Colonization with Multidrug-Resistant *Enterobacteriaceae* is Associated with Increased Mortality Following Burn Injury in Sub-Saharan Africa

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Abstract

Background Multidrug-resistant (MDR) bacteria are an emerging international concern in low- and middle-income countries that threaten recent public health gains. These challenges are exacerbated in immunocompromised hosts, such as those with burn injury. This study sought to describe the epidemiology and associated clinical outcomes of burn wound colonization in a Malawian tertiary burn center.

Methods This is a prospective analysis of burn patients presenting to Kamuzu Central Hospital in Lilongwe, Malawi, within 72 h of burn injury. A swab of each patient's primary wound was collected at admission and each subsequent week. The primary exposure was burn wound colonization with MDR bacteria, particularly *Enterobacteriaceae*. The primary outcome was in-hospital mortality. A log binomial model estimated the association between the exposure and outcome, adjusted for confounders.

Results Ninety-nine patients were enrolled with a median age of 4 years (IQR 2–12) and a male preponderance (54%). Median total body surface area burn (TBSA) was 14% (IQR 9–25), and crude in-hospital mortality was 19%. *Enterobacteriaceae* were the most common MDR bacteria with 36% of patients becoming colonized. Wound colonization with MDR *Enterobacteriaceae* was associated with increased in-hospital mortality with a risk ratio of 1.86 (95% CI 1.38, 2.50, $p < 0.001$) adjusted for TBSA, burn type (scald vs. flame), sex, age, length of stay, and methicillin-resistant *Staphylococcus aureus* colonization.

Conclusion MDR bacteria, especially *Enterobacteriaceae*, are common and are associated with worse burn injury outcomes. In resource-poor environments, a greater emphasis on prevention of MDR bacterial colonization, improved isolation precautions, affordable diagnostics, and antibiotic stewardship are imperative.

Introduction

In an era of increasing global migration, bacterial infections and rising resistance to antimicrobial drugs represent a substantial threat to global public health. Substantial

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evidence exists that the prevalence of antibiotic resistance, even to last-line therapy, among many bacterial families is rapidly increasing [1, 2]. Many of these bacteria are commonly the source of hospital- and community-acquired infections and can lead to substantial morbidity and mortality.

Antimicrobial resistance is the consequence of a variety of biological, pharmacological, and societal variables that occur worldwide, particularly in low- and middle-income countries (LMICs) [3]. In addition, data suggest that antibiotic resistance is developing at a faster rate in LMICs compared to developed countries [4]. Health systems in poor countries often cannot offer the most optimal therapies or the medical technology required to appropriately deliver such medicines. The lack of routine drug sensitivity testing and surveillance in many regions results in the irrational use of antibiotics and other antimicrobial drugs [5, 6]. Furthermore, the overuse of cheap, broad-spectrum antibiotics and poor control of over-the-counter sales have fostered widespread resistance. When therapeutic failure occurs, it often arises from misdiagnosis, drug resistance, or poor drug quality.

The World Health Organization (WHO) has recognized multidrug-resistant (MDR) bacteria as an emerging international concern that threatens the effective prevention and treatment of bacterial infections [7]. While the exact definition of multidrug resistance can vary, it is frequently used to indicate resistance to representatives of three or more classes of antimicrobial agents [8]. Countries in at least five of six WHO regions have reported greater than 50% resistance to commonly used and available antibiotics for bacterial species such as *Escherichia coli* and *Klebsiella pneumoniae*, constraining clinicians in resource-poor environments to use scarce and expensive options such as carbapenems [3].

The problems of antimicrobial resistance faced in regions like sub-Saharan Africa are further exacerbated in immunocompromised hosts, such as those with burn injury. Globally, burn injuries are an important cause of morbidity and mortality in LMICs, ranking fourth in all causes of injuries [9]. Among burn patients, sepsis is the leading cause of death, in both developed and developing countries [10]. Many of the organisms commonly recovered from infected burn patients are members of the ESKAPE (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species) group of pathogens, which are often resistant to several classes of antibiotics [11]. In particular, *Enterobacteriaceae,* a family of gram-negative bacilli with many members of normal intestinal flora such *Klebsiella* and *Enterobacter* spp., are emerging as important pathogens among burn patients [12]. Burn patients are especially vulnerable to invasive infection with a breakdown of the natural skin barrier to microbes, a propensity to bacterial wound colonization, and thermal injury-associated immunosuppression [10]. At facilities in resource-poor countries, wound dressing management is dependent on limited supplies and inconsistent staffing often leading to wound infection and poor healing.

