All-Oral Antibiotic Treatment for Buruli Ulcer: A Report of Four Patients

Claire L. Gordon¹, John A. Buntine²,³, John A. Hayman⁴, Caroline J. Lavender⁵, Janet A. M. Fyfe⁵, Patrick Hosking⁶, Mike Starr⁷, Paul D. R. Johnson¹,⁷,*

¹Department of Infectious Diseases, Austin Health, Melbourne, Australia, ²Department of Surgery, Box Hill Hospital, Melbourne, Australia, ³3Department of Surgery, Monash University, Melbourne, Australia, ⁴Department of Anatomy and Developmental Biology, Monash University, Melbourne, Australia, ⁵WHO Collaborating Centre for Mycobacterium ulcerans (Western Pacific Region) and Victorian Infectious Diseases Reference Laboratory, Melbourne, Australia, ⁶Department of Anatomical Pathology, Box Hill Hospital, Melbourne, Australia, ⁷Department of Infectious Diseases, Royal Children’s Hospital, Melbourne, Australia

The Cases

Buruli ulcer (BU) was treated primarily with wide surgical excision until recent studies confirmed the efficacy of oral rifampicin combined with intra-muscular streptomycin. Whether all-oral antibiotic regimens will be equally effective is unknown. This report describes four patients with Mycobacterium ulcerans infection, all of whom received rifampicin-based oral antibiotic therapy followed by surgical resection (three patients) or oral antibiotics alone (one patient). Following oral antibiotics for between 4 and 8 weeks, viable M. ulcerans was not detectable by culture in three of the patients, or by histology in a fourth patient from whom no specimen for culture was obtained. All cases spent time in a BU-endemic area in coastal Victoria, Australia. Baseline characteristics, diagnosis, treatment received, and histopathology of resected specimens are detailed in Table 1. Clinical photographs are shown in Figures 1–4. All patients gave informed consent for publication.

In all patients, the diagnosis of M. ulcerans was confirmed by positive polymerase chain reaction (PCR) and isolation of M. ulcerans by culture from swabs obtained prior to treatment. Three patients had ulcerative lesions (Table 1: cases 1, 2, and 4; Figures 1, 2, and 4) and one had a pre-ulcerative lesion (Table 1: case 3 and Figure 3) from which a saline-moistened swab of the lesion yielded a positive PCR and culture. For the two adults (Table 1: cases 1 and 2), rifampicin was combined with moxifloxacin for 6 weeks prior to resection. The two children (Table 1: cases 3 and 4) received rifampicin combined with clarithromycin for either 4 weeks prior to resection (Table 1: case 3) or 8 weeks without resection (Table 1: case 4). In cases 1 and 3, resection specimens were culture-negative, and culture was not performed in case 2, although histology showed resolving inflammation and no acid-fast bacilli (AFB) by Ziehl-Neelsen staining. In case 3, a Ziehl-Neelsen stained section showed persistent AFB but culture was negative. He had received a reduced dose of rifampicin due to gastrointestinal and neurological side effects and underwent earlier resection than planned at 4 weeks. Inflammation of surrounding skin and the size of the lesion reduced during antibiotic therapy in all four patients (Figures 1–4). PCR was not performed on surgical excision specimens (cases 1–3). Excision and primary closure, rather than grafting, was achieved in case 2 and 3. Case 4 was a 3-year-old girl who was treated with oral combination antibiotics without surgery. After 8 weeks of rifampicin and clarithromycin syrup, the ulcer had reduced to a very small palpable nodule. However, 4 weeks after ceasing antibiotic therapy the lesion became inflamed and discharged pus. Acid-fast bacilli were seen and PCR for M. ulcerans was positive. However, subsequent culture was negative at 3-months, suggesting an immune-mediated “paradoxical reaction” driven by residual but dead mycobacterial cells, rather than a true failure of oral antibiotic therapy. Following spontaneous discharge only a small blind ending sinus remained.

Discussion

BU is a slowly progressive and destructive soft tissue infection, with the potential for severe scarring and disability [1,2]. The main burden of disease occurs in sub-Saharan Africa [1], although in Australia, there are also active foci in coastal Victoria, the Daintree region in the far north, and near Rockhampton, Queensland [3–6].

Until recently, the practice of wide surgical excision followed by grafting has been the mainstay of treatment [2]. High relapse rates [7], prohibitive cost, and limited access to surgery in endemic areas in Africa led to a renewal of interest in antibiotic therapy, which had not appeared effective when first studied in field trials [8–10]. Based on promising experiments in the mouse footpad model [11–13], a small pilot study established that the combination of oral rifampicin and intramuscular (IM) streptomycin for 8 weeks was able to sterilize early BU lesions in humans. In this small study of 21 pre-ulcerative patients in Ghana, even 4 weeks of rifampicin and streptomycin led to culture negativity when lesions were surgically excised after antibiotic treatment of varying durations [16]. Based on this result, WHO introduced and promoted a new protocol of initial therapy with 8 weeks of daily oral rifampicin and IM streptomycin for all patients with BU, although it was expected that many would still require surgery [17]. Subsequently, Chauty et al. reported a case series of...
224 patients with pre-ulcerative and ulcerative BU who were treated with this regimen [18]. Of the 215 patients whose lesions healed, 47% were treated only with antibiotics and did not require surgery. Although there were no microbiological studies, recurrence of *M. ulcerans* infection occurred in only two patients treated with antibiotics alone. In a recent randomized trial of 151 patients, the majority of whom also did not have surgery, Nienhuis et al. demonstrated that oral rifampicin plus IM streptomycin for 4 weeks then oral rifampicin plus oral clarithromycin for 4 weeks was as effective as 8 weeks of oral rifampicin plus IM streptomycin [19], indicating that a shorter duration of IM streptomycin is also effective.

