufficient to become infected.

1 Locations of Bairnsdale ulcer activity in Victoria



Clinical features

Patients who present with BU are usually otherwise well, and may be male or female, child or adult. Most patients will be residents or visitors to a known endemic area, but isolated cases occur.

BU typically presents as a slowly progressive skin papule that undergoes necrosis and evolves to a deeply undermined ulcer. Lesions are usually painless or minimally painful. Less commonly, the initial lesion may resemble a plaque or necrotic patch of skin. Systemic symptoms (fever, malaise) are rare.

Fully developed ulcers are characteristically deeply undermined, meaning a probe can be passed easily under the edge into the space left by necrotic liquefied fat tissue. Lesions can occur anywhere and may be multiple, but a single lesion on the leg or arm is most common. Infections on the buttock, abdominal wall, ear and face have all occurred in Victoria in the past 10 years. There is also an unusual oedematous presentation that can cause extensive swelling (eg, involving most of a limb).

In patients presenting with unresolved cellulitis[8] or a suspected necrotising spider bite, BU should be considered. At present, there is no evidence connecting spider bites to *M. ulcerans*.[16]

Diagnosis

Once an ulcer is present, diagnosis is usually straightforward, provided BU is considered. Delays are most likely when patients present outside endemic areas, or when the patient has a non-ulcerative presentation (eg, nodule, papule, plaque or acute oedema).

Acid fast bacilli (AFB) smear-positive swabs or specimens from skin ulcers are strongly suggestive of *M. ulcerans* infection in patients from Victoria who have not travelled overseas.

IS*2404* PCR,[8,14,17] which can be performed directly from ulcer swabs, approaches 100% sensitivity and specificity (P D R J, J A M F, independent personal observations). Culture is also diagnostic, but generally takes several weeks. A positive *M. ulcerans* PCR result is sufficient evidence to proceed to treatment.

A negative *M. ulcerans* PCR result, when AFB are detected on the smear, is likely to indicate an alternative diagnosis.

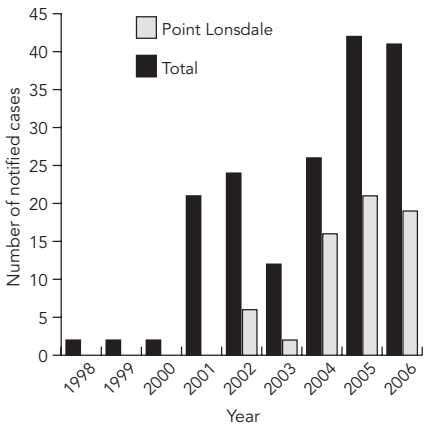
A negative AFB smear and negative *M. ulcerans* PCR result make the diagnosis of BU unlikely, but it should not be completely excluded.

If an ulcer is present, obtain samples deep to the undermined edge using two standard cotton-tipped swabs. These swabs may be dry or of the standard transport medium type (swabs stored in charcoal transport medium should be avoided). Ensure that some material is visible on each swab. The swabs (one labelled "for PCR only") should be sent to your usual pathology service for microscopy for AFB, *M. ulcerans* PCR, and culture. "Possible Bairnsdale ulcer" should be written on the clinical notes. A smear result is usually available within the same working day. Separate swabs or specimens should be obtained for other pathogens or conditions, depending on the clinical situation.

Other specimen types suitable for PCR include fresh tissue biopsies (preferably not stored in large volumes of buffer or saline, nor wrapped in gauze) and paraffin-embedded fixed tissue sections (not suitable for culture).

If an ulcer is not present but there is a suspicious plaque, necrotic patch, nodule or acute oedematous presentation in an at-risk patient, an incisional or excisional biopsy should be performed. Some patients notice an apparent increase in the rate of progression of the disease following biopsy, and this should be carefully discussed.

2 Notified cases of *Mycobacterium ulcerans* infection in Victoria since 1998



Notification was voluntary before 2004. Data for 2006 are only to August. Data are from the Victorian Department of Human Services and reference [7]. ◆

Treatment

Small lesions sometimes resolve spontaneously, but this is thought to be uncommon. The rate of progression varies among patients. Even though host immunity progressively develops during infection, ulcers may become very extensive. Relapse after treatment is not uncommon,[18] so regular follow-up is recommended.

Cure with medical therapy alone is possible, and there is increasing interest in this approach in western Africa.[1,19] However, in Victoria, where there is ready access to surgery, we believe that surgery or combined surgical and medical therapy is the most efficient way of effecting cure. The trend in management is towards conservative surgery with macroscopic removal of necrotic tissue and the use of adjuvant antibiotics. Patients may be best managed by a team, with surgeons working with infectious diseases specialists, GPs and allied health practitioners.