In the setting of emerging antibiotic resistance, we sought to describe the epidemiology of burn wound colonization in a Malawian tertiary burn center hypothesizing that MDR bacteria would be associated with poorer outcomes among burn patients.

Methods

We performed a prospective observational study of patients admitted to Kamuzu Central Hospital (KCH) with acute burn injury from May 2015 through November 2015. KCH is a public 600-bed tertiary care hospital in the capital city of Lilongwe, which serves as a referral center for approximately 5 million people in the central region of Malawi. All adult and pediatric patients in the study were admitted to the KCH Burn Unit, which was established in 2011 and averages 25–40 admissions per month [13]. The KCH Burn unit is a 31-bed unit with 6 full-time nurses and 2 trained clinical officer staff with surgical consultant oversight. Ward dressing changes routinely occur on Monday, Wednesday, and Friday each week in a room equipped with a bathing tank and dressing supplies. Pain control during wound changes is typically achieved with either with an acetaminophen or ibuprofen equivalent, oral morphine when available, or ketamine for large burns.

Pediatric and adult patients were included in the study if they presented with an acute burn injury that required admission, presented within 72 h of their initial injury, and consented to participate in the study. Baseline demographic and clinical data were obtained in addition to vital signs, laboratory investigation results, admission diagnoses, timing of burn excision and grafting, and mortality (lived/died).

Using BD CultureSwabs^{TM}, wound cultures were obtained at the patient's first dressing change, which occurred 24–48 h after admission. If the patient was still admitted, a subsequent culture was obtained 1 week later during their dressing change and then a third culture another week later. Cultures were taken from the patient's deepest burns when possible. Nursing staff obtained the cultures after being trained on appropriate technique. The technique included sterilely swabbing the wound bed once before application of the wound dressing. The culture swabs were immediately hand-delivered to the UNC Project Laboratory, located on the grounds of KCH, for testing.

The UNC Project Laboratory is a state-of-the-art clinical and research laboratory, with the mission to support clinical care, research, and training activities of the UNC Project. This laboratory, with a dedicated team of 24 laboratory professionals and 9 support staff, processes more than 150,000 laboratory orders annually, performs extensive quality control measures, and has been awarded 4 star status by the African Society for Laboratory Medicine.

Initially, we conducted an exploratory analysis of our exposure, defined as wound colonization with MDR bacteria. Colonization was defined as bacterial growth in at least one culture. MDR was defined by the International Expert Proposal for Interim Standard Definitions for Acquired Resistance, which requires non-susceptibility to 3 or more specified categories of antimicrobials [14]. We grouped bacteria into four categories: methicillin-resistant *Staphylococcus* aureus (MRSA), vancomycin-resistant *Enterococcus* (VRE), MDR *Enterobacteriaceae*, and MDR glucose-non-fermenting gram-negative bacilli. Based on the incidence and effect size found in our initial analysis, we defined the primary exposure for subsequent analyses as burn wound colonization with MDR *Enterobacteriaceae*. Exposure groups were binary and defined as having MDR *Enterobacteriaceae* colonization or not regardless of colonization with other MDR bacteria. The primary outcome was in-hospital mortality.

Wound specimens were delivered to the laboratory within 2 h of collection and plated to chocolate, colistin-nalidixic acid, and MacConkey media, and incubated aerobically for up to 96 h at 37 °C. Pathogens with $> 1+$ growth were identified using bioMerieux API® kits. Choice of antibiotics tested for each organism was determined by bacterial genus and based on the national list of medicines available in Malawi. *Enterobacteriaceae* were routinely tested for susceptibility against the following nine antibiotics: ampicillin, amoxicillin-clavulanic acid, cefotaxime, ceftriaxone, imipenem, gentamicin, ciprofloxacin, trimethoprim-sulfamethoxazole, and chloramphenicol by standard Kirby Bauer disk diffusion methods according to Clinical and Laboratory Standards Institute (CLSI) protocol [15].

