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# **Multiple Drug Resistance in Burn Patients**

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#### *Authors' contributions*

*This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.*

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#### **ABSTRACT**

Infections, the most frequent outcomes and the leading cause of death in burn patients, reproduce in milieux generated by burn lesions, Severely burned patient's immunity is weakened, thus systemic infections such as pneumonia and urinary tract infections are likely to develop. New diseases which have come up and are hardly combatted by many drugs offer a major threat in therapy; new antimicrobial medicines and effective measures that prevent infection have to be used. Due to their high mortality, these infections form a major concern to the increasing cases of MDROs in burn victims. Given that the surfaces of burn related injuries are broad, the patients' immune systems are compromised, while they require several surgeries and lengthy hospitalization, they are easy targets for MDROs. Among the published studies, it is revealed that multidrug-resistant organisms (MDROs) are on the rise among burn patients, which poses a threat to patient outcomes as well as the treatment of the condition. As a result of skin degeneration, longterm hospitalizations, and the necessity for invasive procedures, all of which contribute to the development of infections, burn patients are particularly vulnerable.

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#### **1. INTRODUCTION**

Despite the occurrence of burn injuries decreasing globally, and the rate of burns continuing to decline in many countries, advancing age remains the single most important predictor of those likely to present with a burn.mortality rates as a result of improved burn care and systems, burn incidence still continue to be prevalent in the society and are estimated to affect approximately 11million cases annually [1]. These injuries are more common in the low and/or middle-income families and subpopulations such as occupational injuries. lower-middle income countries (LMICs), due to socioeconomic characteristics, insecure working environments, and poor measures on safety make working conditions worse the risk [2,3]. Burns of the skin prepare first-class conditions for an infection attack which are the complications that occur more often and the major cause of death among burn patients [4,5]. The immune suppression following severe is transmitted from the prior research studies as saying that burns, the patient becomes more susceptible to invasive forms of infection, including such as pneumonias, urinary tract infections (UTI), and sepsis (BSIs) [6]. More so, new strains that are multi-drug resistant make the battle against treatable diseases even harder treatment that calls for new approaches towards antimicrobial treatment and very high standards infection control measures [7]. The burden of burns, measured in disability-adjusted life years (DALYs), remains substantial, with significant economic losses, particularly in LMICs where access to specialized burn care is limited [8,9].

The consequence of burns in terms of DALYs still holds a considerable impact, and also, financial losses, especially in LMICs with relatively rare opportunities for access to adequate burn treatments. Infections with MDROs in burn patients have a high potential of morbidity and mortality hence are a matter of great concern. Patients with burn injuries are more vulnerable to acquire MDROs due to the immunosuppressive state that accompanies burn injury, large area of exposed body surface, requirements of long hospital stay and multiple invasive procedures [10-12]. When it comes to the frequency of MDROs in burn cases, it was found that Pseudomonas aeruginosa, Staphylococcus aureus, and Enterobacter species are often cultured from burn patients

especially Pseudomonas aeruginosa [13-15]. The rate of MDROs in burn units depends on combined clinical and organizational factors such as antibiotic administration, invasive devices, and the lack of appropriate antimicrobial therapy [6,16].

#### **2. EPIDEMIOLOGY OF MDROs**

Burns are initially aseptic but become infected by bacteria the later days or a week after the burn; early biofilm formation is usually by the skin flora, gram positive cocci like Staph, Aureus within the first two days [16]. Observing the change of the wound environment, the gram-negative pathogens of respiratory and gastrointestinal origins such as Pseudomonas aeruginosa and Acinetobacter baumannii become more common [17]. It is worth mentioning that the problem of acquiring MDROs is closely connected with burn patients as local studies have shown that 11. 3% to 65. Thus, study concluded that 85 per cent of the analysed burn patients developed MDROs during their hospitalisation. These infections exert complications on the patients' status with high morbidity, mortality, and overall increased length of hospitalization [18,19]. Some of the factors considered to put patient at risk of acquiring MDROs include , TBSA > 45%, length of stay in the hospital and use of invasive catheters and endotracheal tubes among others [20,21,11].

