

# Clinical Review

Clinical Review identifies issues in the medical literature of interest to clinicians in Africa. Essential references are given at the end of each section

## Dermatology Review

### Buruli ulcer: a neglected tropical disease

Buruli ulcer (BU) is a skin infection caused by an environmental bacterium, *Mycobacterium ulcerans*. It is characterised by the development of chronic and large ulcers. Since 2004 combination antibiotic drug therapy has revolutionised disease management. However, even after successful treatment, BU can lead to significant disability. BU is becoming an increasing public health problem and is now listed as a neglected tropical disease (NTD). In endemic regions it is usually well recognised, but lack of recognition and failure to report cases has probably lead to an underestimation of the true burden of this disease. The greatest burden of disease is in sub-Saharan Africa. This article will focus on recognition and management of this debilitating disease.

### Epidemiology and pathogenesis

BU has been reported in more than 33 countries worldwide, in particular in West Africa, Central and South America, and Western Pacific Regions. BU is more common in the tropics but is also seen in some sub-tropical and temperate climate countries. It was first recognised and reported in Australia in the 1930s. It is still regularly reported in Australia, China, and Japan. The highest

incidence has been reported in the West African countries of Ghana, Cameroon, Cote d'Ivoire, Benin, and in Central Africa in the Democratic Republic of Congo. The prevalence rate in the endemic areas of Ghana has been reported as high as 150 per 100 000 of the population.<sup>1</sup> There has been a notable decline in detected cases: approximately 5000 cases were reported in 2009 compared with 2037 cases in 2015 of which 1913 were from sub-Saharan Africa.<sup>2</sup>

The mode of transmission and incubation period for BU remains unclear. Contact with an aquatic environment appears to be relevant as most cases of BU reside close to water sources. Several aquatic fish and animals have been identified as possible reservoirs for *M. ulcerans*. It has been suggested that infection may be acquired via contact with an animal reservoir or even direct inoculation from infected water.

BU disease pathogenesis arises from *M. ulcerans* proliferation in the subcutaneous fatty tissue where it secretes a lipid toxin called mycolactone, which is a polyketide-derived macrolide. The mycolactone causes profound cytotoxicity leading to apoptosis and necrosis of skin tissue cells. Mycolactone also causes downregulation of inflammatory cells leading to local immunosuppression, which in turn significantly promotes its cytotoxic effects.<sup>3</sup>

In resource-limited regions of the world, children under the age of 15 are most commonly affected. In Africa, 48% of cases affect children whereas in Australia only 10% of cases occur in children. There is no difference between rates of infection between men and women.

### Clinical presentation

The clinical characteristics of the disease vary between different countries and settings just as epidemiological aspects vary.

BU most commonly affects the limbs or other exposed areas of the body including the face. Fifty-five percent (55%) of cases have been reported on the lower limbs, 35% on the upper limbs, and 10% on other parts of the



Figure 1. Buruli ulcer affecting hand with necrotic fingers (Accra, Ghana).



Figure 2. Right handed seamstress with burnt out Buruli ulcer with hyper flexed wrist and minimal movement of digits.



Figure 3. Proximal row carpectomy and groin flap to reconstruct the soft tissue defect (Accra, Ghana 2008).

body. BU generally begins as a painless dermal papule or subcutaneous nodule, which gradually enlarges to develop into an ulcer over a one to three month period. The initial papule or nodule usually first enlarges to form a plaque, which then develops central erosions progressing to form a deep ulcer. The initial presentation of BU may also be as a large painless area of induration of the skin. A less common initial presentation is as oedema when there may be a diffuse painless swelling of the legs, arms or face.

Once the ulcer has established it is usually associated with thick yellowish necrotic tissue. The margins of BU are characteristically undermined (Figure 1). Despite the size of the ulcer, patients do not complain of significant pain unless there is secondary bacterial infection. Chronic cases of BU may be complicated by osteomyelitis. Patients with BU are usually systemically well but rarely cases may be associated with fever or local lymphadenopathy. Following treatment and wound healing, extensive scarring at critical sites such as joints can lead to significant deformity and disability.

