Should antibiotics be given for Buruli ulcer?

In *The Lancet* today, Willemien Nienhuis and colleagues describe a randomised trial of two antibiotic combinations for the treatment of Buruli ulcer in Ghana. The main finding, that the two quite similar regimens are equivalent, might seem unremarkable. However, this is an important study that will change clinical practice.

Buruli ulcer is a slowly progressive but very destructive infection of skin and soft tissue that can cause permanent disability. The causative organism, *Mycobacterium ulcerans*, is transmitted from an environmental reservoir. The one established risk factor for contracting the disease is to live in a Buruli-endemic area.

Treatment until recently has been with wide surgical excision of affected skin and surrounding normal tissue; antibiotics have been largely abandoned after inconclusive results from field trials. In Australia, clinicians usually treat patients with a combination of oral antibiotics and surgery and some evidence suggests that this practice reduces relapse rates, but the relative merits of antibiotics alone compared with surgery alone are difficult to assess. In Africa, the increasing number of cases, the unavailability of surgery, and the challenges posed when the ulcer affects the face, eye, or other vital structures, have forced a reappraisal of treatment strategies. On the basis of promising mouse-footpad studies, Etuaful and colleagues did a WHO-sponsored pilot study, which established that rifampicin and streptomycin are active against *M. ulcerans* in people; when Buruli nodules were resected, excision specimens were culture negative after 4 weeks. On the basis of this encouraging result, WHO developed an interim protocol recommending initial streptomycin and rifampicin and surgical excision if necessary at 4 weeks, or, if not, a further 4 weeks of observation and antibiotics. Most patients were expected to still need surgery.

Subsequently, Chauty and colleagues reported a case series of patients with Buruli ulcer in Benin who were treated with this new protocol. Of the 215 patients with healed lesions after 1 year, 47% had received only streptomycin and rifampicin for 8 weeks, without surgery. This result was a welcome surprise to many clinicians experienced in the management of Buruli ulcer, and it stimulated a major reassessment of how this disease should be treated.

The strength of the study by Nienhuis and colleagues is the careful documentation and almost complete follow-up. Their strategy was to compare standard streptomycin and rifampicin for 8 weeks with rifampicin for 8 weeks but streptomycin for only 4 weeks, then oral clarithromycin for a further 4 weeks. Randomisation was done remotely in the Netherlands with cell-phone text messaging to field sites in Ghana—an innovative use of new technology. Of 151 patients randomised, all but four were reviewed at the 52-week endpoint, providing great confidence in the validity of the main conclusions. Only five patients needed extensive surgery, and 73 (96%) in the 8-week streptomycin group and 68 (91%) patients in the 4-week streptomycin plus 4-week clarithromycin group had healed lesions at 1 year and were free of recurrence after antibiotic treatment.

Some subtle evidence suggested that streptomycin and rifampicin for 8 weeks might have been marginally better than the comparator group—five patients had positive cultures for *M. ulcerans* after completion of treatment, all in the 4-week streptomycin group plus 4-week clarithromycin group. However, only three of these five patients were classified as treatment failures, raising questions about whether microbiological eradication is always necessary for clinical cure. Another important observation is that healing of Buruli lesions continues long after antibiotics have stopped, and this slow response probably led earlier investigators to abandon antibiotics in favour of wide surgical excision. Paradoxical reactions during antibiotic
treatment might also contribute to the view that antibiotics are ineffective. Adverse events were few in both groups, although three patients reported vestibular side-effects, which is the most concerning complication of streptomycin treatment (one in the 8-week streptomycin group, two in the 4-week clarithromycin group).

Nienhuis and colleagues have established beyond reasonable doubt that early and limited Buruli ulcer can be effectively treated with antibiotics without surgery. In so doing they have extended the excellent previous work of WHO and others, and established a benchmark for subsequent trials that could assess new antibiotic combinations. Skilled surgery and good rehabilitation will still be needed for some cases of Buruli disease, but the question of whether there is a role for antibiotics in the treatment of Buruli ulcer has now been answered with a resounding yes.

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I declare that I have no conflicts of interest.