In Australia, surgery is widely accessible and remains the main treatment modality for BU, although often in combination with oral antibiotics. As a result, the efficacy of surgery alone compared with oral antibiotics alone is difficult to establish, although relapses may be less when both modalities are used [6,20,21]. Australian consensus guidelines [6], now 4 years old, recommend surgery alone for small lesions or surgery combined with antibiotic therapy for more extensive disease. These guidelines include the use of IV amikacin for severe disease, but in practice amikacin is rarely used due to concerns about ototoxicity. Other oral antibiotics that appear to be active against *M. ulcerans* in mice include moxifloxacin and clarithromycin [11]. Clarithromycin is preferred in children due to its established safety record. There are unpublished accounts of successful treatment of BU with oral rifampicin alone (W. Meyers, personal communication), and the first published report of successful use of oral antibiotics was of a North Queensland farmer with acute, oedematous *M. ulcerans* disease who received oral rifampicin, clarithromycin, and ethambutol for 12 weeks immediately following extensive but incomplete surgical excision [20]. The surgical resection margin showed AFB, but further biopsies taken after 3 weeks of antibiotics due to concern about relapse were smear and culture negative. In retrospect, this apparent clinical deterioration may have been a “paradoxical reaction” [22] and the case demonstrated the principle that oral antibiotics are able to prevent relapse after incomplete surgical excision, even in a severe form of BU.

In the four patients we have described here, combination oral antibiotic therapy prior to excision led to the inability to recover *M. ulcerans* by culture in the three cases from whom a second specimen was submitted for culture, confirming that oral combinations of antibiotics are capable of sterilizing lesions in humans, as Etuafal et al. demonstrated for rifampicin plus IM streptomycin. Two of the three patients we described received oral antibiotics for a total of 12 weeks. However, negative culture results at excision (4 weeks for case 3, 6 weeks for case 1)
suggest that shorter periods may be effective as suggested for the combination of rifampicin and streptomycin [16,17]. Dossou et al. also reported clinical improvement after 8 weeks of oral rifampicin and clarithromycin [23] in a pregnant patient. However, in all patients we have described, the clinical appearance of the lesions only improved slowly over several weeks. As experience with antibiotics increases it has become apparent that healing is slow but continues long
<table>
<thead>
<tr>
<th>Case 2 right elbow, 32-year old male, at presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>After 6 weeks of oral rifampicin and oral moxifloxacin</td>
</tr>
<tr>
<td>Excision; specimen not sent for culture but no AFBs seen on histology</td>
</tr>
<tr>
<td>Immediate primary closure</td>
</tr>
<tr>
<td>Final result</td>
</tr>
</tbody>
</table>

*Figure 2. Thirty-two-year-old male with culture confirmed Buruli ulcer before, during, and after treatment.*
doi:10.1371/journal.pntd.0000770.g002
<table>
<thead>
<tr>
<th>Case 3</th>
<th>After 4 weeks of oral rifampicin and oral clarithromycin</th>
</tr>
</thead>
<tbody>
<tr>
<td>lower back, 12-year old male, at presentation</td>
<td></td>
</tr>
<tr>
<td>After 4 weeks of oral rifampicin and oral clarithromycin</td>
<td></td>
</tr>
<tr>
<td>Excision; AFBs seen on histology but culture was negative</td>
<td></td>
</tr>
<tr>
<td>Immediate primary closure</td>
<td></td>
</tr>
<tr>
<td>Final result</td>
<td></td>
</tr>
</tbody>
</table>

Figure 3. Twelve-year-old male with culture confirmed Buruli ulcer before, during, and after treatment.
doi:10.1371/journal.pntd.0000770.g003
<table>
<thead>
<tr>
<th>Case 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>left upper thigh/buttock, 3-year old female, at presentation</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>After one week of oral clarithromycin and rifampicin</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>No surgery performed in case 4</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Apparent relapse; spontaneous discharge was AFB and PCR positive, but culture negative</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Four months after presentation</td>
</tr>
</tbody>
</table>

Figure 4. Three-year-old female with culture confirmed Buruli ulcer before, during, and after treatment.
doi:10.1371/journal.pntd.0000770.g004
Key Learning Points

- Treatment of patients with limited BU prior to surgery using rifampicin-based oral antibiotics resulted in culture-negative resection specimens.
- Clinical healing is slow despite the microbiological activity of oral antibiotics.
- Apparent relapses that occur during or after treatment may be due to immunologically driven paradoxical reactions rather than primary treatment failure.
- Rifampicin-based oral antibiotic therapy for the treatment of M. ulcerans infection followed by delayed surgery appears to simplify management by allowing excision and closure in one step without relapse.

References

Author/s:
Gordon, CL; Buntine, JA; Hayman, JA; Lavender, CJ; Fyfe, JAM; Hosking, P; Starr, M; Johnson, PDR

Title:
All-Oral Antibiotic Treatment for Buruli Ulcer: A Report of Four Patients

Date:
2010-11-01

Citation:

Persistent Link:
http://hdl.handle.net/11343/223956

File Description:
Published version

License:
CC BY