BURULI ULCER IN WEST AFRICA: STRATEGIES FOR EARLY DETECTION AND TREATMENT IN THE ANTIBIOTIC ERA

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Abstract

Objective: Buruli ulcer (BU), caused by *Mycobacterium ulcerans* infection, has become one of the most rapidly emerging diseases in West Africa in recent decades. Until recently, the definitive treatment involved wide surgical excision. Recent data suggest that antibiotic therapy with rifampin and streptomycin may reduce the extent or prevent excision when initiated during the early phases of the disease. New strategies for BU control are needed, emphasizing early detection and increasing public awareness about the disease and treatment. Here we review current knowledge about BU and examine clinical, public health and anthropological research in the context of this new treatment paradigm to identify potential strategies for more effective control of this disease.

Methods: A comprehensive literature search for articles in English or French using the Medline and INIST databases, World Health Organization publications, and bibliographical references was undertaken using key words *Buruli ulcer*, Mycobacterium ulcerans, community surveillance, and public health.

Conclusion: Studies to identify factors contributing to delayed presentation indicate that awareness of the disease is generally good in endemic regions, but wide variation exists in perceived cause of the disease, and the role of sorcery in its transmission and treatment. The use of traditional healers as first line therapy also contributes to delayed treatment, as do lack of awareness about the availability of effective treatment and financial concerns. Epidemiological data from existing BU control programs indicate that active public awareness campaigns are succcessful in increasing understanding and decreasing treatment delay and disease progression. Community-based surveillance and health education modeled after the village health worker programs used in the eradication of Guinea worm may be successfully applied in BU endemic areas.

Keywords: Mycobacterium ulcerans, Buruli, ulcer, antibiotics, West Africa

Introduction

Buruli ulcer (BU) is a disfiguring disease of the subcutaneous tissues resulting from infection by *Mycobacterium ulcerans*. First described in 1948 in Australia (1), cases of BU have been reported in 30 countries (2), of which West African nations constitute the overwhelming majority (3) . The number of reported cases in West Africa has increased substantially in the past decade, approaching 22,000 cases reported in this region since 2002 alone (3). *M. ulcerans* infection now ranks as the third most common mycobacterial disease worldwide, with prevalence rates rivaling those of tuberculosis and leprosy in some endemic areas (4,5,6).

Until recently, the only definitive treatment for Buruli ulcer was wide surgical excision followed by lengthy hospital convalescence, an intervention that is both taxing on local healthcare infrastructure and a significant economic burden to patients and their families (7,8). However, recently published data suggest that antibiotic therapy with rifampin and streptomycin is effective in reducing and even eliminating BU lesions when initiated during the early phases of the disease, decreasing the extent of surgical intervention and drastically reducing recurrence rates (7,9). These new data appeal for a paradigm shift, one in which control strategies place emphasis on early detection and reporting, readdressing public perceptions of treatment efficacy and availability, and organizing health infrastructure at the regional and village levels in order to deliver therapy appropriate to socioeconomic limitations.

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Background

Buruli ulcer is a disease of rural areas, often escaping detection by national surveillance programs (10). Endemic foci localize to remote regions in proximity to slow-moving or stagnant bodies of water, and are often logistically difficult to access (11). As a result, prevalence rates are likely underestimated (12), and even within endemic areas, significant inter-village variability in prevalence data exists, which may be attributable to geographic proximity to water (13,14). The association between *M. ulcerans* and an aquatic reservoir is supported by epidemiological and environmental sampling data (15-20). Recent landscape-based studies have strengthened this association and confirm a link between *M. ulcerans* transmission and areas of decreased urbanization (16,21).

Despite these data, the mechanism of transmission remains unclear. It has been postulated that transmission may occur after skin contaminated with environmental material harboring the organism is penetrated by trauma or following an insect bite (18,22). Although direct culture of *M. ulcerans* has been obtained from the *Gerris* water strider found in endemic areas (20), this predatory aquatic insect is not known to bite humans, supporting other entomological studies which have not confirmed this as the primary vector of transmission (23). Other risk factors identified by case control studies include age less than fifteen years, comprising up to 50% of cases; unprotected domestic water source, exposed skin, and farming in endemic riverine areas; whereas use of soap and water and proper hygiene appear to convey protection (15,24-27). As with leprosy, there is some evidence to suggest an immunogenetic predisposition toward a Th2 response, and thus a greater likelihood of infection upon exposure (28).