The burn patients have higher risks of developing MDROs because the bacteria are commonly drug-resistant complicating the treatment of these patients, thus increasing mortality and morbidity rates. From the various papers that have done there is evidence that in burn patients a number of particular pathogens are considered to have high infection rates. For example, research done on a patient population in a specifically a burn intensive care unit in a U S military hospital over the period 2003- 2008 found Acinetobacter baumannii, Pseudomonas aeruginosa, Klebsiella pneumoniae and S. Aureus to be the most common bacteria; these organisms contributed to 76% of all the infections. This is in consonance with what other several studies have revealed. For instance, the common organisms isolated in burn units include Pseudomonas aeruginosa and Staphylococcus aureus of which Pseudomonas aeruginosa is cited to be highly resistant and has linked to increased case fatality rate [11,22,23].

Additionally, Enterococcus spp. and Enterobacter spp. Although they are relatively rare, they are attributed to contributing to a large fraction of the infection load in burn patients [12,14,20]. Presence of these pathogens has highlighted the need for constant microbiological sampling as well as the adherence to Infection Prevention and Control measures in form of hand washing and proper use of antimicrobial drugs [16,24]. Moreover, the risk factors for MDRO acquisition in burn patients include prolonged hospital stays, the use of invasive devices, and inadequate antimicrobial treatment, which necessitate targeted interventions to improve patient outcomes [25].

#### **3. MULTI-MODEL STRATEGIES FOR PREVENTION AND CONTROL**

The use of dressed and gloved hands decreases infections caused by the patients' own microbes or from the health facility environment with multidrug resistant organisms (MDROs), and therefore proper infection prevention and control is essential in burn centers. A proper and effective way of cleaning and disinfection of the hospital surfaces can go a long way in minimizing the spread of MDROs. Some disinfection practices like UV devices and hydrogen peroxide have been found to reduce the incidences of infections with a range of up to 85% of some MDROs [26,27]. Patients who have burn injuries are at high risk for infections because of the loss of skin integrity and immunomodulation, which affects their resistance to both site-specific and systemic infections [11,14]. Essential measures in the care of burn patients that affect MDRO spread include use of hand hygiene, proper environmental cleaning, and protective clothing [25,28]. Specific to MDRO healthcare-associated infections, several research investigations have shown that implementation of multi-modal approach comprising of staff training and education, patient cohorting or isolation, and use of barriers and protective apparel before dealing with the infected patient can help to minimize the transmission of the associated pathogens [28,29]. Also, improving in burn and wound grafting in early days also helps to reduce the days of hospital stay, risk of infection, and mortality rates. Newer modalities of antimicrobial treatment like cold plasma and topical antiseptics [15], use of rapid diagnostics, and antimicrobial stewardship as other strategies that help to contain MDRO infections [30].

In a study by Rubin et al.2023 about the impact of whole patient cohort decolonization on an emerging MRSA outbreak in a burn ICU, the authors established that decolonization played a crucial role in controlling nosocomial infections in such high-risk group of patients [31]. Likewise, Yahia et al. 2023 identified a decreased incidence of MRSA infection when nasal mupirocin was used in the implementation of targeted decolonization protocols [32]. However, single interventions that include universal contact precautions including the wearing of gloves only have been proven to have minimum success in stopping the spread of MDROs possibly due to high hand contamination rate after removal of gloves which defeats the aim of supporting the use of the precautions [33]. This is in agreement with other studies that stress the need for strict universal precaution measures among which is hand washing [34]. Furthermore, the restrictive use of antibiotics abbreviated as antimicrobial stewardship has been found to enhance the patients' status and minimize the spread of MDROs especially when augmented with other measures like decontamination and proper cleaning the environment [35]. For instance, a study on the implementation of a nasal antiseptic decolonization program in ICUs reported a reduction in healthcare-associated infections (HAIs), including MRSA bacteremia, further validating the effectiveness of decolonization measures [36].