Baseline characteristics of the study population are described. Means are reported with standard deviations (±) and medians with inter-quartile ranges (IQR). Patients who were admitted to the hospital but missed a scheduled culture were included in the analysis. Bivariate analyses were performed to examine the associations between those with MDR *Enterobacteriaceae* colonization and baseline variables, as well as MDR *Enterobacteriaceae* colonization and risk factors for inpatient mortality. The two-sample *t* test was used for normal continuous variables, the Wilcoxon rank-sum test for non-normal continuous variables, and the Pearson Chi square test for categorical variables.

A log binomial model was used to estimate the risk ratio for in-hospital mortality between those with and without MDR *Enterobacteriaceae* colonization. After fitting the initial model with in-hospital mortality and all potential confounders, we used a change-in-effect method to remove covariates that did not substantially contribute to the model to estimate an adjusted risk ratio with 95% confidence intervals.

All statistical analysis was performed using Stata/SE 13.1 (StataCorp LP, College Station, TX). The University of North Carolina Institutional Review Board and the Malawi National Health Services Review Committee approved this study.

Results

During the study period, 100 patients were enrolled and 99 included in the analysis. One patient was not included in the analysis as consent was revoked after initial enrollment. Ninety-nine patients had an initial culture obtained. Eighty patients were still admitted at the scheduled time of the second culture of which seventy-seven (96%) had a culture obtained. Forty-eight patients were admitted at the time of their scheduled third culture with 46 patients (96%) having a culture obtained.

Median age was 4 years (IQR 2–12), with a male preponderance at 53.5% (Table 1). Scald burns were the most common at 61.6%, followed by flame burns at 37.4%, with one patient having an electric burn. Most burns (52.5%) were cooking related, and nearly 90% of patients presented within 24 h. The median percent total body surface area burn (%TBSA) was 14% (IQR 9–25). Among all patients, 20.2% had surgical intervention, such as burn excision and skin grafting. The median length of stay was 15.5 days (IQR 9–28). Fifty-four patients (55%) received antibiotics: 41 patients had antibiotics started on admission, and 13 patients were initiated on antibiotics after admission. Among patients who received antibiotics, ceftriaxone was used in 76% of patients.

Over the study period, the proportion of patients with wound bacterial colonization increased substantially each week. Bacterial colonization, excluding coagulase-negative Staphylococcus, was present in 37% of patients on the first culture and increased with each subsequent culture to 64 and 83%, respectively. (Fig. 1) The prevalence of MDR bacteria also increased each week. MDR *Enterobacteriaceae* colonization was present in 8% of patients on the first culture, in 28% on the second culture, and in 40% on the third culture. Methicillin-resistant *Staphylococcus aureus* (MRSA) colonization was similarly present for 12% of patients on the first culture, for 28% on the second culture, and for 39% on the third.

During their hospital course, 36% (36 of 99) patients developed MDR *Enterobacteriaceae* colonization. (Table 1) Other than MRSA, which was detected in thirty-three patients (33.3%), other MDR bacterial species were not common. No patients were colonized with VRE, and only 4 patients (4.0%) were colonized with MDR glucose-non-fermenting gram negative bacilli. Among the 36 patients colonized with MDR *Enterobacteriaceae*, the most common genera were *Klebsiella* (13 patients, 36%), *Proteus* (13 patients, 36%), *Enterobacter* (7 patients, 19%) and *Serratia* (7 patients, 19%). Seven patients (19.4%) were colonized with more than one MDR *Enterobacteriaceae* species.

Table 1 compares characteristics of patients with and without MDR *Enterobacteriaceae* colonization. Notably, patients colonized with MDR *Enterobacteriaceae* had larger burns with a median TBSA of 18% (IQR 11–30) compared to 10% (IQR 7–20, $p = 0.001$). MDR *Enterobacteriaceae* colonization was more common in those with flame burns than scald burns (58.3 vs. 25.4% ($p = 0.004$), and more patients with MDR *Enterobacteriaceae* colonization had surgery for their burn injury, 41.7% compared to 7.9% ($p < 0.001$). However, all but one patient had a positive culture for MDR *Enterobacteriaceae* prior to their first surgery. Patients with MDR *Enterobacteriaceae* colonization also had a longer length of stay than those without MDR *Enterobacteriaceae* colonization with a median of 27 days (IQR 18–49) versus 12 days (IRQ 7–21), $p < 0.001$.