BU has been classified into three categories depending on disease severity: Category I for a single small lesion (32%), Category II for non-ulcerative plaque, ulcerative plaque and oedematous forms (35%), and

Category III for disseminated infections with complications such as osteitis, osteomyelitis, and joint involvement (33%). In Australia and Japan, most lesions (>90%) are diagnosed as category I.

In endemic regions the differential diagnoses for BUs includes tropical phagedenic ulcers, ulcers associated with leprosy, extensive ulcerative yaws, chancroid caused by *Haemophilus ducreyi*, leishmaniasis, and ulcers of traumatic origin with superimposed infection. Chronic ulcers of the lower limbs associated with diabetes mellitus or arterial and venous insufficiency may also be considered in the differential diagnosis depending on the setting. The differential diagnosis of the early nodular lesions includes boils, lipomas, lymph node tuberculosis, and subcutaneous fungal infections.<sup>4,5</sup>

### Diagnosis

In endemic regions the diagnosis of BU is usually made clinically on the basis of its distinctive clinical features. However, the World Health Organization (WHO) recommends disease confirmation where possible by laboratory methods. It recommends four diagnostic tests: direct microscopy, histopathology, culture, and polymerase chain reaction (PCR). The most reliable test with the highest sensitivity and specificity is PCR, which detects IS2404 insertion sequence, which is specific to *M. ulcerans*. The WHO has published a manual on these four diagnostic methods in order to guide health workers.<sup>6</sup> A WHO network consisting of 17 laboratories in 14 endemic and non-endemic countries support national control programmes to confirm cases.

### Treatment

The management of BU involves the eradication of *M. ulcerans* with antibiotic therapy together with surgical intervention for advanced cases. There are several antibiotic combinations with high efficacy against *M. ulcerans*. Since 2004 the WHO has recommended an eight-week course of combination antibiotic therapy with oral rifampicin (10mg/kg daily) and intramuscular streptomycin (15mg/kg daily). The limitations of this treatment include the nephrotoxicity and ototoxicity associated with streptomycin and the need for good access to healthcare facilities to ensure delivery and compliance with intramuscular injections, which is a logistical challenge in resource-limited regions. Streptomycin is also contraindicated in pregnancy. Newer combination antibiotic regimens, which have a better adverse effect profile and which can be administered orally, are being trialled. These include dual therapy with rifampicin and either clarithromycin or a fluoroquinolone (ciprofloxacin or moxifloxacin), and triple therapy with a combination of rifampicin, clarithromycin, and the fluoroquinolone levofloxacin.<sup>7</sup>

Antibiotic therapy of BU may be associated with a paradoxical deterioration of the original lesion or the development of a new lesion on another part of their body. This is a consequence of a host inflammatory response to *M. ulcerans*. It usually occurs during the course of antibiotic therapy, but may also occur after antibiotic therapy if the patient still harbours any residual bacilli. Tissue cultures and swabs of the lesions, which have deteriorated or have newly developed, are characteristically negative.

Paradoxical reactions may be very severe, in which case they may require treatment with systemic steroids.<sup>8</sup>

Following eradication of *M. ulcerans* with the recommended course of antibiotic therapy, patients should be monitored for adequate healing and provided with good wound care. The success of combination antibiotic therapy has led to a decline in surgical interventions, including amputation. However, some severe cases may still require surgical debridement and skin grafting. Any surgical intervention must not be considered for at least four weeks after microbiological cure (Figures 2 and 3).

Physiotherapy is an important part of the rehabilitation of the patient as any resultant contractures following healing of the BU can be more disabling than the infection itself.

### HIV co-infection

There is some preliminary evidence suggesting that HIV infection may increase the risk of acquiring BU. In the Médecins Sans Frontières project in Akonolinga, Cameroon, HIV prevalence was approximately three to six times higher among BU patients than the regional estimated HIV prevalence.<sup>9</sup> There is similar data from Benin and Ghana.<sup>10</sup>

HIV co-infected individuals present with more severe BU disease and HIV immunosuppression is associated with poorer outcomes as BU disease progresses more aggressively and treatment outcomes are less satisfactory. Patients co-infected with HIV often present with larger and multiple lesions that ulcerate more quickly. Lesion size has been reported to significantly increase with decreasing CD4 cell counts. HIV co-infection also increases the risk of disseminated BU disease and bone involvement.