Once infection is established, the natural course of the disease comprises three stages: pre-ulcerative, ulcerative, and healing. The pre-ulcerative stage can present as a nodule, a papule, an indurated plaque, or an edematous lesion, and is not accompanied by systemic symptoms. Untreated, pre-ulcerative lesions evolve into well-

demarcated, painless ulcers with characteristic undermined edges. Bone involvement (29) and super-infection (12) are known to complicate this phase. Ulcers may last months to years, before an efficient immune response is mounted and the healing phase begins, although recurrence is known to occur, even with surgical excision (31). While lesions can resolve spontaneously, the healing stage is often marked by extensive scarring and contractures, resulting in gross disfigurement or functional disability in as many as 20% of cases (30). Thus while the mortality rate of BU is low, the burden of disease in terms of morbidity, functional disability and socioeconomic strain on endemic regions is immense (10,32).

Early Detection

Given recent evidence that a rifampin-streptomycin therapy regimen has the potential to decrease the extent or even obviate the need for surgery, early detection and prompt treatment of pre-ulcerative lesions represents the single most effective method of improving clinical outcomes and minimizing economic burden on resource-limited regions. Delayed presentation for medical treatment is correlated with evolution of pre-ulcerative lesions to the ulcerative form (6), increased risk of osteomyelitis (6,29), more extensive surgical intervention and skin grafting (32), and longer hospital stays (5,6,12). In data from the Zou province in Benin, the median delay in seeking medical attention in cases presenting with pre-ulcerative lesions was 30 days, while patients presenting in the ulcerative stage or with osteomyelitis reported median delays of 61 and 91 days, respectively (6).

Clinical stage can also serve as an indicator of progress in public early detection campaigns. Data from prevalence studies in Côte d'Ivoire, Cameroon, the Democratic Republic of Congo and Benin reported rates of ulcerative lesions of 89.5%, 92.8%, 94.4%, and 96.4% respectively, reflecting areas of endemicity where no public control strategies had yet been implemented (12,30,33,34). In contrast, data collected in Benin following a successful public health campaign, "Programme National de Lutte contre l'UB", which has become a model in West Africa, demonstrated a decrease in ulcerative forms to near 50%, as well as a reduction in mean delay to treatment from four months to one, and a decline in median hospital stay from nine months to one month (6).

In terms of socioeconomic impact, data from Ghana, where the gross domestic product per capita in 1998 was estimated at USD $399.41 (35), the cost of surgical excision of a large ulcer, including 3 months' inpatient expenses, transportation, food and income lost was USD $783. Even in Cameroon, when treatment is provided at no cost, financial impact has been reported to be as high as 25% of yearly household income (8). By comparison, the medication cost of an 8 week course of rifampin-streptomycin is USD $10 (7). The key to this potential reduction in morbidity and economic burden lies in the detection of the disease in the early pre-ulcerative stages where antimicrobial therapy is most likely to decrease the extent of surgical intervention and shorten recovery time.

Public Disease Perception and Health Seeking

Factors contributing to delayed presentation for treatment of BU are complex, and include misconceptions regarding the cause of BU disease, the percieved role of sorcery, reliance on traditional medicine as first line therapy, fear of or lack of confidence in western treatment, and financial concerns (5,32,36,37,38). Surveys exploring public knowledge and perception of the disease have been valuable in elucidating these factors and represent a useful tool in designing and assessing the success of public health strategies (37).

In surveys on public perception of BU disease completed in two endemic regions, the Ga West district in Ghana (5) and in the Zou province of Benin (36), adults and children were able to accurately describe the disease, indicating a general public awareness, although significant variation exists regarding the cause of the illness (38). In West Africa, where belief in sorcery is known to affect perceptions of illness and health care seeking behavior, an inverse correlation appears to exist between the prevalence of these beliefs and the extent of health education disseminated in the area (5,36). For example, in Cameroon, where a focus of endemicity was recently rediscovered, the majority of patients with BU described the source of their illness as a malediction known locally as “Atom,” and more than two-thirds were being treated by traditional healers (30). Conversely, in the Ga West district of Ghana, where BU has been acknowledged by government health officials for some time, only 5.2 % of patients identified their illness as a curse or product of witchcraft (5). In Benin, survey participants reported that the perceived cause of the disease both dictated, and was affected by the success of a particular mode of treatment. For example, sorcery was suspected in BU if healing of lesions is delayed, while a natural cause was more likely to be ascribed to a lesion that was refractory to treatment by a traditional healer (36).

Traditional healers factor heavily into the health care infrastructure in West African nations, and are used by as many as 80% of the population (40). Traditional healers can be broadly classified as phytotherapists, practitioners using traditional herbal remedies to treat diseases of natural cause, and diviners dealing primarily with the supernatural (36). This group is considered by some to be the most important link between rural communities and health care delivery (40), although their role in the integration of western health programs in Africa has been called into question (41). In either case, there is no doubt that traditional healers contribute to the delay in seeking medical assistance, both in BU disease as well as in leprosy and tuberculosis control programs (42,43).

