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REVIEW

Challenges associated with the treatment of Buruli ulcer

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Abstract

Buruli ulcer (BU), caused by *Mycobacterium ulcerans* (MU), is the third most important mycobacterial diseases after tuberculosis and leprosy in immunocompetent individuals. Although the mode of transmission remains an enigma, disease incidence has been strongly linked to disturbed environment and wetlands. The blunt of the diseases is recorded in West African countries along the Gulf of Guinea, and children 15 years and below account for about 48% of all cases globally. Prior to 2004, wide surgical excisions and debridement of infected necrotic tissues followed by skin grafting was the accepted definitive treatment of BU. However, introduction of antibiotic therapy, daily oral rifampicin (10 mg/kg) plus intramuscular injection of streptomycin (15 mg/kg), for 8 weeks by the WHO in 2004 has reduced surgery as an adjunct for correction of deformities and improved wound healing. An all-oral regimen is currently on clinical trial to replace the injectable. It is thought that a protective cloud of the cytotoxic toxin mycolactone kills infiltrating leucocytes leading to local immunosuppression and down-regulation of the systemic immune system. Our studies of lesions from BU patients treated with SR have demonstrated treatment-associated initiation of vigorous immune responses and the development of ectopic lymphoid tissue in the BU lesions. Despite these interventions, there are still challenges that bedevil the management of BU including paradoxical reactions, evolution of lesions after therapy, prolong viability of MU in BU lesions, and development of secondary bacterial infection. In this paper, we will mainly focus on the critical and pertinent challenges that undermine BU treatment toward effective control of BU.

KEYWORDS

Immune-suppression, Leukocytes, Mycobacterium ulcerans, Mycolactone, Paradoxical reactions, Pathogenesis, Secondary bacteria infections

1 | INTRODUCTION

Buruli ulcer (BU), a necrotizing skin condition, is the third most important mycobacterial disease globally after tuberculosis (TB) and leprosy in immunocompetent individuals.[1,2] In highly endemic countries, such as Ghana, BU is second after TB as the most prevalent mycobacterial disease.[2] BU was first described in 1879 by a British physician, Sir Albert Cook, and the etiologic agent of BU was later isolated from a farmer and named as *Mycobacterium ulcerans* (MU).[3] The name "Buruli ulcer" was designated in the 1960s after the Buruli County in Uganda where the largest number of cases was recorded then.[4] The disease is currently being reported in 33 countries globally, but highest disease burden is found in West African countries along the Gulf of Guinea and include Ivory-Coast, Ghana, Togo, Benin, and Cameroon.[5]

BU affects equally both sexes and all age groups and no ethnic preference has been reported.[6] The clinical and epidemiological aspects of cases vary considerably within and across different geographical settings, especially in Africa children 15 years or less constitute about 48% of all cases, whereas in Australia, 10% are children under 15 years and in Japan 19% are children under 15 years.[7] The mode of transmission of MU is not understood, but cases are mostly associated with disturbed environments and wetlands.[8] The initial stage presents as a nodule, papule, and plaque or in the more diffuse case as an edema. If the early forms are not treated, extensive skin destruction leads

Abbreviations: AFB, acid-fast bacilli; ART, antiretroviral therapy; BU, Buruli ulcer; IRIS, immune reconstitution inflammatory syndrome; MU, *Mycobacterium ulcerans*; SR, Streptomycin and rifampicin; TB, tuberculosis

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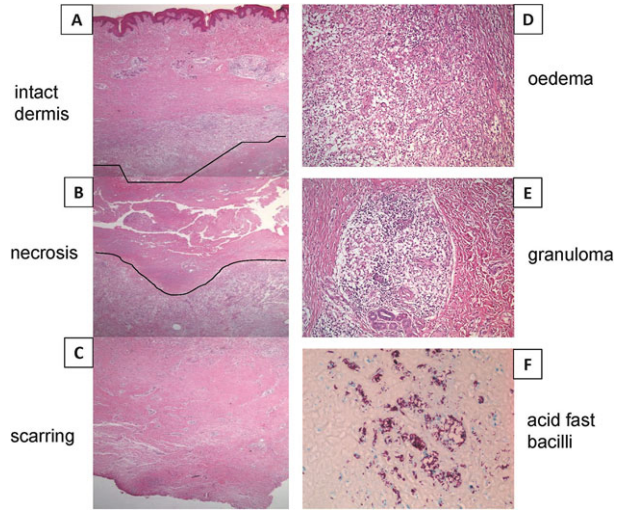

