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# Relationship between prognosis and timing of antimicrobial use in the treatment of severe flame burns: a single-centre retrospective study

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*Received August 26, 2022, accepted October 2, 2022*

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*Pharmazie 77: 348-351 (2022)* *doi: 10.1691/ph.2022.2500*

Infections are the most common cause of mortality in patients with burns and are, therefore, a major challenge in burn treatment. Appropriate infection control measures are required for a good prognosis with respect to wound infections. Infection prevention improves the outcomes of burn patients. We aimed to determine the efficacy of early antimicrobial therapy in patients with severe flame burns. We conducted a single-centre, observational, case-control study to assess the relationship between prognosis and timing of antimicrobial therapy in the treatment of severe burns in emergency department patients from April 2018 to March 2020. The primary outcome was the association between the initiation of antimicrobial use and prognosis in patients with severe burns. Twenty-three participants were included in the study: 14 in the Control group, and nine in the Case group (patients with severe flame burns). Analysis of the association between the number of days from admission to the emergency department to the start of antimicrobial therapy and length of hospital stay showed a significant correlation in the Case group ($P = 0.0006$) but not in the Control group ($P = 0.9630$). Furthermore, in the Case group, the number of days from admission to initiation of antimicrobial therapy was significantly shorter in the group with a good skin condition prognosis (median, 4; range, 2–5) than in the group with a poor skin condition prognosis (median, 9; range, 7–14) ($P = 0.0256$). This study showed that early use of antimicrobials in patients with severe burns leads to improved skin graft outcomes and shorter hospital stays for patients.

## 1. Introduction

Severe burns are highly traumatic and leave physically debilitating injuries. They affect nearly all organs, leading to significant morbidity and mortality. Early burn wound excision and skin grafting are clinical modalities that can reduce mortality and hospital stays, thereby significantly improving clinical outcomes for patients with severe burns (Wood 2014). However, slow wound healing, infection, pain, and hypertrophic scarring remain major challenges for burn management. Wound infections are the most common cause of mortality in patients with burns and are therefore, a major challenge in burn treatment (D'Avignon et al. 2010; Merchant, Smith, and Jeschke 2015; Norbury et al. 2016). Burn wound infections caused by *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and *Escherichia coli*, as well as the gram-positive bacterium *Staphylococcus aureus*, are independent predictors of mortality (D'Avignon et al. 2010). *Staphylococcus aureus* is the leading cause of gram-positive burn infections worldwide (Norbury et al. 2016) and a common cause of sepsis (Branski et al. 2009; Bang et al. 2004)

There is insufficient evidence showing the efficacy of prophylactic systemic administration of antimicrobials immediately after burn injuries, or during the perioperative period. According to a 2013 systematic review, the incidence of burn wound infection was unchanged when antimicrobials were given prophylactically in three randomized controlled trials (Barajas-Nava et al. 2013) However, this studies involved a uniform antimicrobial intervention rather than a targeted therapy. In addition, prophylactic systemic antimicrobial administration with consideration of the causative organisms is often recommended in certain conditions, such as in susceptible hosts or patients with extensive burns, burns with contaminated wounds, or complicated respiratory tract burns. Considering the prognosis of patients with burns, appropriate infection control is required for wound infections. Furthermore, screening patients for antimicrobial agent use is extremely important to provide the correct antimicrobial to be used. If infections can be prevented, the overall treatment of these patients will improve.

We conducted this retrospective study to examine the usefulness of early antimicrobial administration in patients with burns, especially those with severe flame burns.

## 2. Investigations and results

### *2.1. Characteristics of study participants*

After applying the exclusion criteria, we included 23 participants in the study: 14 in the Control group, and nine in the Case group. We found no significant differences in sex, age, body size, blood count data, laboratory data, renal function, and type of the first antimicrobial agent administered between the two groups (Table). Burn size (%TBSA) in the Case group (median, 10.0; range, 0.0–33.0) tended to be slightly higher than that in the Control group (median, 15.9; range, 8.0–25.0) ($P = 0.0545$).