For difficult or recurrent disease or when antibiotics and surgery are failing, other modes of therapy, including continuous heat therapy or hyperbaric oxygen, may be considered.

Surgery

In most situations, we recommend surgery that aims to remove all necrotic tissue, but preserves any involved deep structures (eg, tendons, nerves, joint capsules, major blood vessels). If bone is involved, it should be conservatively debrided.

Where possible, remove a small buffer of normal tissue, if doing this will not unduly

3 Recommendations for oral antibiotic use in the treatment of Bairnsdale ulcer

Combination antibiotics are recommended

- For a total of 3 months when the histology of resection margins shows either necrosis or acid fast bacilli or granulomata
- *or* when the initial lesion was large enough to require grafting
- *or* for complex, recurrent disease or where surgical resection is necessarily incomplete. Consider including intravenous amikacin in this situation (see Box 4)

Recommended oral antibiotics

- Rifampicin 10 mg/kg per day up to 600 mg daily for 3 months, *plus*
- clarithromycin 500 mg twice daily for 3 months
- *or* ciprofloxacin 500–750 mg twice daily for 3 months
- *or* moxifloxacin 400 mg once daily for 3 months (not recommended for children)

Doses for children

- Rifampicin 10–20 mg/kg per day in one daily dose; not to exceed 600 mg per day
- Clarithromycin 15–30 mg/kg per day in two divided doses for children < 12 years; dose as for adults when > 12 years, not to exceed adult doses
- Ciprofloxacin 20 mg/kg per day in two divided doses, not to exceed adult doses ◆

increase the morbidity of the procedure. The skin defect should then be closed primarily, or by grafting if necessary.

An orientated resection specimen that includes the skin and subcutaneous tissue should be submitted for histopathology. There is evidence from a recent case series that AFB or granulomatous inflammation or necrosis at the margins predicts relapse and the need for antibiotic treatment.[20] If margins are clear, drug therapy is usually not necessary. However, clinicians are advised to discuss the risk of relapse versus antibiotic cost and risk of side effects to assist patients in making an informed choice. PCR testing of resection margins is not recommended.

Large lesions

While preparations are being made for surgery, combination drug therapy should be commenced (see below). If significant oedema makes it difficult or impossible to determine how much tissue is involved in the infection, preoperative antibiotic therapy (eg, for 2–4 weeks) is recommended, as this may significantly reduce the extent of the resection required.

The use of negative pressure dressings to encourage healing and reduce the area requiring grafting should be considered.

Decisions about further debridement and timing of grafts, whether immediate or delayed, should be individualised.

Heat therapy

There is anecdotal evidence that continuous warming of the affected skin at 38–39°C using one of a range of available servo-controlled devices improves outcome, particularly when lesions are extensive or relapse has occurred. The theoretical basis for this is the organism's preference for growth at 32°C and enhanced human effector cell function at 39°C.

There is a recent trend away from heat therapy because of its cumbersome nature and our increasing confidence in the effectiveness of antibiotics.

Hyperbaric oxygen

Some clinicians favour the use of hyperbaric oxygen to assist healing, and there are supportive data from a mouse model.[21] An Italian group is investigating the use of adjuvant hyperbaric oxygen for BU in Benin, but results are not yet available.

Antibiotic therapy

In the laboratory, *M. ulcerans* is susceptible to a range of antibiotics. The WHO recommends the combination of oral rifampicin and parenteral streptomycin for initial treatment.[1] The use of streptomycin (replaced by amikacin in Australia) combined with oral rifampicin is supported by animal data,[22] a published case series from western Africa,[19] and observational data presented at the annual meetings of the WHO Global Buruli Ulcer Initiative.[23] In Victoria, where many patients are elderly, clinicians have encountered problems with toxicity from amikacin (renal, balance or hearing difficulties), and may prefer less toxic oral combinations. However, there is less human evidence to support this practice, and in animal models, oral-only combinations are less effective at killing *M. ulcerans*,[24] with the possible exception of rifampicin plus moxifloxacin.[25]

Antibiotic treatment is relatively expensive, may require monitoring for toxicity, and is generally given for at least 3 months in total, with the intravenous component typically for 4 weeks. However, appropriate use of antibiotics allows more conservative surgery and reduces the risk of relapse. Box 3 presents recommendations for use of oral antibiotics, and Box 4 contains recommendations for use of intravenous amikacin.