FIGURE 1 Histological features of Buruli ulcer lesion. Histological sections of punch biopsies of BU lesions stained with hematoxylin-eosin (A–E, original magnification 50×) and Zeihl–Neelsen (F, original magnification 100×)

to the formation of an ulcer. Laboratory methods for confirmation of clinical diagnosis include culturing for MU from lesion samples, direct acid-fast bacilli (AFB) detection by microscopy, and PCR to detect bacterial DNA.[9–16] The major hallmarks of MU infection, which are also used for histopathological confirmation, are the presence of coagulative necrosis, fat cell ghosts, epidermal hyperplasia, and extracellular clusters of AFB in the absence of major inflammatory infiltrates in central parts of the lesions (Fig. 1).[17,18]

Prior to 2004, wide surgical excisions and debridement of infected necrotic tissues followed by skin grafting to correct deformities was the mainstream management protocol for BU.[19,20] A study initiated by the WHO and conducted in Ghana indicated that BU lesions can be sterilized by treatment with streptomycin and rifampicin (SR).[19,21] Based on this finding, a treatment guideline was released in 2004; daily oral rifampicin (10 mg/kg) plus intramuscular injection of streptomycin (15 mg/kg) daily for 8 weeks, reducing surgery as an adjunct for correction of deformities and facilitating wound healing.[21,22] An all-oral regimen is currently on clinical trial. Although the introduction of antibiotics therapy has proved successful in the management of BU cases including reduction in length of hospital stay, cost of treatment, and reduction of relapse to less than 2%,[21,22] there are still challenges in BU treatment.

2 | IMMUNE SUPPRESSION ASSOCIATED WITH BU DISEASE

The pathogenesis and host immune response mechanism are not clearly understood; however, most of the observed pathology is linked to the secretion of a polyketide macrolide toxin called mycolactone. Upon entry into the host, MU is confined under the skin and the long incubation period, which has been suggested to be between 2.0–4.5 months, favors its proliferation within the dermis.[23] The temperature requirement of MU offers optimal conditions for the development of lesions in cooler tissues, particularly, the skin and subcutaneous tissues.[23,24] BU may manifest initially as a painless nodule, papule, nodule, plaque, or edema. Subsequent obliteration of the subcutaneous adipose tissue results in the breakdown of the epidermis and formation of characteristic ulcers with undermined edges.[25,26] It is thought that a protective cloud of the cytotoxic toxin mycolactone kills infiltrating leucocytes leading to local immunosuppression and down-regulation of systemic immune response.[24,27] Mycolactone caused cytopathic effects on cultured L929 murine fibroblasts and inoculation of purified mycolactone into guinea pigs intradermally also produced lesions that were histologically like BU with necrosis of subcutaneous fat.[27] In contrast to other pathogenic mycobacteria, which are intracellular pathogens of macrophages, histology of MU lesion finds extracellular clusters of MU bacilli lying within areas of coagulative necrosis that extend some distance from the site of bacterial colonization.[28,29] Nevertheless, inoculation of an isogenic toxin-negative mutant of MU caused a granulomatous lesion typical of the inflammatory response to other mycobacteria with phagocytozed MU visible within macrophages and none of the characteristic fat necrosis.[27]

Despite some antiphagocytic activity of mycolactone, other studies have shown that phagocytes can internalize MU in vitro. Coutanceau et al. using mouse models found that MU was initially captured by phagocytes and transported to draining lymph nodes within host cells; however upon ulceration, tissue necrosis and extracellular bacteria as seen in human BU were seen.[30] Torrado et al. also demonstrated that mycolactone-producing MU isolates are efficiently phagocytozed by murine macrophages.[31] The authors further note that MU multiplies inside cultured mouse macrophages when low multiplicities of infection are used to prevent early mycolactone-associated cytotoxicity and subsequently induced lysis of the infected host cells to become extracellular.[31]

The innate response involves the release of proinflammatory cytokines, such as IL-6 and lipids, to recruit and activate other immune cells and apoptosis.[32-37] If the infection persists, the phagocytes stimulate the adaptive immune system by presenting Ags to activated T and B cells.[38] It appears that adaptive immune responses associated with IFN-γ secretion may be crucial. The cytopathic effect of the macrolide toxin causes apoptosis of mammalian cells[39] and down-regulates local and systemic immune responses by interfering with the activation of immune cells, which may account for poor inflammatory responses in BU lesions[30,34–37,40–42] (Fig. 2). Gooding et al. examined immune responses to MU and *Mycobacterium bovis* bacillus Calmette–Guérin in patients with MU disease and in healthy control subjects. They found that infection with MU is associated with T cell anergy as PBMCs from individuals with BU exhibited reduced lymphoproliferation and production of IFN-γ following stimulation with living or heat-killed mycobacteria.[43] These same authors investigated cytokine profiles of PBMCs from patients and household contacts and showed that BU patients mounted a Th2-type response, which was manifested by the production of mRNA for IL-4, IL-5, IL-6, and IL-10, whereas unaffected contacts responded mainly with the Th1 cytokines IFN-γ and IL-12.[44] This suggests that a Th1-type immune response to MU may prevent the development of BU in people exposed to MU.[44] In Guyana, Prevot et al. demonstrated that in active BU patients, in vitro production of IL-10 in PBMCs after stimulation with MU was significantly increased