Overall, crude in-hospital mortality was 19.2%, consistent with previously published data from our patient population [16, 17]. Among those with MDR *Enterobacteriaceae* colonization, in-hospital crude mortality was significantly higher at 36.1% compared to those without MDR *Enterobacteriaceae* colonization at 9.5% ($p = 0.001$) (Table 2). The unadjusted risk ratio of death for those with MDR *Enterobacteriaceae* colonization compared to those without was 3.79 (CI 1.58, 9.11). When controlling for TBSA, burn type (scald vs. flame), sex, age, MRSA colonization, and length of stay, the adjusted risk ratio of death for patients with MDR *Enterobacteriaceae* colonization was 1.86 (CI 1.38, 2.50).

Discussion

Patients with burn wounds are frequently exposed to antimicrobial agents throughout their hospitalization, increasing the likelihood of colonization or infection with drug-resistant organisms. The presence of burn wound colonization with MDR *Enterobacteriaceae* was associated with an increasing TBSA, flame burns, and an increased length of stay. The prevalence of these bacteria increased notably each week with over one-third of patients colonized by their second week in the hospital. Most importantly, colonization with MDR *Enterobacteriaceae* was associated with an 86% increased risk of mortality after adjustment for significant covariates.

The sources of MDR bacteria in our unit were not elucidated by this study but evidence suggests most patients acquired their MDR bacteria in the hospital. Data over the last few decades have demonstrated that hospitals, especially acute care tertiary facilities, are a common "breeding ground" for antibiotic resistance [18]. The presence of MDR bacteria is especially concerning for burn centers in low-resource settings where overcrowding and limited supplies make isolation nearly impossible, creating a hazardous environment for the spread of infection and the development of resistance in an immunocompromised population. Evidence from the literature and our experience in Malawi also suggests several possibilities for community-acquired colonization among the 10% of our patients that presented to the hospital colonized with MDR bacteria. The use of antibiotics in Malawi and in many LMICs is largely unregulated leading to overuse of certain classes [19]. There is also a dearth of clinicians available for diagnosis and treatment, and when they are accessible they have often have very limited diagnostic adjuncts for managing infections [5, 19, 20].

Unfortunately, there is a paucity of data from sub-Saharan Africa on the incidence of MDR bacterial colonization and infection among burn patients. Limited evidence from Nigeria, Ghana, and Malawi suggests that bacterial antibiotic resistance is common among burn wound cultures [21–24]. Several evaluations of burn wound microbiology in middle- or low-income countries outside of this region have demonstrated similar findings [25–33]. However, from the published literature, the relationship between burn wound colonization with MDR bacteria and patient outcomes in LMICs is unclear. In high-income countries, retrospective data has shown conflicting evidence on the association between MDR bacterial colonization or infection and hospital length of stay. Furthermore, the literature is equivocal on the relationship between MDR bacterial colonization and burn-associated mortality [34, 35]. While our study did not show burn wound colonization progressing to systemic infection, we clearly demonstrated an association between MDR *Enterobacteriaceae* colonization and mortality after adjusting for relevant confounders in our patient population. Increased mortality may result from a failure to recognize the progression from wound colonization to invasive disease or from inappropriate empirical antimicrobial therapy, which can lead to eventual sepsis, multi-organ failure, and death [36–38]. Given the limitations, our unit faces in the prevention, diagnosis, and treatment of sepsis, the risk of

Table 1 Characteristics of all study patients with a subgroup comparison of patients by colonization of multidrug-resistant (MDR) *Enterobacteriaceae*. *p* values are based on subgroup bivariate analysis using two-sample *t* test for normal continuous variables, Wilcoxon rank-sum for non-normal continuous variables, and Pearson Chi square test for categorical variables