Therefore, individuals with BU should be tested for HIV co-infection, particularly in regions with a high prevalence of HIV infection, which is the case in several areas of sub-Saharan Africa endemic for BU. It is recommended that antiretroviral therapy (ART) should be initiated in all BU—HIV co-infected patients with advanced symptomatic HIV disease (WHO clinical stage 3 or 4), regardless of CD4 cell count and in those asymptomatic individuals with CD4 count less than 500 cells/mm<sup>3</sup>. However, the risk of significant interactions between antibiotics used for BU and some anti-retroviral drugs also need to be considered. It is therefore recommended that combination antibiotic therapy for BU should be commenced before starting ART in order to prevent drug interactions.<sup>10</sup>

The cornerstone of BU management remains early recognition and treatment before the disease has advanced, as this is associated with the best prognosis. Future challenges include the need to fully understand the mode of transmission of *M. ulcerans* in order to establish preventative measures, the development of sensitive and rapid diagnostic tools, which can be used in the field and in resource-limited regions of the world, and the development of oral antibiotic regimens associated with high efficacy but low toxicity. To this end the WHO has initiated randomised clinical trials of oral antibiotic regimens in Benin and Ghana.

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## Family Medicine Review

### Obesity

There is increasing concern internationally about the double burden of malnutrition, which 'is characterised by the coexistence of undernutrition along with overweight and obesity, or diet-related non-communicable diseases, within individuals, households and populations, and across the life course'.<sup>1</sup> The World Health Organization (WHO) indicates that, in 2015, more than 1.9 billion adults worldwide were overweight, of which more than 600 million were obese, while 462 million were underweight (ibid). The obesity 'epidemic' requires both clinical and public health interventions. In terms of management interventions for obesity, lifestyle change and reduced caloric intake should be the focus. While limited by potentially serious side effects, pharmacological therapy may be indicated for obese persons (body mass index (BMI)  $\geq 30$  kg/m<sup>2</sup>), or overweight individuals with a BMI  $\geq 27$  kg/m<sup>2</sup> with associated complicating risk factors such as diabetes mellitus, hypertension, dyslipidaemia, sleep apnoea and symptomatic osteoarthritis. A helpful review article in *South African Family Practice* explains that anti-obesity drugs must demonstrate a reduction of at least 5% in the baseline body weight and must be prescribed within a context of dietary caloric restriction and exercise.<sup>2</sup> The review describes the range of agents used to treat obesity (including sympathomimetic appetite suppressants, pancreatic lipase inhibitors, antidiabetic drugs, serotonin agonists, antiepileptic agents, atypical antidepressants, and hormones), and offers guidelines on the broad indications and risks for these groups of drugs, with a specific focus on those available in South Africa, and warns against unscientific remedies. The bottom line is that patients should be informed that drug therapy is not a cure for obesity, that further weight loss will cease when the maximal therapeutic effect of a drug is reached, and that any pharmacotherapy must be re-evaluated if a weight loss

of at least 5% is not achieved after six months.

A small study in Durban, South Africa, surveyed 100 obese and overweight patients with a BMI above 25 kg/m<sup>2</sup> and their perceptions regarding their weight.<sup>3</sup> It was found that 17% of these patients saw themselves as having a normal weight and 97% felt that they were not unattractive. While 96% recognised that being obese was a health risk mostly have a positive image of obesity, and 70% cited their reason for being overweight as a choice. This indicates the challenge that healthcare providers face in dealing with the problem, the approach to which requires individual and cultural sensitivity.

A strategy that can be used by clinicians to prevent overeating by overweight and obese patients is improving hydration. Counselling patients to drink water when they have the urge to eat is a common approach. While the evidence for this recommendation is mixed, Chang and colleagues in the US found that adequate hydration may play a role in weight and suggest the need for discussion regarding adequate hydration during weight management counselling.<sup>4</sup> They point out that the current guidelines for water intake (3.7 L/d for adult men and 2.7 L/d for adult women) are calculated independently of obesity status, whereas there is a greater water requirement among those with higher BMIs, which should be incorporated in counselling. They further note the negative effects of inadequate hydration, independent of any association with weight, which include worsened mental, physical, and emotional health.