**Table: Patient characteristics**

| | Control Median (range) | Case Median (range) | *P*-value |
|---|---|---|---|
| **Male/Female** | 6/8 | 6/3 | 0.4003[a] |
| **Age (years)** | 69 (43–84) | 55 (42–83) | 0.1652[b] |
| **Height (cm)** | 160.1 (146.0–172.4) | 160.0 (151.0–168.0) | 0.9245[b] |
| **Body weight (kg)** | 57.3 (38.8–95.7) | 49.9 (37.2–80.8) | 0.2985[b] |
| **Body surface area ($m^2$)** | 1.52 (1.26–2.09) | 1.50 (1.29–1.90) | 0.6433[b] |
| **Burn size (%TBSA)** | 10.0 (0.0–33.0) | 15.9 (8.0–25.0) | 0.0545[b] |
| **Burn index** | 5.0 (0.0–25.5) | 9.1 (6.0–21.5) | 0.3642[b] |
| **Length of hospital stay (day)** | 39 (10–114) | 26 (18–81) | 0.4307[b] |
| **WBC ($10^3/\mu L$)** | 9.1 (5.8–22.6) | 13.6 (6.9–21.8) | 0.1563[b] |

| | | | |
|---|---|---|---|
| **CRP (mg/dL)** | 0.48 (0.02–11.30) | 0.40 (0.05–11.30) | 0.5705[b] |
| **Haemoglobin (g/dL)** | 14.0 (9.6–16.3) | 15.3 (11.3–16.5) | 0.1751[b] |
| **Platelet ($10^3$/μL)** | 240 (143–475) | 284 (129–458) | 0.8748[b] |
| **PT-INR** | 1.07 (0.95–2.82) | 1.07 (0.89–1.20) | 0.5685[b] |
| **Serum albumin (g/L)** | 3.63 (1.93–4.85) | 3.15 (1.77–4.31) | 0.3164[b] |
| **Serum creatinine (mg/dL)** | 0.76 (0.54–2.42) | 0.86 (0.47–1.02) | 0.6361[b] |
| **Serum Na (mmol/L)** | 139 (126–142) | 138 (123–234) | 0.8989[b] |
| **Serum K (mmol/L)** | 4.0 (3.3–5.0) | 4.2 (3.5–5.1) | 0.1841[b] |
| **Serum Cl (mmol/L)** | 104 (81–107) | 105 (88–109) | 0.2793[b] |
| **Serum Ca (mg/dL)** | 8.6 (7.6–9.9) | 8.7 (7.4–9.2) | 0.9670[b] |
| **Serum AST (U/L)** | 27 (15–324) | 20 (14–40) | 0.2420[b] |
| **Serum ALT (U/L)** | 17 (9–41) | 16 (6–23) | 0.7026[b] |
| **Serum BUN (mg/dL)** | 18.3 (7.8–26.7) | 16.6 (14.6–21.6) | 0.8254[b] |
| **Serum glucose (mg/dL)** | 147 (98–246) | 150 (102–292) | 0.6183[b] |
| **eGFR (mL/min/1.73m$^2$)** | 65.03 (22.17–117.00) | 69.99 (53.60–106.55) | 0.4767[b] |
| **First antimicrobial administered** | | | 0.7874[a] |
| **Ceftazidime** | 1 | 2 | |
| **Cefazolin** | 8 | 3 | |
| **Ceftriaxone** | 1 | 0 | |
| **Sulbactam/ampicillin** | 2 | 1 | |
| **Tazobactam/piperacillin** | 2 | 3 | |
| **Vancomycin** | 1 | 1 | |

TBSA: total body surface area, WBC: white blood cell, CRP: C-reactive protein, PT-INR: prothrombin time- international normalized ratio, AST: aspartate aminotransferase, ALT: alanine aminotransferase, BUN: blood urea nitrogen, eGFR: estimated glomerular filtration rate
[a] Fisher's exact test, [b] Mann–Whitney *U* test

