

Mycobacterium ulcerans infection (Buruli or Bairnsdale ulcer): challenges in developing management strategies

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Results of studies on the use of antibiotics, alone or in combination with surgery, are encouraging

Although Buruli or Bairnsdale ulcer (BU) was described in Uganda, Africa, in 1897, the causative organism, *Mycobacterium ulcerans*, was only identified in 1948, in Australia.¹ Today, the disease has been reported in over 30 countries, mainly in tropical and subtropical regions of Africa, Latin America, Asia and the western Pacific.² BU is poorly recognised within the medical community, and there is gross underreporting of cases. Australia is the only developed country that has major foci of infection, and BU is now a notifiable disease in the state of Victoria. Over the past decade, the World Health Organization has played a central role in quantifying the problem and bringing together scientists, health experts and funding organisations to increase understanding of the disease, improve management and broaden the delivery of care to patients.

There are some differences in BU as it is seen in Australia compared with Africa. Small papular lesions are often seen in Australian cases, and this may not be entirely explained by patients presenting earlier — Australian strains of *M. ulcerans* produce a slightly different form of the toxin mycolactone.³ Outbreaks of BU in Australia have tended to affect small towns, and patients are usually adults, including the elderly. In Africa, endemic areas are poor rural farming communities, and the average age of affected patients is 5–15 years.⁴ Although the mode of transmission of infection is still unknown, *M. ulcerans* has been found in environmental water and water insects, and the epidemiology in both Africa and Australia suggests that people become infected through contact with a contaminated environment rather than with infected people. Much recent research has focused on the role of mycolactone in pathogenesis, and it is clear from animal studies that most of the tissue destruction observed in human lesions is caused by diffusion of this highly toxic macrolide molecule from clusters of *M. ulcerans* organisms replicating in subcutaneous fatty tissue. This raises the possibility that killing the organism with antibiotics, or even suppressing its ability to produce toxin, may be adequate management. Traditionally, BU is managed by surgical excision of the lesion followed by primary closure or skin grafting. Until recently, antibiotics were thought to have little role in management, despite the fact that *M. ulcerans* is sensitive to a number of drugs, including rifampicin, aminoglycosides, macrolides and quinolones, in vitro.⁴ Studies have shown that a combination of rifampicin and an aminoglycoside given to mice with footpad or tail lesions both healed the lesions and prevented recurrences. The combination of rifampicin and moxifloxacin is also effective,⁵ as is rifampicin alone. However antibiotic-resistant mutant strains of *M. ulcerans* can emerge when single-drug treatment is used.⁶ Findings in animals provide no guarantee of success in humans, but it has now been shown that a combination of rifampicin and streptomycin for a minimum of 4 weeks kills *M. ulcerans* in early human lesions,⁷ and longitudinal studies of this combination of antibiotics in all forms of the disease

for 8 weeks in Benin, in western Africa, showed that 50% of lesions, including ulcers, healed without requiring surgery.⁸ Although these results are very encouraging and have led to many physicians in African countries where BU is endemic using antibiotics without recourse to surgery, there have been no controlled trials to validate the treatment. Equally, there are no controlled data on the use of antibiotics together with surgery. The rate of recurrence after surgery is dependent on the surgeon's ability to guess the extent of infection from the appearance of the lesion, and polymerase chain reaction (PCR) testing of excised tissue has shown that infection extends well beyond the visible margins of disease.⁹

In this issue of the Journal, O'Brien and colleagues report their experience of managing BU with surgery, antibiotics or a combination of the two (page 58).¹⁰ The main findings from this retrospective, purely observational study were that antibiotics appeared to reduce the recurrence rate when *M. ulcerans* was detected in the margin of the excised lesion and when the lesion was large (meaning that skin grafting was needed). The choice of antibiotics was not planned in advance, and depended on the preference of individual clinicians, but rifampicin was included in the regimen for most patients. Interestingly, the recurrence rate in this study was 10% after antibiotic treatment for up to 3 months in patients who had all had their lesions surgically excised, while the recurrence rate after therapy with rifampicin and streptomycin for 2 months in 208 patients in Benin was less than 2% with or without surgery.⁸ The Australians did not use intramuscular streptomycin in their older group of patients, and found amikacin poorly tolerated. We do not know if their favoured combination of ciprofloxacin with rifampicin adds any bacterial killing benefit, or whether this combination is sufficient to prevent resistance emerging. In the context of a disease that is mainly a problem for children in rural parts of humid tropical Africa, it is no surprise that the approach to management is different in south-eastern Australia where surgery is easily accessible. There is no doubt that more children in Africa are receiving treatment and at an earlier stage of disease now that physicians are offering antibiotic therapy. The opportunity to have lesions excised is available to relatively few of these patients, and they typically present late with large ulcers, both for economic reasons (treatment has a major impact on a family's finances) and because they fear surgery. Treating large numbers of patients in Benin and Ghana has shown that most lesions become culture-negative after treatment with rifampicin and streptomycin for 8 weeks, and they go on to heal during or after that time.⁸ The combination of two orally administered antibiotics with powerful bactericidal activity is the therapeutic goal at present, and surgical grafting should only be necessary to speed the healing of ulcers. More work is needed to develop an ideal treatment strategy, in both developing countries and more sophisticated medical settings.