#### **4. ANTIMICROBIAL STEWARDSHIP**

Antimicrobial stewardship (AMS) is strategic in the health care system to ensure efficient usage of antimicrobial agents that will increase patient benefits, safety and the prevention of infection for instance Clostridium difficile [37]. The appearance of multidrug-resistant organisms (MDROs) is a challenge here, especially in burn infections because they are receptive to such resistant flora [38]. AMS programs are endowed to have devised various strategies, prudent selection of the antimicrobial therapy, dosing, duration of therapy and de-escalation empirics on the basis of the microbiologic data [39]. These programs also put priorities on the ways of stopping the bacteria from spreading, namely, hand washing and computerized alert methods within the healthcare setting [40]. Studies have found that ICU is the area of highest antimicrobial resistance rates and pharmacological intercessions and that AMS interventions can enhance the rank and quality of AB usage while not subsiding patient outcomes [41]. Moreover, the works about the AMS programs show that the programs have positive effects on shortening the length of hospital stay, readmission rates, and the mortality linked to the infections, as well as decreasing the healthcare costs and occurrence of Clostridium difficile colitis [42].

#### **5. RAPID IDENTIFICATION AND ANTIMICROBIAL SUSCEPTIBILITY TESTING**

Conveyance and testing of antimicrobial susceptibility are crucial in the right utilization of antibiotics so that patients benefit by having a reduced risk of mortality or other poor BSIs outcomes. The Accelerate PhenoTest BC Kit is one such innovation capable of identifying the pathology, as well as the likely antibiotic resistance patterns, in about 7 hours, in contrast to the typical 48 to 72 hours incurred by conventional methods [43]. It is critical since changes may be required for patients at a much faster rate, which may lower the morbidity/mortality of their infections. Other rapid testing systems, like Biofire Filmarray and Verigene, also perform the versatility of testing various bacteria and antibiotic resistance genes which leads to prompt and perfect diagnosis. [44] For example, EUCAST-RAST may give results within 4 to 8 hours, although depending on the pathogen, its performance differs; S.aureus was found to have a 100% categorical agreement in 4 hours [45]. Other new strategies include the use of the FAST™ System, which enriches and captures microbial flora from right blood cultures for identification within 30 min and can be used directly for other downstream testing with resistance identification [46]. Also, such techniques as microfluidic ladder-based system and automated platforms for rRNA flourescent probes made AST shortened to 4-5 hours with high sensitivity and concordance with conventional techniques [47-49].

Pneumonia developing on a ventilator is a real problem among burn patients, the development of which contributes to a worst outcome if not treated timely and correctly. The following outcomes are worsened by the first use of wrong antibiotics; these include; The first course of incorrect antibiotics increases the occurrences of these results since the targeted healthcare facilities have a notorious reputation for causing multidrug-resistant organisms (MDROs). There is the development of rapid diagnostic methods as important means by which the pathogens

causing the infection and their patterns of resistance to antimicrobial agents can be determined to enable the right decisions as to which stiff narrower-spectrum antibiotics to use. Some molecular methods like multiplex PCR, can detect in hours a broad spectrum of pathogens and resistance markers improving diagnosis accuracy and time [50]. Likewise, in the case of nanopore-based metagenomic nextgeneration sequencing (mNGS), pathogens together with AMR genes can be identified within approximately 5 hours, which is far more efficiently than in cultures [51,52]. Other methods such as GeneXpert Carba-R that targets carbapenem-resistant genes straight from the clinical specimen similarly reported very high sensitivity alongside specificity which helped in greatly improving the detection of the resistant strains including the Acinetobacter baumannii and the Klebsiella pneumoniae [53]. These advancements are most useful in the ICU where VAP is prevalent and which incurs hefty morbidity and mortality rates [54]. These quick diagnostic tests could be of value for the early institution of effective antimicrobial therapy and minimize the chance of MDROs and enhanced clients' outcomes [55].