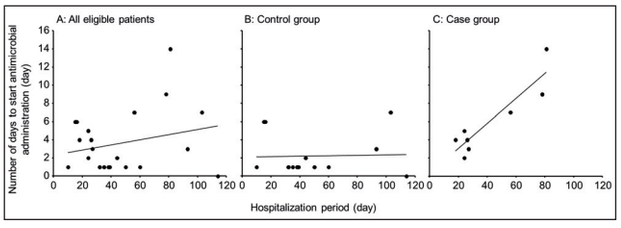


Fig. 1: Scatterplot showing the relationship between the number of days to antimicrobial therapy initiation and the duration of hospitalization period. Solid lines indicate regression lines.
A: All eligible patients, B: Control group, and C: Case group.

### *2.2. Main results*

To evaluate the impact of antimicrobial use on the prognosis of patients with severe burns, we analysed the association between the number of days from admission to the start of antimicrobial administration, and length of hospital stay. The correlation coefficients (r) for all patients in the Control and Case groups were 0.2402, 0.0137, and 0.9122, respectively (Fig. 1). There was no significant correlation in all patients ($P$ = 0.2696) or the Control group ($P$ = 0.9630); however, there was a significant correlation in the Case group ($P$ = 0.0006). Thus, early use of antimicrobial agents may lead to shorter hospital stays in patients with severe burns.

To evaluate the relationship between early use of antimicrobial agents and the treatment course, we compared the number of days from admission to the start of antimicrobial administration between patients with good and poor skin condition prognoses in the Case group. The number of days from admission to antimicrobial initiation in the group with good skin condition prognosis (median, 4; range, 2–5) was significantly shorter than that in the group with poor skin condition prognosis (median, 9; range, 7–14) ($P$ = 0.0256) (Fig. 2A). We also attempted to evaluate the relationship between the early use of antimicrobial agents and treatment costs. The results showed a significant correlation between the number of days from admission to antimicrobial therapy initiation and hospitalization costs in the patient group with severe burns (Case group) (r = 0.8339, $P$= 0.0052) (Fig. 2B). Therefore, early use of antimicrobial agents may lead to an improved treatment course in patients with severe flame burns.

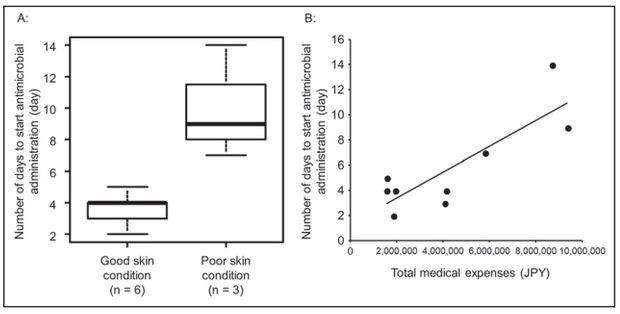


Fig. 2: Relationship between early antimicrobial agent use and treatment course. A: Comparison of the number of days from admission to antimicrobial therapy initiation between patients with good and poor skin condition prognoses. Boxes indicate the medians and interquartile ranges. Vertical lines above and below the boxes indicate the minimum and maximum values. B: Scatterplot showing the relationship between the number of days to antimicrobial therapy initiation and total medical expenses. Solid line indicates regression lines. JPY, Japanese Yen

## 3. Discussion

In this study, we analysed the association between antimicrobial use in patients with severe burns and their prognoses. We found that early antimicrobial use in patients with severe burns leads to improved skin graft outcomes, shorter hospital stays, and reduced hospitalization costs for patients. Among patients with burns, conditions that are considered severe include extensive injury area; severe burns of the face, hands, and feet; and combined airway burns. At the same time, infection risks and antimicrobial agent use are also considered for patients with severe burns. Therefore, infection management in patients with burns contributes to improved clinical outcomes.