	All Patients (*n* = 99)	Colonized with MDR *Enterobacteriaceae* (*n* = 36)	Not colonized with MDR *Enterobacteriaceae* (*n* = 63)	*P* value
Age (years)				
Median (IQR)	4 (2–12)	5 (2–28)	3 (2–9)	0.06
Sex, *n* (%)				
Male	53 (53.4)	23 (63.9)	30 (47.6)	0.1
Female	46 (46.6)	13 (36.1)	33 (52.4)	
Burn type, *n* (%)				
Scald	61 (61.6)	15 (41.7)	46 (73.0)	0.004
Flame	37 (37.4)	21 (58.3)	16 (25.4)	
Electric	1 (1.0)	0 (0.0)	1 (1.6)	
Cooking-related injury				
n (%)	52 (52.5)	14 (38.9)	38 (60.3)	0.040
Presented within 24 h of injury				
n (%)	86 (86.9)	30 (83.3)	56 (88.9)	0.5
Total body surface area burn (%)				
Median (IQR)	14 (9–25)	18 (11–30)	10 (7–20)	0.001
Received surgical intervention for burn				
n (%)	20 (20.2)	15 (41.7)	5 (7.9)	< 0.001
Received antibiotics				
n (%)	54 (54.6)	22 (61.1)	32 (50.8)	0.3
Length of stay (days)				
Median (IQR)	16 (9–28)	27 (18–49)	12 (7–21)	< 0.001
Colonized with methicillin-resistant *Staphylococcus aureus*				
n (%)	33 (33.3)	17 (47.2)	16 (25.4)	0.027

inadequately treating infection with MDR *Enterobacteriaceae* may be magnified in our patient population compared to higher resource settings.

In order to adequately address this crisis, it is imperative to identify specific practices that contribute to the development of multidrug resistance and implement cost-effective strategies to address them. In the context of burn care, substantial improvements are required in basic isolation practices such as disposable dressings, cleaning supplies, and sufficient hospital rooms to admit patients. In addition, diagnostic resources are lacking in many institutions, where even basic laboratory studies are not available, making it very challenging to appropriately target antibiotic therapy to patient-specific infections. Evidence also suggests that early excision of burn wounds significantly reduces bacterial colonization and clinical wound infection [39]. While we have shown that early excision is associated with increased mortality in our patients, more aggressive excision may play a role in an effort to control wound infection [17]. Antibiotic stewardship is also important in preventing resistance. Recommended strategies include avoiding antibiotic prophylaxis for acute burn injury as well as monitoring for appropriate use of antibiotics in both the inpatient and outpatient settings [40]. Lastly, a need exists to make additional classes of antibiotics available in LMICs as well as to develop new antibiotics. In February 2017, the WHO issued an urgent call to develop new antibiotics for twelve families of bacteria, including *Enterobacteriaceae* in their critical category [41].

The strength of our study is its prospective methodology and the quality of our laboratory. We are the only prospective study to assess the microbiology of burn wounds serially during hospitalization in sub-Saharan Africa and the only study to our knowledge to examine the association between MDR bacterial colonization and mortality in LMICs. Our study is limited by a lack of blood cultures and other diagnostic adjuncts such as basic laboratory studies. However, given our resource constraints, it was not possible to obtain these data for every patient. In addition, we chose to use wound swabs for culture rather than tissue biopsies due to feasibility and based on data that have shown relative equivalence between the two