Eaton and colleagues recently reported on a randomised clinical trial of a tailored lifestyle interventions for obese patients; on the positive side they demonstrated that individually tailored weight loss interventions that involve minimal face-to-face contact can be effective for helping patients reach clinically significant weight loss and increased physical activity goals, but on the other hand they note that only 25% to 35% of participants are able to maintain a 5% clinically relevant weight loss at 24 months.<sup>5</sup> This highlights the need to be modest in one's expectations, recognising that obesity is a chronic problem that will require us as primary care clinicians to walk a long road with our patients.

### Emergency care

Lifestyle conditions such as obesity are of course not only associated with chronic illness, but also with acute events such as ischaemic heart disease and other causes of acute chest pain, which is a common clinical presentation. There is a paucity of African studies describing the prevalence and aetiology of patients with acute chest pain presenting in the emergency department (ED). Geyser and Smith studied the prevalence, causes, demographics, and disposition of all adult patients with a main complaint of chest pain presenting at the ED of a regional hospital in South Africa over four months.<sup>6</sup> They were able to examine the files of 210 out of the 312 patients presenting with chest pain. The prevalence of non-traumatic chest pain in the ED as a whole was found to be 1.7%; amongst these respiratory disease was the most common cause (36.2%), with pneumonia being the single most common diagnosis (24.4%). The other most important causes were musculoskeletal problems (21.9%) and cardiovascular disease (21.4%),

within which 64.4% were ischaemic heart disease (13.8% of the total). In the African context, the aetiology of acute chest pain differs from that in the developed world, thus, as the authors note, clinicians should therefore pay careful attention to respiratory conditions during diagnosis and management of patients with acute chest pain.

An important component of high quality emergency care is good triage. Two recent studies looked at the implementation of the South African Triage Scale (SATS) in different countries. Mulindwa and Blitz explored whether the introduction of the SATS was seen as valuable and sustainable by outpatient and emergency staff in the International Hospital Kampala, Uganda.<sup>7</sup> SATS improved the sorting of patients, as well as nurse-patient and nurse-doctor communication, and led to the development of new skills amongst staff, with nurses particularly becoming more involved inpatient care. SATS was found to have many more strengths than weaknesses; it was seen to be valuable because it improved overall efficiency of triaging and care, with significantly more strengths than weaknesses. Adequate nurse staffing, a computer application for automated coding of patients, and regular training were identified as key factors to promote consistent use and sustainability of SATS. Tshitenge et al aimed to determine the proportion of each priority level of patients and the reliability of the SATS tool at the Mahalapye District Hospital Emergency Department, Botswana, with a panel of experts reviewing the priority levels assigned by triage nurses.<sup>8</sup> Reviewing 315 case records, both the nurse triage and the panel of expert triage assigned the majority of cases in the routine category (green), namely 46% and 40% respectively, or in the urgent category (yellow), viz 44% and 35% respectively. The overall agreement in the prioritising of patients was satisfactory for routine patients, adequate for urgent patients, and poor in very urgent patients; while there were more overtriaged cases by nurses (28%) than undertriaged (8.6%), it was of concern that this very urgent category was the most undertriaged group (4.8% vs 20%). There is thus a need to enhance training in the triage and management of very urgent cases in the emergency department and for clinicians to review this regularly.