In the present study, we excluded patients who were severely ill and given antimicrobials on the day of admission, such as those judged to require immediate antimicrobial therapy, from the Case group. Specifically, patients with severe burns deemed appropriate for antimicrobial administration during the treatment process comprised the Case group. We found no significant differences in patient characteristics between the Control and Case groups, at the time of admission. Only the burn size tended to be larger in the Case group, which was a reasonable observation since this was also a criterion for patient selection. Regarding antimicrobial agents used for the first time, we detected no significant differences, suggesting that the antimicrobial agents used in the Case group were generally used for the same purpose as those used in the Control group. Moreover, severe burn cases often require prolonged hospitalization and intensive care unit admission (Cleland et al. 2016). Resuscitation with large volumes of intravenous fluids, hemodynamic instability, respiratory support, repeated surgical interventions, end organ failure, metabolic abnormalities, and nutritional deficiencies affect the patient's course (Snell et al. 2013). The pharmacokinetic (PK) and pharmacodynamic (PD) characteristics of these patients were specific and were variously affected by the significant pathophysiologic changes encountered in severe burns (Blanchet et al. 2008). Although the PK and PD of the antimicrobials used may have also varied from patient to patient, it is assumed that guidelines were followed during their use and that the treatment intensity was not extremely inadequate. Cardiovascular, respiratory, renal, and hematologic dysfunction are common in patients with severe burns, making it difficult to distinguish from symptoms of newly developed organ damage. Therefore, it is difficult to diagnose sepsis clinically, although early detection and treatment are essential (Evans et al. 2021). Indeed, patients with burns are quite susceptible to nosocomial infections because of loss of skin integrity, the need for prolonged invasive

organ support, and some degree of functional immunosuppression (Heideman and Bengtsson 1992). Although prophylactic systemic antibiotic therapy is not mandatory for major burns according to current interpretations (Avni et al. 2010), most patients will require antimicrobial therapy at some point during hospitalization (Vincent et al. 2009; Norbury et al. 2016). In the present study, the earlier the antimicrobials were initiated in patients with severe flame burns, the better the clinical outcomes were.

One of the clinical outcome improvements demonstrated in this study was the association between early use of antimicrobials and improved skin condition prognosis. Inflammation is essential for successful burn wound healing, and inflammatory mediators provide immune signals that recruit leukocytes and macrophages to initiate the proliferative phase (Singer and Clark 1999). Wound re-epithelialization during the proliferative phase *via* activation of keratinocytes and fibroblasts or migration from dedifferentiated follicles and other epidermal analogues is mediated by cytokines recruited during the inflammatory phase (Claudinot et al. 2005; Ito et al. 2005). This indicates that inflammation is essential for wound healing, although aberrant inflammatory pathways are also associated with hypertrophic scars (Shih et al. 2010; Curran and Ghahary 2013). Infection triggers a pronounced immune response, accompanied by sepsis and septic shock, and lead to hypotension and impaired end organ perfusion, including the skin – all processes that delay wound healing. Therefore, we hypothesized that early use of antimicrobials might lead to successful infection management and avoidance of excessive inflammatory responses, resulting in improved skin condition prognosis and even shorter hospital stays.

In addition, the early use of antimicrobials in patients with severe flame burns contributed to reduced hospitalization costs. This is undoubtedly associated with a significant reduction in hospitalization days. Treatment of burns has traditionally been considered expensive (Hop et al. 2014) because it requires specialized care in centres for a considerable period, including time- and material-intensive surgical and nonsurgical wound care, intensive care, and long-term rehabilitation (Stavrou et al. 2011). Therefore, the reduction of high hospitalization costs brought about by early antimicrobial use can reduce the psychological burden on patients and their families and avoid depleting the country's health care cost-related financial resources.

This study was a single-centre study, and the number of participants was small owing to the strict inclusion criteria. Furthermore, because this was a single-centre study, bias in treatment policies (i.e., surgical techniques, equipment, and drugs used) cannot be denied, and different trends may be obtained at other centres. In this study, we only included the presence or absence of antimicrobial administration and the timing of its initiation in the analysis. Evaluations related to drug selection, starting dose, and total dose were not incorporated, resulting in data without consideration of treatment intensity. Furthermore, we did not discuss the necessity of antimicrobial administration in burn treatment and instead focused on the relationship between the timing of antimicrobial administration and clinical outcomes in patients for whom antimicrobial administration was indicated.

