Which trial do we need? Evaluation of systemic antibiotics as primary prophylaxis in mechanically ventilated patients with burn injuries

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Burn injury is a frequent source of morbidity and mortality worldwide, and infection is a leading cause of death [1,2]. In mechanically ventilated patients who sustain a burn injury, ventilator-associated pneumonia (VAP) is common and associated with poor outcomes and a high risk of recurrence [3,4].

Antibiotic use is common in patients admitted with burn injuries. Current guidelines do not recommend general antibiotic prophylaxis in patients with burn injuries, yet approximately 35% to 60% of patients receive broad empirical systemic antibiotics early in hospitalization [5,6]. Overuse of antibiotics in patients who are likely to be hospitalized for a prolonged amount of time contributes to the development of infection and colonization with multidrug-resistant organisms. Notably, in patients with burn injuries, infections with multidrug-resistant organisms are common and are associated with prolonged hospital length of stay (LOS), more days of mechanical ventilation, increased surgical procedures, and, unsurprisingly, more days on antibiotics [4,7].

Current data do not support the use of antibiotic prophylaxis in paediatric and adult patients with burn injuries who are not mechanically ventilated [8–10]. However, limited data are suggesting that the use of antibiotics as primary prophylaxis for the prevention of VAP may be of utility in mechanically ventilated adult patients with burn injuries [5,10]. In support of this, there have been multiple studies in mechanically ventilated patients in intensive care unit (ICU) looking at the effects of antibiotics versus no antibiotics for the prevention of VAP. These studies looked at the administration of systemic antibiotics, such as amoxicillin-clavulanate, ampicillin-sulbactam, or piperacillin-tazobactam, ranging from 1 to 2 doses and up to 2 days compared with no antibiotics or placebo. They found a significant decrease in early-onset but not late-onset VAP [11–13]. Additionally, although some of these studies suggested an association of systemic antibiotic prophylaxis with a reduction in overall hospital LOS, no observed differences in the length of mechanical ventilation or ICU mortality were observed.

At present, there have been only a few, small randomized controlled trials (RCTs) addressing the use of systemic antibiotics as primary prophylaxis in patients with burn injuries [10]. More recently, a large retrospective, observational study of outcomes in patients with burn injuries in Japan was performed [5]. In patients who were mechanically ventilated within the first 2 days of admission, receiving antibiotics within 2 days of admission (either ampicillin-sulbactam or first-generation cephalosporins) was associated with decreased mortality compared with ventilated patients who did not receive antibiotics. Although the mortality outcome in this study may be confounded by factors, including heterogeneous burn care practices in varied hospital settings across the country, it again suggested a potential benefit to empirical antibiotics in mechanically ventilated patients with burn injuries.

Given the importance of antimicrobial stewardship and the high incidence of VAP in this patient population who are critically ill, a sufficiently powered RCT to clarify and validate these prior data in the burn population is imperative to guide recommendations regarding early antibiotic prophylaxis for the prevention of VAP.

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Regardless of current guidelines, which do not recommend general antibiotic prophylaxis, patients with burn injuries still frequently receive early empirical antibiotics, a practice that can be improved with further data. There are notably few RCTs in patients with burn injuries and these are mainly at single centres with a limited number of enrolled patients. Studies of critically ill patients with burn injuries can be difficult to design and time intensive because these patients are not admitted to ICUs in large numbers. In addition, patients with burn injuries are managed in burn centres, medical, or surgical ICU settings depending on the resources available at a particular hospital, and differences in care practices in these heterogeneous settings would need to be addressed because differing ICU care practices can confound outcomes.

The proposed RCT would study adult patients with burn injuries who require mechanical ventilation within hours of admission to a burn centre. Patients transferred to a burn centre from another hospital after 72 hours of admission or who have already received empirical systemic antibiotics would be excluded. This study would be multicenter, double-blind, and placebo-controlled, and take place in established burn centres to make the specialized clinical care of these patients as homogenous as possible. Randomization would be stratified based on burn total body surface area of less than or greater than 10% and by the presence of inhalational injury on admission. Although there will always be some practice differences at clinical sites, recruiting patients from several large, academic burn centres that report to the same National Burn Repository would serve to make patient care practices more homogenous. Burn facilities provide complete care to burn victims of all ages and backgrounds. From 2009 to 2018 in the United States, burns were common in low-income populations (14% uninsured and 25% Medicaid), racial/ethnic minorities (Black 21% and Hispanic 10%), women (38%), children, and adolescents (22% of cases aged <16 years old), and the elderly (9% 60–70 years old, and 8% > 70 years), making this a relatively diverse population for study [14].