PNA-FISH, short for Peptide Nucleic Acid Fluorescence In Situ Hybridization, is a type of molecular technique that enables the identification of microorganisms within a comparatively short time span from clinical specimens without the need to culture the specimens. This method employs Fluorescently tagged Peptide Nucleic Acid probes that binds to RNA of specific targets' ribosomal RNA of pathogenic bacteria, hence can be visualized using fluorescence microscope. Commercial quantitative DNA probe PNA-FISH has been cleared by FDA for its use in blood cultures and in animal model the technique has been used to identify pathogens in wound of burn patients. The use of PNA-FISH especially in cases of burn wounds is desirable since it is very timely not only in detection but also in management. In some cases, the culture methods may even take several days, while PNA-FISH can take not more than a few hours, thereby making clinical decisions faster. This is the reason why this rapid identification is critical especially in burn wound care where infections can lead to sepsis or other complications [56-58]. Also, through the application of PNA-FISH, the number of cases where empirical broad-spectrum antimicrobials are utilized will be minimized; thereby preventing possible emergence of MDROs [59,60]. It has been documented that these culture-independent techniques such as PNA-FISH and FISHseq give other relevant and maybe otherwise unnoticed kinds of diagnostic data such as novel bacterial forms, non-plankton forms and microbial biofilms, which are usual in chronic and non-healing wounds [61,62].

#### **6. TREATMENT OPTIONS FOR MDROs**

#### **6.1 Methicillin-Resistant** *Staphylococcus aureus*

Vancomycin remains the first-line treatment for methicillin-resistant *Staphylococcus aureus* (MRSA) infections, but its use is challenging in burn patients due to variable renal function, necessitating careful dosing to achieve therapeutic trough concentrations of 15-20 mg/L. However, AUC-based dosing is preferred to minimize nephrotoxicity and ensure efficacy, especially when the minimum inhibitory concentration (MIC) exceeds 2 mcg/mL, at which point alternative therapies are recommended [63,64]. Daptomycin serves as a viable alternative for MRSA wound and bloodstream infections, offering simpler renal dosing and higher efficacy at doses of 8-10 mg/kg daily for critically ill patients, although it is ineffective for lung infections due to inactivation by pulmonary surfactant [65,66].

Linezolid, an oxazolidinone antibiotic, is frequently employed to treat methicillin-resistant *Staphylococcus aureus* (MRSA) pneumonia and skin infections due to its efficacy against Grampositive bacteria and its ability to achieve high concentrations in lung fluid and tissues [67,68]. Its mechanism involves binding to the 50S ribosome, inhibiting protein synthesis, which is effective against a range of Gram-positive organisms, including multi-resistant strains [69,70]. However, its bacteriostatic nature, which inhibits bacterial growth rather than killing the bacteria outright, makes it less suitable for bloodstream infections (BSI) where bactericidal (bacteria-killing) activity is often preferred [71]. In critically ill patients, the pharmacokinetics and pharmacodynamics of linezolid can be<br>significantly altered, necessitating careful significantly altered, necessitating careful consideration of dosing regimens to ensure therapeutic efficacy while minimizing the risk of adverse effects [72,73]. Due to side effects seen with long-term use of linezolid, reported to range from severe to life threatening, patients with underlying diseases should not take the drug because it can cause acute multiorgan failure

[74,75]. However, linezolid in particular and has demonstrated a favourable clinical success rate of 82.2% in Gram positive infections in a multicenter studies in the critically ill patient population [74-76].