In summary, the use of antimicrobials in patients with severe flame burns tends to improve clinical outcomes if it is initiated earlier. Although no direct recommendations can be made from the analysis of this study, the results suggest that prophylactic administration of antimicrobials may also be effective in patients with severe flame burns. Larger, prospective studies may further confirm the efficacy of antimicrobial chemotherapy in patients with severe flame burns.

## 4. Experimental

### *4.1. Study design and setting*

We conducted a single-centre, observational, case-control study on the relationship between prognosis and timing of antimicrobial use for severe burn treatment in emergency department patients. This study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Review Committee of the Faculty of Medicine at the University of Miyazaki, Japan (O-0913).

### *4.2. Selection of participants*

This study included patients who were admitted to the Emergency and Critical Care Centre of the University of Miyazaki Hospital for emergency burn treatment between April 2018 and March 2020. Patients with minor burns (criteria: second-degree burns covering less than 15% of the total body surface area or third-degree burns covering less than 2% of the total body surface area), no antimicrobial use, age <20 years, and those who died were excluded from the study. Based on these criteria, patients with severe flame burns, according to Artz's criteria, who received antimicrobial agents on days 2–14 after admission to the emergency department were designated as the Case group, and the remainder were designated as the Control group (Fig. 3).

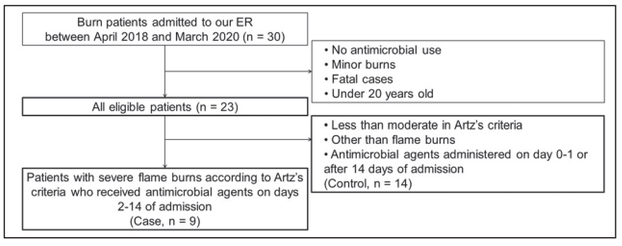


Fig. 3: Screening of participants based on exclusion criteria. ER, emergency room

### *4.3. Measurements*

Patient information (age, sex, height, body weight, clinical laboratory data, medical history, and medication use) was collected from the electronic medical records. We obtained information on medical expenses from the Medical Affairs Division. We classified burn severity according to Artz's criteria, which was based on the extent of injured body surface area, burn location, burn depth (first to third-degree), and patient age. Artz's classification and burn index were taken from the diagnostic data on the electronic medical records. We assessed the skin condition prognosis to be poor if infection has occurred and the grafted skin failed to grow.

### *4.4. Outcomes and analysis*

The primary outcome was the association between the timing of antimicrobial initiation and prognosis of patients with severe burns. First, patients admitted to the emergency department with burns were divided into two groups according to severity i.e Control and Case groups. We then compared patient characteristics at the time of admission between the two groups. We used the Mann–Whitney *U* test to compare continuous variables and Fisher's exact test to compare categorical data. Regarding the effect of antimicrobial initiation on burn prognosis, we first analysed the correlation between the number of days from admission to the initiation of antimicrobial therapy and the number of hospital days for all participants from the Control and Case groups. Second, we further divided the Case group into two groups according to skin condition prognosis, and compared the number of days from admission to the start of antimicrobial administration in each group. Moreover, we analysed the correlation between the number of days from admission to the start of antimicrobial administration, and medical costs in the Case group. We used Pearson's product-moment correlation analysis to examine the correlation and the Mann–Whitney *U* test to compare continuous variables. We used R software (v.4.1.2.; R Foundation for Statistical Computing, Vienna, Austria) for the statistical analyses, and statistical significance was set at $P < 0.05$.

Acknowledgments: We would like to thank Editage (www.editage.com) for English language editing.

Funding: This research was funded by a grant for clinical research from Miyazaki University Hospital.

Conflicts of interest: The authors declare no conflict of interest.

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