Drug toxicity

The use of antibiotics for the treatment of *M. ulcerans* is "off label". The usual precautions should be taken whenever new drugs are prescribed. Always refer to the full product information. Ciprofloxacin is not generally recommended in prepubertal children, as studies in animal models have demonstrated arthropathy.[26] However, there is limited evidence from human studies that short

4 Recommendations for use of intravenous amikacin in the treatment of Bairnsdale ulcer

When to use intravenous amikacin (with oral rifampicin)

- Severe or extensive disease
- When deep structures (such as tendons, nerves, joint capsules, major blood vessels) that need to be preserved are involved
- Large lesions that could not be fully resected
- Major relapses
- Osteomyelitis
- When trying to avoid or minimise surgery (eg, lesions involving the eye or face)
- Initial therapy of acute oedematous disease

How to administer intravenous amikacin (in adults)

- Amikacin 15 mg/kg (ideal weight) intravenously (maximum 1000 mg) daily on 5–7 days each week for 4–8 weeks
- Monitor renal function
- Monitor hearing and vestibular function at least monthly
- Monitor trough levels once or twice weekly
- Aim for trough level < 1 mg/L. Dosing should be spaced to three times weekly if drug accumulation is detected (ie, trough levels begin to rise) or if prolonged continuation therapy is envisaged ◆

courses of ciprofloxacin may be safe in children.[27] Patients should be warned about the small risk of drug-related hepatitis associated with combinations that include rifampicin, and liver function tests 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.

Some clinicians would commence amikacin in combination with two oral antibiotics (eg, rifampicin plus moxifloxacin). The toxicity of intravenous amikacin needs to be balanced against the potential benefit, particularly in the elderly and when renal impairment is present. Patients should be warned about the risk of hearing loss and balance disturbance, and be asked to report tinnitus or hearing or balance disturbance immediately. The use of amikacin beyond 4–8 weeks is not usually recommended, but it may be given for up to 12 weeks if necessary.

Prevention of Bairnsdale ulcer

It is not understood why *M. ulcerans* outbreaks occur in new areas or why the disease has spread westwards from the original endemic area near the Gippsland Lakes. There are no public health interventions that can remove *M. ulcerans* from the environment, although there may be a natural cycle of human infection that lasts several years, after which the incidence of new cases in a given area abates. There is circumstantial evidence that nutrient enrichment of very low-lying coastal environments may be a factor in the appearance of outbreaks.[7,12,28]

M. ulcerans has been detected by PCR in plant material and mud obtained from swamps in endemic areas,[29] a golf course irrigation system that used recycled water,[28,29] and from aquatic water insects in Africa.[30] At Point Lonsdale, *M. ulcerans* has been detected by PCR in soil and leaf litter from a stormwater drainage system, mud from a lake, and about 0.5% of more than 10 000 mosquitoes trapped during 2004–2006 (unpublished data). It is yet to be determined whether mosquitoes play a role in human disease.

Studies from African endemic areas have reported that farming activities close to rivers[31] and swimming[32] may be risk factors, and that wearing trousers[31] and a shirt[33] when working outdoors appears protective. A recent case–control study performed on the Bellarine Peninsula has shown that direct exposure to the environment and to mosquitoes are risk factors, and wearing protective clothing and insect repellent appears protective (unpublished data).

Morbidity and cost can be reduced by early diagnosis. Therefore, local doctors are central to early detection. When an outbreak occurs in a new area it may take some time for this disease to be recognised, so public health authorities need to provide timely information to both clinicians and the general public about disease activity and the location of new endemic areas.

Recommendations

Personal protection

People living in endemic areas should be encouraged to wear long-sleeved shirts and trousers when outdoors and to use insect repellent to avoid insect bites. Prompt cleaning and covering of cuts and abrasions is also recommended.

Public awareness to aid diagnosis

BU is notifiable in Victoria and up-to-date figures are displayed on a publicly accessible website.[34] However, it is recommended that the exact location of cases be documented (eg, by postcode), and that clinical photographs and notes on diagnosis be made available through the site.

The Victorian Department of Human Services should consider effective ways to raise the awareness in newly endemic areas.

Planning and research

Local authorities in endemic areas should consider implementing an integrated mosquito management plan.

Significant new case clusters should be investigated in an attempt to identify a remediable point source.[12,15]

The potential implications of proposals to create new wetlands in low-lying coastal areas close to homes should be carefully considered by planning authorities.

Future research should focus on what determines why a particular area becomes endemic.

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Competing interests

None identified.

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