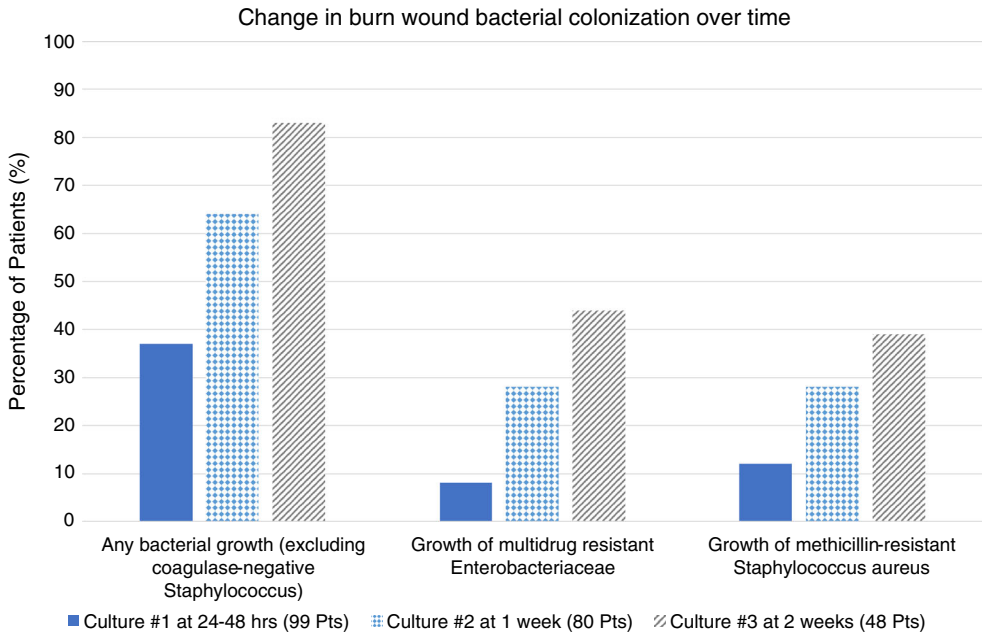

Fig. 1 Changes in colonization with any bacterial species (excluding coagulase-negative *Staphylococcus*), multidrug-resistant *Enterobacteriaceae*, and methicillin-resistant *Staphylococcus aureus* comparing first, second, and third cultures

Table 2 In-hospital crude mortality based on multidrug-resistant (MDR) *Enterobacteriaceae* colonization with the unadjusted and adjusted risk ratio of death for those patients with MDR *Enterobacteriaceae* colonization compared to those without

	Colonized with MDR *Enterobacteriaceae* (n = 36)	Not colonized with MDR *Enterobacteriaceae* (n = 63)	P value
In-hospital crude mortality			
N (%)	13 (36.1)	6 (9.5)	0.001
Unadjusted risk ratio of death	3.79 (CI 1.58, 9.11)	1.00	0.003
Adjusted risk ratio of death	1.86 (CI 1.38, 2.50)	1.00	< 0.001

The adjusted risk ratio is adjusted for total body surface area, burn type (flame vs. scald), sex, age, length of stay, and methicillin-resistant *Staphylococcus aureus* colonization

modalities [42]. While we were not able to show causality between positive wound cultures with MDR *Enterobacteriaceae* and the cause of death, we were able to adjust for relevant confounders in our model including risk factors for mortality in our patient population.

Conclusion

Our study demonstrates that among burn patients in an urban sub-Saharan African burn center, MDR bacterial wound colonization is very common, and MDR *Enterobacteriaceae* are associated with an increased risk of death. MDR bacteria are a critical global health issue, and an urgent response is required. In resource-poor environments, a greater emphasis on prevention of MDR bacterial colonization, improved isolation precautions, affordable diagnostics, and antibiotic stewardship are imperative.

Author contributions JRG, MD, MPH contributed to this paper by design of study, acquisition, analysis, and interpretation of data, drafting and revision of the manuscript, and statistical analysis. AML, MD, MPH contributed to this paper by interpretation of data, critical drafting and revision of the manuscript, and statistical analysis. WB, MB, BS contributed to this paper by design of study, critical revision of the manuscript for important intellectual content, and administrative and technical support. RK, MS contributed to this paper by design of study, acquisition of data, critical revision of the manuscript for important intellectual content, and administrative and technical support. BAC, MD contributed to this paper by design of the study, revision of the manuscript for important intellectual content, supervision, and the obtaining of funding. AGC, MD, MPH contributed to this paper by conception and design of the study, acquisition, analysis,

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Data availability Jared R. Gallaher, MD, MPH and Anthony G. Charles, MD, MPH had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Compliance with ethical standards

Conflict of interest The authors have no conflict of interest to disclose. The authors have no financial relationships to disclose. A.M.L.: Destum Partners and KPB Biosciences, Consulting. GlaxoSmithKline, Research funding. No other disclosures.

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