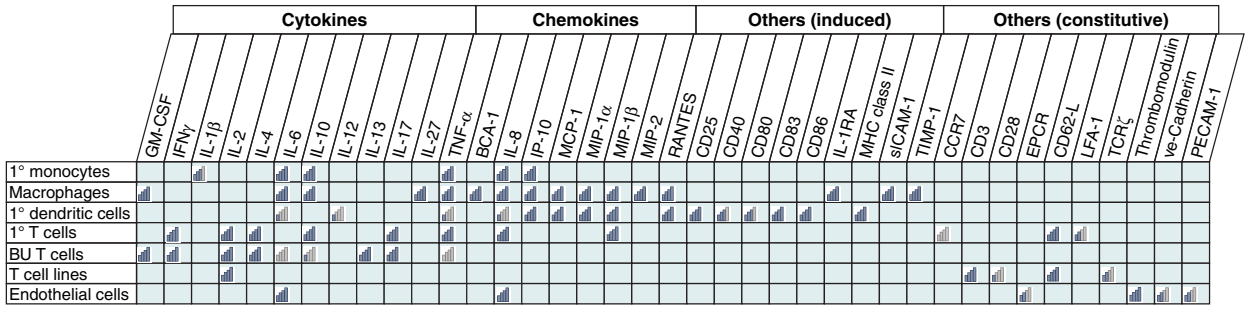

FIGURE 2 Compiled studies showing the effects of mycolactone on the production of cytokines, chemokines, other proteins by monocytes, macrophages, dendritic cells, primary T cells, T-cell lines, and endothelial cells[33–37,40,50]

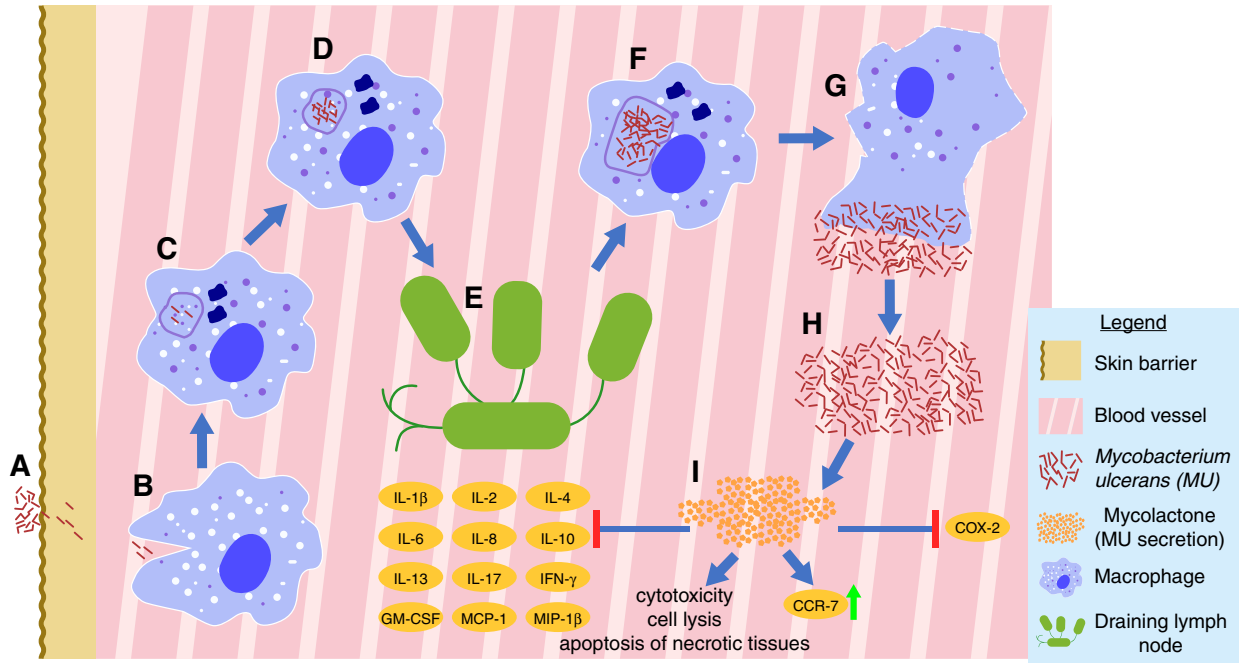

FIGURE 3 **Plausible immunological events underlining *M. ulcerans* (MU) pathogenesis.** [A] MU, an environmental pathogen may enter the host by an unclear mechanism (s). [B-D] Upon entry, the bacilli is phagocytosed and transported to the draining lymph nodes [E] whiles multiplying within the macrophages [F] and subsequent lysis [G] to become extracellular. Extracellular MU [H] secretes a polyketide toxin called mycolactone [I] which causes apoptosis of mammalian cells, down-regulation of local and systemic immune responses by interfering with activation of immune cells