The treatment intervention would be the administration of ampicillin-sulbactam for 48 hours compared with a placebo, with the first dose administered within 12 hours of tracheal intubation. Ampicillin-sulbactam has been previously studied, is considered a relatively narrow-spectrum, and would cover some of the most common etiologies of infection early in burn admissions, gram-positive bacteria, including *Staphylococcus aureus* [4]. The primary outcome will be a composite of VAP, the need for additional empiric antibiotics, and all-cause mortality during the first 30 days of hospitalization. Secondary outcomes would include the individual components of the composite primary outcome, hospital LOS, and ICU LOS. Exploratory outcomes of interest would include days on mechanical ventilation, antibiotic-free days, and rates of positive cultures for multidrug-resistant organisms. The essential practices recommended by the CDC for the prevention of VAP will be applied to both study groups [15]. Subgroup analyses would compare patients who undergo early burn eschar excision and grafting and/or selective decontamination of the digestive tract with those who do not because these practices have the potential to independently impact hospital LOS and mortality [16–18]. To assess external validity, characteristics, and outcomes in an observational cohort of patients eligible for the trial but not included would be evaluated, as previously described [19].

Conducting a placebo-controlled RCT would require significant resources and funding and organizational or governmental grants to support this initiative. Our estimated sample size to show an absolute risk reduction for the primary outcome from 25% in the placebo group to 15% in the antibiotic group with 80% power is 248 patients in each group. With enough funding, this proposed study could additionally function as part of a larger umbrella trial evaluating the effects of early prophylactic antibiotics on respiratory, gastrointestinal, and skin colonization. Mechanically ventilated burn patients with inhalational injury frequently undergo bronchoscopy with the culture [20]. Some hospital centres routinely collect rectal swabs for screening for vancomycin-resistant *Enterococcus* species and skin swab cultures for *Acinetobacter baumannii* and *Candida auris* in patients with burn injuries. Finally, skin wound swab cultures are frequently collected in patients with burn injuries. It has been recently suggested that early anti-anaerobic antibiotics in critically ill patients who were critically ill affect the microbiome and subsequent dissemination of gram-negative organisms, and for all specimens, longitudinal cultures in the two comparison groups could provide insight into the effect of early antibiotics on bacterial colonization [21].

In summary, patients with burn injuries represent a unique, immunocompromised, and understudied population, with infection as a leading cause of death, and have a high risk of VAP when mechanically ventilated. This population often receives empirical systemic antibiotics despite a lack of data to support this use in all patients with burn injuries. However, there is the suggested utility of prophylactic antibiotics in a subset of mechanically ventilated patients with burn injuries for the prevention of VAP and decreasing hospital LOS. A randomized control study is essential to inform the use of prophylactic antibiotics in this patient population and has the potential to improve antimicrobial stewardship and patient outcomes.

Author contributions

Conceptualization by DvD and NAM; Writing – Original Draft by NAM; Writing – Review & Editing by FNW, DY, and DvD; Supervision by DvD.

Transparency declaration

The authors declare that they have no conflicts of interest.

Potential conflict of interest

DvD has served as a consultant for Actavis, Tetraphase, Sanofi-Pasteur, Medimmune, Astellas, Merck, Allergan, T2Biosystems, Roche, Achaogen, Neumedicine, Shionogi, Pfizer, Entasis, Qpex, Wellspring, Karius, Utility, and Union, and received honoraria for presentations from Pfizer, received research funding from NIH, Merck, Shionogi, and receives an Editor's stipend from the British Society for Antimicrobial Chemotherapy. All other authors declared that they have no conflicts of interest.

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