Ceftaroline is a fifth-generation cephalosporin; it has shown the best activity against MRSA because of its high affinity to PBP-2a [77]. They are approved for the management of CAP and cSSTIs in adults and children; their clinical and microbiological outcomes are comparable to current agents [78,79]. Ceftaroline has also been used in MRSA pneumonia including burn patients at a dose of 600mg every 12h although 8h dosing is also standard [80,81]. Ceftaroline resistance in MRSA strains has been reported in the literature, though, the level of resistance tend to differ from one region to another. For example, one study showed that 2.9% of pediatric MRSA isolates had intermediate resistance to ceftaroline of which health care associated infections were predominant [82]. Others found that 7.69% of MRSA isolates had developed high minimum inhibitory concentrations MICs for ceftaroline a sign of the developing resistance [83]. The resistance is frequently connected to mutations of the mecA gene, which codes PBP2a, but one can also mention chromosomal mutations of the second level [84]. Nonetheless, ceftaroline still offers an important option in the management of severe infection associated with resistant pathogens such as MRSA, because of its dosing versatility and favorable safety profile [85].

Newer generation tetracycline, eravacycline and omadacycline demonstrated good activity against MRSA in vitro. Omadacycline is approved for use in two conditions, namely community acquired bacterial pneumonia- CABP and acute bacterial skin and skin structure infections- (ABSSSI) [86,87]. It has shown non inferiority to the other antibiotics in the phase III clinical trials for these indications and better tolerability profile and significantly less risk of events that would lead to withdrawal from the trial [88,89]. On the same note, omadacycline exhibits excellent activity against M. abscessus , a hard-coded strain in both laboratory and animal models, implying pale into the treatment of hard to fight lung infections [90,91]. On the other hand, eravacycline is used to treat complicated intra abdominal infections, has demonstrated potent efficacy against MDR-A. baumannii especially when used together with other antibiotics such as amikacin [92]. Each of the antibiotics belongs to the broad-spectrum group, and their pharmacokinetics was studied in patients with different diseases, which means that dose modification is not required in case of comorbidities [93]. Omadacycline also has immunosuppressive/immunostimulatory activity, and this property might improve the drug's effectiveness in treatment options where immune modulation is useful [94].

### **6.2 Therapeutics for Vancomycin-Resistant Enterococcal**

Vancomycin-resistant enterococci or VRE are important health care or nosocomial acquired pathogens and E.faecium is more resistant to vancomycin than E.faecalis [95]. These bacteria are well known to be resistance to most if not all the anti-gram-positive agents, a factor that presents a great deal of difficulty in clinical practice [96]. While VRE may occasionally be susceptible to β-lactams, such instances are rare, necessitating alternative treatment strategies [97]. Linezolid and high-dose daptomycin are commonly used treatment options for VRE infections. Linezolid, an oxazolidinone, has been particularly effective, although resistance to this drug has also been reported in some strains [98]. High-dose daptomycin, often combined with other antibiotics such as ampicillin, ceftriaxone, or ceftaroline, has shown efficacy in treating VRE infections, especially in cases of persistent bacteremia and infective endocarditis [99]. Though eravacycline is less effective for urinary tract infections (UTIs), newer antibiotics including omadacycline have shown action against VRE [100]. Particularly in intensive care units (ICUs), the frequency of VRE in clinical settings emphasizes the need of strict infection control strategies and antibiotic stewardship programs to stop the dissemination of these resistant organisms [101].

### **6.3 Addressing Carbapenem Resistance in** *Klebsiella pneumoniae*

Particularly in immunocompromised individuals, Klebsiella pneumoniae carbapenemases (KPCs) are a major cause of carbapenem resistance in Enterobacteriaceae, therefore constituting a major public health risk [102,103]. Introduction of new innovative β-lactam/β-lactamase inhibitors such ceftazidime-avibactam has shown successful against KPC-producing bacteria; nevertheless, resistance is occurring owing of alterations in the KPC enzyme [104-106]. These inhibitors are ineffective against class B metalloβ-lactamases (MBLs) and some class D βlactamases, necessitating alternative treatments

[107,108]. Combination therapies and novel drugs such as cefiderocol, which has shown high activity against MBL-producing isolates, are being explored to address these resistant strains [109,110]. Plazomicin and eravacycline are also effective against carbapenem-resistant K. pneumoniae (CRKP), but their clinical data is limited, and resistance issues persist [109].