compared to tuberculin positive controls and the reverse was true for IFN-γ.[45] The production of distinct cytokines was also found to be dependent of lesion stage. In resected tissues, the level of IFN-γ mRNA was higher, and IL-10 mRNA was lower in nodular lesions than ulcerative lesions after stimulation with heat-killed MU.[45] Westerbrink et al. using in a whole blood assay demonstrated a systemic reduction in IFN-γ production in response to purified protein derivative Ags in patients with early lesions compared to those with later stage lesions.[46] Shown in Fig. 3 are plausible immunological events that underline MU pathogenesis.

Although we confirmed BU-associated systemic immunosuppression but showed for the first time that BU-associated immunosuppression is resolved upon healing, contrary to previous notion based on work done in Australia. By analyzing PBMCs from the same patients before surgery and after healing in parallel by ELISpot analysis, we showed that the numbers of INF-γ secreting cells after Ag stimulation increased significantly after surgical treatment.[40] This observation has been confirmed by later studies. Philips et al. subsequently reported that BU patients with active ulcers showed distinctive profile of immune suppression marked by down modulation of selected cytokines and an impaired capacity to produce Th1, Th2, and Th17 cytokines when stimulated with mitogenic agents.[47] Immunohistopathological studies of lesions from BU patients after SR regimen have demonstrated treatment-associated initiation of vigorous immune responses and the development of ectopic lymphoid tissue in the BU lesions.[13,39,48] Three different general types of infiltration, diffuse mixed infiltrates, granulomas, and dense lymphocyte aggregation, near vessels were observed. Results indicate that the relatively short antibiotic treatment reverses local immunosuppression and that the curative effect may be sustained by immune defense mechanisms. Mycobacterial material ("acid-fast debris") was primarily located inside phagocytes. The role of antibody-mediated immunity is not evident, but BU patients were able to produce antibodies against MU culture filtrate. The mechanism of suppression is not clearly understood.

Boulkroun et al. identified 2 mechanisms by which cell responsiveness to antigenic stimulation is suppressed by mycolactone.[49] At noncytotoxic concentrations, mycolactone blocked the activation-induced production of cytokines by a posttranscriptional, mammalian target of rapamycin, and cellular stress-independent mechanism. In addition, mycolactone triggered the lipid-raft association and activation of the Src-family kinase, Lck. Mycolactone-mediated hyperactivation of Lck resulted in the depletion of intracellular calcium stores and down-regulation of the TCR, leading to impaired T cell responsiveness to stimulation.[49] An investigation by Pahlevan et al. on the activity of partially purified mycolactone on different human immune-competent cells found that the toxin produced greater than 95% inhibition of LPS-induced release of TNF-α and IL-10 from human monocytes. It also causes loss of adherence of monocytes without cell death.[35] Hall et al. also showed that mycolactone does not prevent translation of TNF, IL-6, and cyclooxygenase-2 mRNAs in macrophages rather it inhibits their production together with other induced and constitutive proteins that transit through the endoplasmic reticulum.[50] George et al. further showed that addition of mycolactone to macrophages and fibroblast affected the organization of the cytoskeleton that leads to growth arrest and apoptosis.[27] Furthermore, IL-2 production from activated T lymphocyte was blocked by the toxin.[27]

3 | SECONDARY LESIONS OCCURRING AFTER BU TREATMENT

The occurrence of new lesions at the site of infection during the era of surgical excision was high and it can be up to 47% due to insufficient excision of infected tissues.[51] However, this has been reduced greatly following antibiotic therapy and most secondary lesions are not due to relapse but rather increased immune reactivity. In mycobacterial infections, such as TB and leprosy, studies have shown that effective antimicrobial killing may be accompanied by clinical deterioration[52–54]; a phenomenon normally described as paradoxical reaction. Although commonly it occurs in severely immunosuppressed patients, it can also occur in immunocompetent hosts.[52,55] This reaction may be due to increased exposure to mycobacterial Ags, a decrease in suppressor mechanisms, or improved host cell-mediated immunity following antimycobacterial therapy.[54,56]

Recently, paradoxical reactions have been recognized to complicate up to 20% of patients receiving BU therapy, and sometimes leads to evolution of multifocal BU lesions.[13,57] Nienhuis et al. prospectively investigated 134 BU patients for evolution of lesion during antimicrobial treatment and found peaked paradoxical reactions at week 8 of treatment with 30% participants showing increased lesion size as compared with week 6 in Ghana.[58] Also 83% of nonulcerative lesions ulcerated after start of treatment and 9 participants developed new lesions during or after SR treatment.[58] O'Brien et al. reported 2 cases of paradoxical reactions in Australia; in both cases, improved antibiotic treatment was followed by worsened clinical conditions, which were interpreted as treatment failure leading to change in treatment regimen, but later the conditions were understood as immune-mediated reaction to effective antibiotic therapy.[59]