### HIV/AIDS prevention and care

The effectiveness of antiretroviral therapy (ART) in reducing HIV-related mortality and morbidity in people living with HIV/AIDS is well-accepted. This is, however, based on the understanding that adherence of more than 95% is required to achieve effective suppression of viral load. A study at a clinic in Gauteng, South Africa, found that the adherence to antiretroviral therapy (ART) was only 77%; factors that were significantly associated with adherence included gender (females were more adherent than males), level of education (greater adherence with higher education levels), and co-treatment of HIV and other infections (29% of the patients who had to co-manage HIV and other diseases did not adhere to ART).<sup>9</sup> The study also indicated that patients felt they had received good counselling about ART, and their privacy was assured, which are factors in promoting adherence. Such issues were explored more specifically

in another ART site in the Vhembe District of South Africa, where patients were generally positive about their experience with healthcare professionals and the environment in which they were treated, though there were concerns raised about stigma and infection control practices.<sup>10</sup> The authors conclude that the effective implementation of medical and support services requires a provider who knows each patient and can facilitate the provision and integration of care, in addition to standard operating procedures and principles of infection control in health facilities.

Client satisfaction is an important component in the acceptance of HIV counselling and testing (HCT) services. A survey was conducted through interviews with 498 clients purposefully selected at the end of an HCT visit at 56 HCT sites throughout South Africa to assess clients' satisfaction with the services.<sup>11</sup> The authors reported high levels of satisfaction with HCT service (89.8%) and perceived confidentiality of the HIV test results (94.6%), with low levels of difficulty in making the decision to have an HIV test (27.7%). The most common barrier to HIV testing noted by respondents was lack of awareness about the HCT service (98%), while staff attitudes (37%), confidentiality (29.6%) and privacy (23.6%) were considered to be facilitators of the HCT service. It is thus important that primary care clinicians do not assume that patients know about HCT services, and make sure that they provide this information and encourage patients to access HCT.

At the same time a small qualitative study in South Africa explored the reluctance of men to seek HCT in primary health facilities in the rural Vhembe District, through 15 semi-structured interviews.<sup>12</sup> The authors found a high level of HCT awareness among the men interviewed, but many barriers, including negative attitudes (such as male pride, fear of testing positive and distrust of lay counsellors) poor communication by administrators, stigma, and persistent beliefs in cultural practices as opposed to medical professional practices. Primary care clinicians should spend time addressing such issues with their male patients.

Preventing HIV spread remains important and topical. One of the key interventions for achieving this is the use of condoms. A study in a rural clinic in Vhembe District, South Africa, sought to understand the perceptions of 372 young adults (18–25 years) regarding condom use.<sup>13</sup> The findings indicated a relationship between positive perceptions toward condom use and actual condom use; 55% of respondents believed that using condoms during sexual intercourse offers less satisfaction, 25% that condom use delays sexual intercourse and ejaculation, and 24% that using a condom displays lack of affection for one's partner. Of those reporting inconsistent use of condoms, 43% attributed this to difficulty in negotiating with partners and 29% attributed it to problems with accessing condoms. This indicates that much work in education is still needed, but also in ensuring that condoms are available and accessible. Participants suggested sex education at schools needs greater attention.

Concerns about acceptability also arise with the female condom, where issues of size and shape are frequently raised. A study in Tshwane District, South

Africa, examined these concerns by conducting in-depth interviews with 28 female healthcare providers (nurses, managers and lay counsellors) about the second generation female condom (FC2).<sup>14</sup> They report that the healthcare providers found the size and shape of FC2 to be undesirable, felt insertion is complicated related to the size and shape of female genitalia, and believed that the size and shape of FC2 results in pain and discomfort during coitus, exposing women to unwanted pregnancies and HIV/AIDS. These attitudes amongst those who are supposed to be promoting the FC2 makes the likelihood of success of any campaign to promote female condom use very low. The authors argue that there needs to be better preparation of primary healthcare providers, with interactive experiential participative training that includes reflections on values and practice.

Male medical circumcision (MMC) is another significant HIV prevention strategy that WHO recommended following the results of three randomised controlled trials in Uganda, South Africa and Kenya, which demonstrated that circumcision has a protective effect against contracting HIV of up to 60%. In 2009, Zimbabwe introduced a voluntary MMC programme, but uptake has been disappointing. In order to understand this, a household survey was conducted in Mutare rural district, Zimbabwe, amongst 234 men aged 15–29 to understand attitudes towards MMC.<sup>15</sup> The authors found that circumcised men are viewed as worthless (37%), shameful (30%) and promiscuous (20%), and that participants were concerned about infection and delayed healing (39%), being ashamed (58%) and stigmatised (40%), having an erection during treatment period (89%), and that complications might arise leading to spending money on treatment (84%). Once again it is clear that a more comprehensive education programme, including schools and community leaders, is needed.