#### **6.4 Effectiveness of Ceftolozane-Tazobactam Against Resistant**  *Pseudomonas aeruginosa*

Ceftolozane-tazobactam (C/T) is a potent combination drug used to treat serious infections caused by Pseudomonas aeruginosa, including multidrug-resistant (MDR) and carbapenemresistant strains. Despite tazobactam's inability to inhibit carbapenemases, C/T remains effective against many resistant strains due to ceftolozane's robust activity against P. aeruginosa, including carbapenem-resistant isolates when resistance mechanisms other than carbapenemase production are involved [111,112]. Studies have shown that C/T is highly active against P. aeruginosa, with susceptibility rates exceeding 90% in various regions, although resistance can occur, particularly in strains harboring metallo-beta-lactamases (MBLs) like blaIMP and blaVIM [113-115]. Comparative studies indicate that C/T and ceftazidimeavibactam (CAZ-AVI) have similar effectiveness and safety profiles for treating MDR P. aeruginosa infections, with no significant differences in clinical outcomes such as mortality and clinical cure rates [116]. Additionally, imipenem-cilastatin-relebactam (IMI-REL) has shown efficacy against P. aeruginosa, including strains resistant to C/T, although resistance patterns vary geographically [117]. Cefiderocol (CFD) is another promising agent, demonstrating high effectiveness against various resistant strains, including those resistant to C/T, and showing synergistic effects when combined with other antimicrobials like CAZ-AVI and Fosfomycin [118].

### **6.5 Carbapenem-Resistant** *Acinetobacter baumannii*

Acinetobacter baumannii, a significant nosocomial pathogen, often exhibits resistance to carbapenems, posing a substantial treatment challenge [119,120]. Polymyxins, such as colistin, are effective against carbapenemresistant A. baumannii (CRAB) but are

associated with severe nephrotoxicity and neurotoxicity, limiting their use [121,122]. Minocycline remains a viable option, although its efficacy can be compromised by biofilm formation, which necessitates higher antibiotic concentrations to eradicate biofilm-associated cells compared to planktonic cells [123]. Tigecycline, while useful, has shown higher mortality rates when used as monotherapy compared to combination therapies, such as cefoperazone/sulbactam, which have demonstrated better clinical outcomes in CRAB bloodstream infections (BSI) [124,125]. Cefiderocol, a novel siderophore cephalosporin, has shown potent activity against multi-drugresistant Gram-negative pathogens, including CRAB, and is particularly effective against strains with various β-lactamase enzymes [125,126].

### **7. CONCLUSION**

The increasing prevalence of multidrug-resistant organisms (MDROs) in burn patients poses a significant threat to effective treatment and patient outcomes. Burn patients are particularly vulnerable due to their compromised skin barrier, prolonged hospital stays, and frequent use of invasive devices, which facilitate the spread of infections. The rise of MDROs such resistant strains of Pseudomonas and methicillin-resistant Staphylococcus aureus (MRSA) complicates therapy even further. To stop the spread of these organisms and lower antibiotic pressure that chooses for resistant strains, effective infection control strategies including strict hygienic standards and antimicrobial stewardship are important. Appropriate antibiotic usage depends on regular microbiological surveillance and sensitivity testing, which also help to prevent the spread of resistance.

#### **DISCLAIMER (ARTIFICIAL INTELLIGENCE)**

Authors therefore affirm that text-to-- picture generators and NO generative artificial intelligence technologies like Large Language Models (ChatGPT, COPILOT, etc) have been utilized while authoring or editing of papers.

#### **CONSENT AND ETHICAL APPROVAL**

It is not applicable.

#### **COMPETING INTERESTS**

Authors have declared that no competing interests exist.

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