Recently, Barogui et al. described an association between paradoxical reactions, trunk localization, large lesions, and genetic factors. They showed that individuals carrying homozygous ins/ins genotype of 3′UTR TGTG 285 polymorphism in the SLC11A1 gene have increased risk of paradoxical reactions.[60] In BU, paradoxical reactions may result from reversal of the mycolactone toxin induced immune-inhibitory state via the antibiotic-mediated killing of MU allowing intense immunological reaction to develop against the persisting mycobacterial agents.[58,59] Considering the prevailing evidence, clinical deterioration during antibiotic treatment can be interpreted as treatment failure, leading to further expensive and potentially disfiguring surgery, and a change in antibiotic regimens or a prolongation of their use.[59] In TB cases with paradoxical reactions, steroid therapy is mostly recommended. A randomized placebo-controlled trial in TB with paradoxical reactions found prednisone to reduce the need for hospitalization, therapeutic procedures, and hastened improvements in symptoms, performance, and quality of life.[61] Friedman et al. used prednisone therapy for 4–6 weeks for BU patients with paradoxical reactions, which yielded an improved clinical outcome. The lesions healed 9–12 months after initial treatment.[62] O'Brien et al. asserts that rather than progression of the lesions because of failure of antibiotic treatment, these cases represent an adverse consequence of effective antibiotic treatment.[61] When initial improvement on antibiotic treatment is followed by clinical deterioration of lesion, histopathological examinations and mycobacteria culture need to be conducted to assess the possibility of a paradoxical reaction.

3.1 | Superinfection of BU wounds

The occurrence of secondary infection in BU disease was previously believed to be uncommon[7] and therefore was not well characterized and documented. Mycolactone secretion by MU during active disease was formerly hypothesized to exert a sterilizing effect on the wounds thus preventing secondary infection due to the fact that other macrolides have broad spectrum activity against many bacterial species.[63] Recent studies however have shown that secondary infection is more common than formerly thought (Fig. 4). Studies documenting the occurrence of secondary infection with the isolation of infecting pathogens[60,63–68] and the growth of microbial pathogens in the presence of mycolactone[64] have given evidence to support the occurrence of secondary infection in BU and proven that mycolactone does not prevent its occurrence. Secondary infection in BU should be suspected when a wound becomes painful or develops cellulitis.[7] Studies identifying the microbial flora of secondarily infected BU lesions isolated a diverse and broad range of infecting bacterial species[58,65,66] including *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Proteus mirabilis*, Coagulase negative Staphylococcus, *Chryseomonas luteola*, *Enterobacter cloacae*, *Klebsiella pneumonia*, *Escherichia coli*, *Streptococcus dysgalactia*, *Providencia stuartii*, *Staphylococcus haemolyticus*, Group A streptococci, Group B or C streptococci, *Morganella morganii*, *Streptococcus agalactia*, *Staphylococcus warneri*, *Proteus vulgaris*, *Pseudomonas pseudomallei*, *and Burkholderia cepacia*. *S. aureus* and *P. aeruginosa* however dominated among the isolated