The suggested guidelines for diagnosis, treatment and control of *M. ulcerans* infection in Victoria in this issue of the Journal (page 64)¹¹ mark a significant step in developing standardised protocols for local use. Although individual doctors in Australia see relatively few cases, if a standard management protocol is followed, considerable experience will be amassed, which may guide future research. It would be useful, for example, to establish whether after treatment with rifampicin and moxifloxacin for 2 weeks before surgery, the excised tissue is culture-negative and the recurrence rate lower.

Australians have made major contributions to understanding and diagnosing this disease, and another article in the Journal (page 62) highlights the role of PCR testing,¹² originally developed in Melbourne,¹³ in tracing the source of infection by means of a PCR-based DNA fingerprinting method. Several new pockets of infection have been identified worldwide in recent years, and while the causes of outbreaks remain obscure, PCR has been a key tool in tracing environmental sources of *M. ulcerans*, as well as in diagnosis, where it is not only the most sensitive method available (>90%), but also quicker than all except microscopy for acid-fast bacilli (sensitivity <50%).¹⁴ The challenges now are to make this technology accessible to African countries, and to develop simpler diagnostic tools.

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References

1 MacCallum P, Tolhurst JC, Buckle G, Sissons HA. A new *Mycobacterium* in man. I: Clinical aspects. *J Pathol Bacteriol* 1948; 60: 93-122.

- 2 Asiedu K, Scherpier R, Raviglione M. Buruli ulcer — *Mycobacterium ulcerans* infection. Geneva: World Health Organization, 2000.
- 3 Mve-Obiang A, Lee RE, Portaels F, Small PL. Heterogeneity of mycolactones produced by clinical isolates of *Mycobacterium ulcerans*: implications for virulence. *Infect Immun* 2003; 71: 774-783.
- 4 Wansbrough-Jones M, Phillips R. Buruli ulcer: emerging from obscurity [review]. *Lancet* 2006; 367: 1849-1858.
- 5 Ji B, Lefrancois S, Robert J, et al. In vitro and in vivo activities of rifampin, streptomycin, amikacin, moxifloxacin, R207910, linezolid, and PA-824 against *Mycobacterium ulcerans*. *Antimicrob Agents Chemother* 2006; 50: 1921-1926.
- 6 Marsollier L, Prevot G, Honore N, et al. Susceptibility of *Mycobacterium ulcerans* to a combination of amikacin/rifampicin. *Int J Antimicrob Agents* 2003; 22: 562-566.
- 7 Etuafu S, Carbone B, Grosset J, et al. Efficacy of the combination rifampicin-streptomycin in the treatment of early human *M. ulcerans* disease. *Antimicrob Agents Chemother* 2005; 49: 3182-3186.
- 8 Chauty A. Antibiotic treatment at Pobè Centre in Benin — update. In: World Health Organization. Abstracts (draft). Annual meeting of the WHO global Buruli ulcer initiative, 15-17 March 2006. Geneva: WHO, 2006: 54-55. http://www.who.int/buruli/information/Abstracts_Draft.pdf (accessed Nov 2006).
- 9 Rondini S, Horsfield C, Mensah-Quainoo E, et al. Contiguous spread of *Mycobacterium ulcerans* in Buruli ulcer lesions analysed by histopathology and real-time PCR quantification of mycobacterial DNA. *J Pathol* 2006; 208: 119-128.
- 10 O'Brien DP, Hughes AJ, Cheng AC, et al. Outcomes for *Mycobacterium ulcerans* infection with combined surgery and antibiotic therapy: findings from a south-eastern Australian case series. *Med J Aust* 2007; 186: 58-61.
- 11 Johnson PDR, Hayman JA, Quek TY, et al. Consensus recommendations for the diagnosis, treatment and control of *Mycobacterium ulcerans* infection (Bairnsdale or Buruli ulcer) in Victoria, Australia. *Med J Aust* 2007; 186: 64-68.
- 12 Lavender CJ, Senanayake SN, Fyfe JAM, et al. First case of *Mycobacterium ulcerans* disease (Bairnsdale or Buruli ulcer) acquired in New South Wales. *Med J Aust* 2007; 186: 62-63.
- 13 Ross BC, Marino L, Oppedisano F, et al. Development of a PCR assay for rapid diagnosis of *Mycobacterium ulcerans* infection. *J Clin Microbiol* 1997; 35: 1696-1700.
- 14 Phillips R, Horsfield C, Kuijper S, et al. Sensitivity of PCR targeting the IS2404 insertion sequence of *Mycobacterium ulcerans* in an assay using punch biopsy specimens for diagnosis of Buruli ulcer. *J Clin Microbiol* 2005; 43: 3650-3656. □