In the Ghana survey, 71.8% of respondents sought treatment at the herbalist first, and only 7.7% of these patients presented to a community hospital when their condition deteriorated (5). The benign early course of the disease, painless nature of the lesions and potential for spontaneous resolution are also known to contribute to an inappropriate lack of urgency in seeking definitive care (11). In Benin, patients reported attempting self-treatment first, followed by soliciting the care of traditional healers,

then religious figures, and finally health centers or hospitals if other options have failed, and then only if western medical treatment was known to be effective (36,37,39). Lack of confidence in the effectiveness of surgery in preventing recurrence, and concern about social consequences of scarring secondary to skin grafting are also factors affecting health care choices (36). Other determinants of health care seeking behavior include fear of prolonged hospitalization, difficulty traveling to treatment centers, and loss of earnings while receiving care (5,36,37).

Community-based Surveillance and Education

In order to effectively complement successful antibiotic treatment programs, BU control strategies should be structured to combine early detection programs and community education campaigns encouraging early presentation and increasing public awareness of the availability and efficacy of treatment. A model that is likely to be both efficient and self-sustaining in achieving these objectives draws upon the successful community-based surveillance programs widely employed in the campaign for the eradication of Guinea worm (46,47).

In this model, volunteers chosen at the village level are trained as village health workers (VHWs), each with responsibility for active case-finding and education in several villages within a geographic zone. VHWs make monthly visits to households within their assigned territory and report to a district supervisor, often a nurse at a central district health center experienced in the clinical diagnosis of BU, who verifies suspected cases (46). In areas where laboratory resources remain underdeveloped, WHO diagnostic criteria have been validated in endemic areas with limited resources when applied by experienced clinicians (13,30). Case finding data suggest that local populations within endemic areas are quite accurate in identifying manifestations of BU, even in early lesions, facilitating this approach (30,36).

The strength of such programs lies in the selection of community representatives. Successfully treated former patients are most successful at advocating for treatment and making referrals, and are excellent choices for community representatives (6,12). In addition, because of the high prevalence rates in children, school teachers may also be an appropriate resource in early detection strategy. Data from the Guinea worm experience indicate that VHW literacy is not necessary for success, and that inclusion of women increases reliability in reporting (46). Volunteers may be motivated by clothing imprinted with a program logo or modest training grants or travel stipends, but more often simply by an elevation in social status (46). Debacker et al. found community volunteers to be enthusiastic and concerned about public health, further evidence for the sustainability of such a program (11).

In addition to facilitating timely case detection, VHWs play a key role in providing public education about BU. Monthly household visits represent an ideal opportunity for preventive education, and may be augmented by public meetings and visual aids (46). BU education programs such as have been instituted in Benin and Ghana are proven to increase recruitment to treatment centers and to decrease presentation delay (6,45). Because psychosocial and economic obstacles preventing prompt referral to medical care are often unique to a region, surveys of local attitudes and knowledge regarding BU are indispensible in the design of education campaign (8,47). Data from such studies suggest that health care workers and traditional healers are likely to foster misconceptions regarding the disease, and may benefit from training targeted to their groups (5,36). Greater public health emphasis on BU is likely to reinforce the perception of BU as a natural disease, further reducing treatment delay, and diminishing social stigma associated with the infection (11). Lastly, it is important to ensure that public awareness campaigns are undertaken in proportion to the local availability of treatment resources (46).

Another benefit to such a system is its cost-effectiveness in reducing the socioeconomic impact of disease through early detection and education. Community-based surveillance programs generally cost between USD $100 -$200 per village per year, a figure that, while not insignificant, pales when compared to the cost per case of surgical treatment mentioned earlier (46). In addition, several VHW networks established during the Guinea worm campaign exist in BU endemic regions such as the Zou province of Benin, and as part of a national surveillance program in Ghana (44,46). In other areas, such as the Lalo province in Benin, community representatives have already been identified in conjunction with case-finding studies, or as part of other health surveillance programs such as nutrition or vaccination, providing an existing foundation upon which to build (13,46).

Conclusion

Buruli ulcer is one of the most significant emerging tropical diseases of the last decade, both in terms of prevalence, and of socioeconomic burden imposed upon endemic regions. Recent data suggesting the effectiveness of antibiotic therapy has the potential to alleviate much of this burden, but will only benefit communities where control strategies are employed in such a way as to encourage early presentation and guide public perception of the disease and available treatment.

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