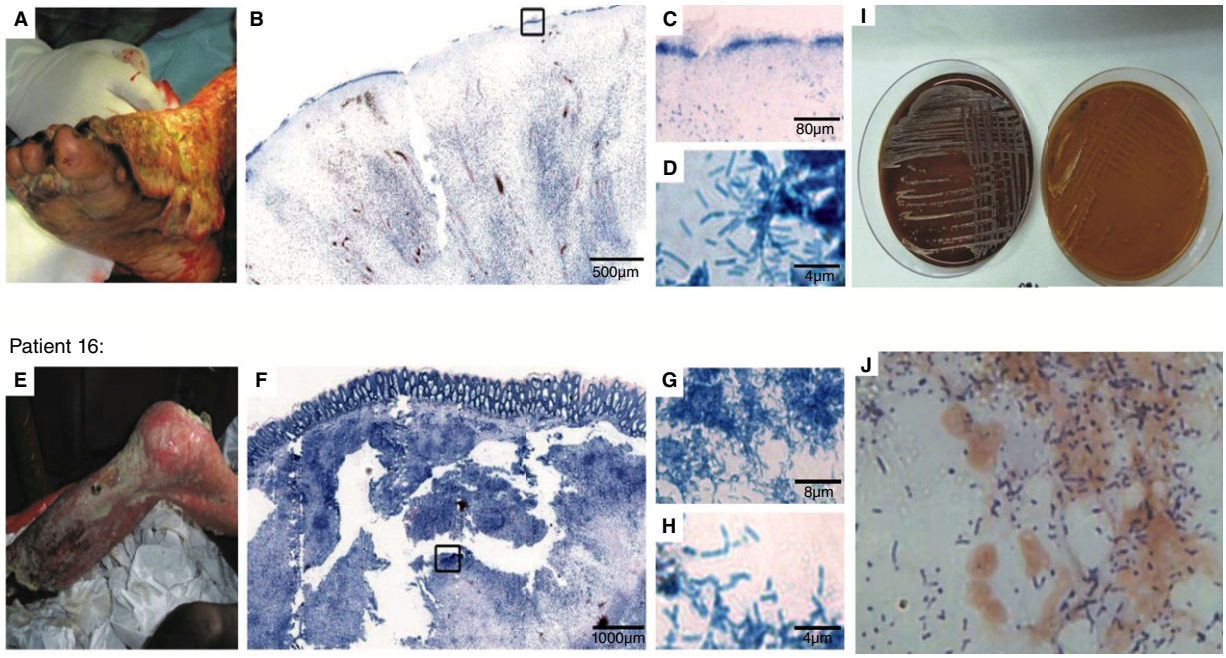

FIGURE 4 **Histopathological analysis of tissue from two patients excised weeks after SR8 treatment respectively.** Histological sections were stained with Ziehl-Neelsen (acid fast bacteria) and methylene blue (DNA, secondary infection). A: clinical presentation of a patient presenting with a large lesion on the right foot. B: overview over excised tissue specimen (open ulcer surface) revealing the presence of an infection (blue band, box). C/D: higher magnification confirming the presence of densely packed rods. E: clinical presentation of a patient presenting with a large lesion covering the left leg. F: overview over excised tissue specimen revealing an epidermal hyperplasia as well as a strong edema. G/H: secondary infection with rods of the dermal and subcutaneous tissue. I/J: microbiological analysis [65]

species. These bacteria are associated with infection and healing delay,[69–72] are frequently implicated in healthcare-associated infections, and demonstrate increased resistance to antimicrobials both intrinsically and through acquired mechanisms.[73,74] Biofilm formation by these bacteria contributes to antibiotic tolerance[70] and persistence, which could ultimately result in worse patient outcomes.[75] Secondary infection is assumed to result in severe complications, such as sepsis, tetanus, and death.[68] To prevent or reduce the occurrence of secondary infection, wound contamination and the events that could potentially lead to it must be arrested, and this will involve dealing with the sources of pathogens and optimizing wound management practices. Guidelines are released by the World Health Organization (WHO) for the prevention and management of wound infection (www.who.int/gpsc/SSI-outline.pdf?ua=1) and for prevention of surgical site infection (www.who.int/hac/techguide/tools/guidelines_prevention_and_management_wound_infection.pdf).

3.2 | BU and HIV co-infection

The synergy between *Mycobacterium tuberculosis* infection and HIV/AIDS is well established but not so in BU. HIV commonly presents with clinical anemia as part of a pan-cytopenic cell line presentation.[76–78] The severity of the anemia correlates with the extent of immunosuppression as expressed by declining CD4 count.[79] Some studies have revealed association of mycobacteria infections with worsening peripheral blood cytopenia even though such has not been proven with MU infection.[80–83] What is rather proven as a common cause of anemia in BU patients is nutritional anemia because the disease is mainly associated with persons of lower socioeconomic status.[84,85] Susceptibility to BU is associated with polymorphism in the gene for the iron transporter protein NRAMP1.[86] There are models developed to explain iron deficiency anemia in mycobacterial diseases, such as BU. Notable among them suggests sequestration of Fe^{2+} from the body into phagosomes and the lack of NRAMP1 to export the iron back, as the possible cause of the anemia,[87] which could be worsened with an HIV coinfection depending on the clinical stage and state of immunity. The combined effect of BU/HIV coinfection is therefore RBC cytopenia in addition to nutritional anemia, and the severity mostly correlate with the extent of immunosuppression developed.[85,88] Anemia negatively affects all the processes of wound healing thus leading to delay in wound healing of BU/HIV coinfected patients.[89–92] It also increases the tendency for scar breakdown leading to recurrence of ulcers.[90,93,94] Patients may therefore require periodic blood transfusion corresponding to clinical symptomatic state, but this is not without risks ranging from transfusion reactions and risk of other infections.[95–97] The incidence of severe anemia in BU/HIV coinfection may also require that a first choice drug namely Zidovudine be replaced with Tenofovir as per protocol in most Sub-Saharan regions.[85,98,99] Tenofovir however is not readily stocked at most antiretroviral therapy (ART) centers at the sub-districts and may pose serious treatment challenges.[98] In terms of effectiveness of drug therapy in BU/HIV coinfected cases, there are concerns about interaction between one of the first option ARTs (Nevirapine) and the antimycobacteria drug rifampicin, where it has been noted that the drug concentration of Nevirapine tends to decrease with such interactions.[85,99]