### Health education interventions in schools

A number of the article cited above refers to the importance of interventions at school level. I thus decided to continue this topic briefly in relation to a number of other issues. A survey of 381 learners in six secondary schools situated in the rural Makhado Municipality, Limpopo, South Africa, focused on awareness of prevention of teenage pregnancy, found that despite gaps in knowledge about sexual health, learners do know about how to prevent teenage pregnancy.<sup>16</sup> Thus, while sex education at school should continue, there needs to be a greater focus on reasons for avoiding teenage pregnancy and empowering girls to be in control of their sexuality. The issue of control was addressed completely differently in a study on substance abuse, in relation to addiction to *nyaope* (a mix of a heroin-based drug cocktail with cannabis) in Tshwane, South Africa, in which the authors looked at the issue of internal and external locus of control (LOC) amongst 192 *nyaope* users.<sup>17</sup> They found that 25% of respondents had an external LOC orientation, while 75% had an internal LOC orientation, and argue that rehabilitation programmes should be aligned to suit the personality of the user in order to have a better chance of successful recovery. Clinicians involved in drug addiction management should give further consideration to this.

While substance abuse is an increasingly large problem in some parts of Africa, a study to determine the prevalence of substance abuse amongst rural secondary school learners administered a questionnaire to 338 randomly selected learners (aged 14 to 18 years) from 10 secondary schools in the Limpopo Province, South Africa, and found a very low prevalence rate.<sup>18</sup> Further investigation in other rural areas on the continent would be worthwhile.

Another study using the same data set assessed the exposure of rural secondary school learners to health education and promotion.<sup>19</sup> They found that most learners had been taught a range of topics related to health education and promotion, including changes that occur during adolescence (66.1% of male and 67.6% of female learners), sexually transmitted diseases (84.4% and 85.4%), HIV and/or AIDS (94.7% and 95.0%), and alcohol and drug abuse (92.1% and 90.5%). If clinicians are aware of what adolescents have been taught, they can draw on this when conducting consultations with such patients.

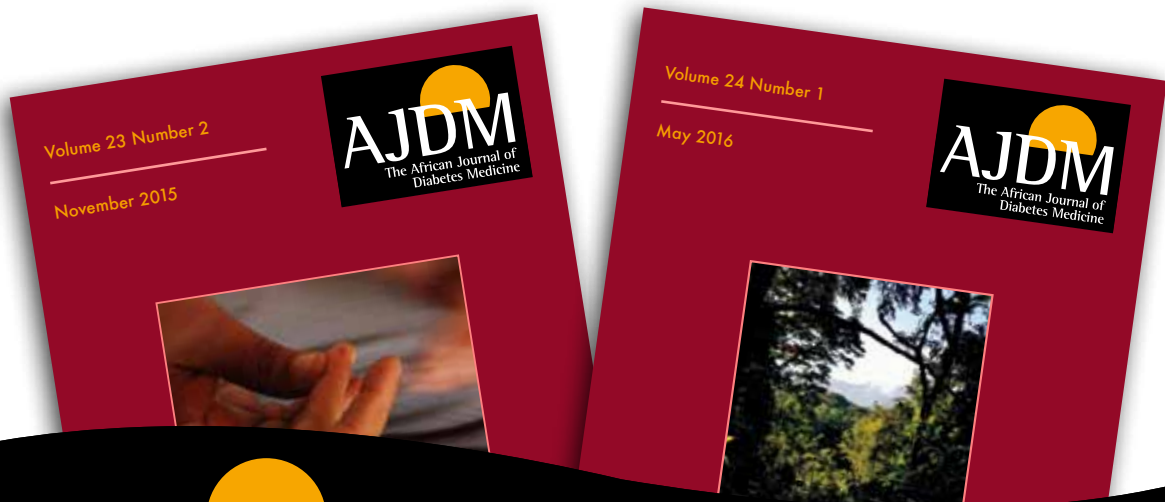
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