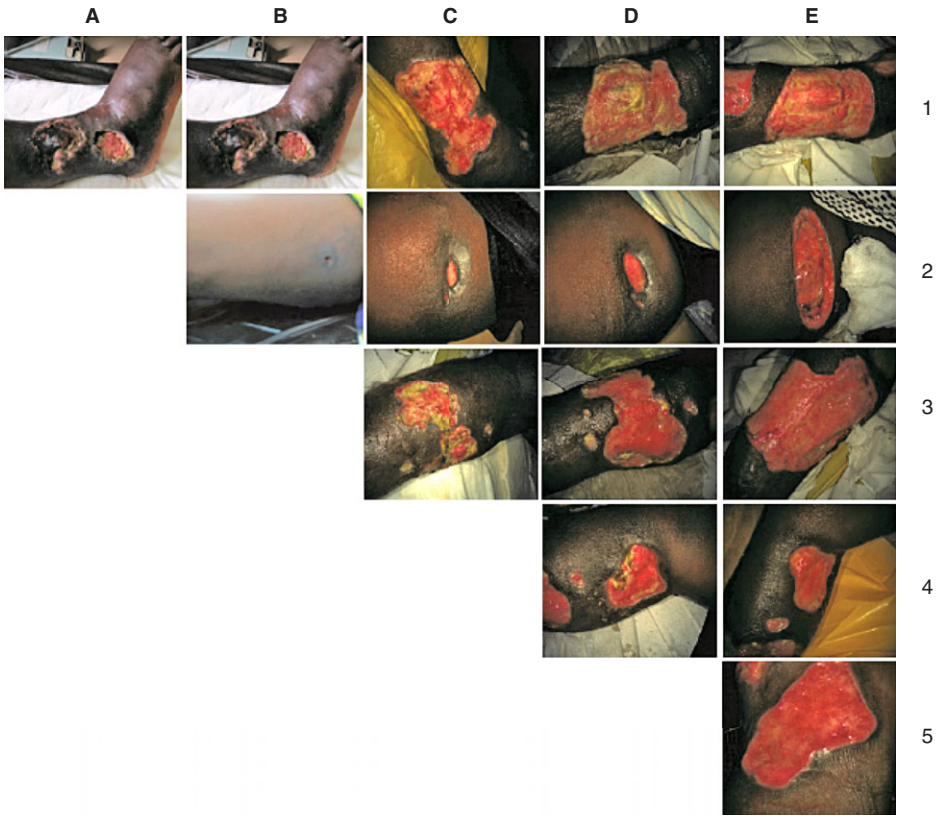

FIGURE 5 Emergence of new lesions during SR treatment in one of the enrolled coinfected patients. (A) Features of the first lesion before the start of SR treatment, (B) appearance of a new lesion after 2 weeks of antibiotic treatment, (C) appearance of a third lesion after 4 weeks of SR treatment, (D) appearance of a fourth lesion after 6 weeks of SR treatment, and (E) increase in wound sizes after surgical excision and appearance of a fifth lesion after start of the SR treatment [85]

HIV infection in BU patients worsens their disease clinical course that leads to bad prognosis and sometimes to treatment failure or to immune reconstitution inflammatory syndrome (IRIS).[85,88] The outcome results in paradoxical exaggeration of wound sizes and at times evolution of new ulcers after starting ART in patients on BU treatment.[57,58,85,100,101] Studies have demonstrated that IRIS occurs in the setting of ART initiation and it is considered as a deregulated immunologic response to a previously existing pathogen, such as MU, in BU.[101,102] Komenan has categorized IRIS into 2 stages clinically; the unmasking IRIS in which a previously unrecognized infection becomes clinically apparent as immune reconstitution occurs, and the paradoxical IRIS, which causes clinical deterioration of previously recognized and sometimes treated infections.[102,103] As previously described, paradoxical reactions are proposed to result from reversal of the mycolactone toxin-induced immune-inhibitory state via the antibiotic-mediated killing of MU organisms allowing intense immunological reaction to develop against the persisting mycobacterial Ags.[55–57] This is a common phenomenon in HIV patients starting ART with other coinfections, such as TB, cryptococcus, and *Mycobacterium avium* complex.[57] Wanda et al. showed in TB/HIV coinfection, occurrence of IRIS is increased in patients who start ART within 30 days of TB treatment initiation.[57] In one of our recent publications,[85] we followed up on the management of 7 BU/HIV-coinfected patients. We showed that during the recommended BU treatment with SR8, all patients developed immune infiltrates including CD4 T cells in their lesions. However, one patient who received ART 1 week after beginning SR treatment developed 4 additional lesions during antibiotic treatment (Fig. 5). The appropriate time to start ART in HIV patients with opportunistic infection has always been a dilemma to clinicians because ART can trigger severe IRIS-like reactions when it is commenced early; we recommend further studies to ascertain the most appropriate time to commence ART in relation to SR treatment to minimize paradoxical reactions.[85]

The goal of BU wound management is to achieve wound closure within the shortest possible time devoid of extensive limb restrictions and deformities.[85,88,104] Various studies have shown that there are challenges in achieving timely wound closure of BU/HIV wounds.[85,104] Wound closure duration of BU/HIV cases could be more than 2 times the duration to healing of HIV negative BU cases.[85,101] This could occur irrespective of the diligent wound care practices adhered to in the management of these ulcers. It is believed that the immunosuppressive state has a tendency to stall the progress of certain phases of the wound healing process, thereby leading to wounds failing to heal.[105,106]

4 | PROLONG VIABILITY OF MU IN BU LESIONS

The SR8 treatment regimen was based on observational study of patients with early lesions, which were excised after SR treatment for

2, 4, 8, or 12 weeks.[19] All lesions were culture positive until 2 weeks but thereafter all were culture negative.[19] Some follow-up studies have indicated that healing delay may occur in up to two-thirds of patients within 25 weeks from the start of SR treatment.[47,65,107–109] Sarfo et al. showed that BU cases who received SR8, MU still persisted by culture in some lesions 4 weeks after completion of antibiotic treatment despite full adherence to therapy.[110] The authors also detected mycolactone in lesions, which were both culture negative and positive. A recent publication by Sarpon-Duah et al. indicated high bacterial load at baseline contributes to persistent infection leading to slow healing.[111] In TB, subpopulations consisting of dormant or semi-dormant, antibiotic tolerant persisters survive longest during chemotherapy and are difficult to kill even with new antibacterial drug.[112–114] Likewise, it is possible that MU may enter into an altered physiological state such that it can reactivate to cause recurrent disease later, which might accounting for the prolong viability after chemotherapy. Nienhuis et al. demonstrated that antimycobacterial treatment alone was effective in patients with early BU clinical forms.[107] However, positive cultures were obtained after treatment completion in 5 patients with large ulcerated lesions. In those cases, the efficacy of antibiotics could be compromised by the extent of the necrosis.[115] There is also the possibility that the prolong viability of MU in BU lesions may be due to resistance to the currently available drugs or immune suppression by other ailments albeit data on the status of resistant MU strains circulating within endemic communities is limited. More recently, Owusu et al. investigated the susceptibility profiles of 70 MU isolates from 2 BU endemic areas in Ghana to SR at critical concentrations of 40 μg/mL and 4 μg/mL, by the Canetti proportion method. The authors reported 17.1% resistance to rifampicin and 2.9% to streptomycin.[116] The outcome although does not reflect all BU endemic areas, still it is essential for antibiotic stewardship in terms of disease surveillance and control.

4.1 | Improper wound care management

The median time to healing of early limited BU lesions has been reported to be about 18 weeks.[104,107] The long healing times therefore implies that wound management is an important component of BU wound management especially postantibiotic therapy. Good wound management is believed to reduce time to healing ultimately decreasing the risk for secondary infection, pain, and morbidity.[117] According to the authors, in several health centers in endemic countries, improper wound management was practiced.[117] Reported practices, including not washing of wounds and surrounding intact skin, removal of old dressings without moistening exposing the wounds to trauma, wounds being cleaned by rubbing cotton wool soaked with dressing solutions on the wound instead of the application of moderate-pressure irrigation, the choice of using different topical antiseptics instead of normal saline for wound cleaning, frequency of dressing changes not based on wound characteristics but on hospital policy, and the use of unsterilized materials for dressing wounds,[117] have the potential of negatively impacting the healing of patients, increasing the risk of secondary infection of wounds, and ultimately delaying their reintegration into their families and society.[117] The WHO guidelines for wound management exist and reports have shown that health workers have adequate knowledge and training on these guidelines[105,117]; however, in some health facilities, adherence to the guidelines and delivery of proper wound care is hampered by the lack of adequate infrastructure, equipment, and wound dressing supplies.[105,109] Providing appropriate facilities and tools to these health centers will empower them to be able to provide good care to patients. Periodic training of health care workers on the guidelines for wound management and monitoring to ensure compliance will go a long way to ensure compliance and increase the standard of wound care.

5 | CONCLUSION

Antibiotic therapy has proven to be essential in the management of BU requiring surgery only as an adjunct to correct deformities. Nevertheless, some patients experience poor clinical outcomes in the course of treatment. In this review, we have explored several probable factors that challenge BU case management. There is the need for more biomedical and behavioral studies for understudying the evolution of BU wounds during treatment and adherence to proper wound care for improved case management, ultimately reducing the associated long hospital stays.

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DISCLOSURES

The authors declare no conflicts of interest.

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