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Evaluating the impact of de-escalating antimicrobial therapy in burn patients: a retrospective cohort study

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Antimicrobials should be used appropriately to minimise the risk of resistant strains arising in association with overuse. De-escalation of antimicrobial therapy is one strategy used to ensure appropriate use, but its safety and efficacy in burn patients are unclear. The aim of this study was to evaluate the safety and efficacy of de-escalation therapy for treating infections in burn patients. This retrospective cohort study investigated patients admitted to our intensive care unit with burns and treated for infection between October 1, 2013, and September 30, 2020. Patients were classified into a de-escalation group (Group D) comprising patients treated with empiric antimicrobial therapy followed by de-escalation and a non-de-escalation group (Group ND) comprising patients who did not undergo de-escalation. Characteristics and outcomes were compared between groups. Forty-three patients met the inclusion criteria, including 15 patients in Group D and 28 patients in Group ND. Bacterial species commonly detected in these patients were *Corynebacterium* spp. (17.3%), *Pseudomonas aeruginosa* (16.1%), and *Staphylococcus aureus* (9.6%). No inter-group difference was seen in 28-day mortality (6.7% vs 21.4%, p=0.391). Multidrug-resistant strains were detected significantly less frequently in Group D (13.0%) than in Group ND (26.1%, p=0.003). De-escalation was associated with use of two or more antimicrobials as empiric antimicrobial therapy. As the use of de-escalation in infection treatment did not impact 28-day mortality, de-escalation might be safe for treating infections in burn patients.

1. Introduction

Sepsis and multi-organ failure are common causes of death among burn patients (Krishnan et al. 2013). The compromised functionality of the physical barriers of the epidermis and dermis (Barret and Herndon 2003) and reduced cellular immunity due to cell consumption (Faunce et al. 2003) leave burn patients prone to infection.

Early administration of effective antimicrobials in severe infections is an important factor in improving prognosis, and inappropriate antimicrobial therapy increases the risk of mortality (Yokota et al. 2014; Kumar et al. 2006; Paul et al. 2010). However, since excessive use of broad-spectrum antimicrobials contributes to the emergence of resistant strains and higher costs (Kollef and Micek 2012), appropriate use of antimicrobials should be promoted. De-escalation–in which a patient is started on empiric antimicrobial therapy to cover all possible responsible pathogens and then de-escalated once culture results become available–is one approach now in clinical use to achieve such appropriate use (Silva et al. 2013). Most studies on the efficacy and safety of de-escalation have focused on ventilator-associated pneumonia and other specific infections (Rello et al. 2004) or intensive care units (ICUs) or other specific departments (Morel et al. 2010; Kano et al.2018), but efficacy and safety in burn patients remain uncharacterised. Assessing the efficacy and safety of de-escalation in burn patients would help to substantially improve outcomes for this patient population and advance the appropriate use of antimicrobials. The aim was to evaluate the efficacy and safety of de-escalation therapy for treating infections in burn patients.

2. Investigations and results

2.1. Patients

Of the 218 burn patients admitted during the study period, 175 were excluded, and 43 were included in the study population. Reasons for exclusion were as follows: 27 did not receive an antimicrobial while in the ICU; 22 were <18 years old; 92 had a mild burn; 15 were in the ICU for <24 h, 10 died <72 h after admission to YCU Medical Center, and 9 had a chemical or electrical burn (Fig.). Fifteen patients were classified into Group D, and 28 into Group ND.

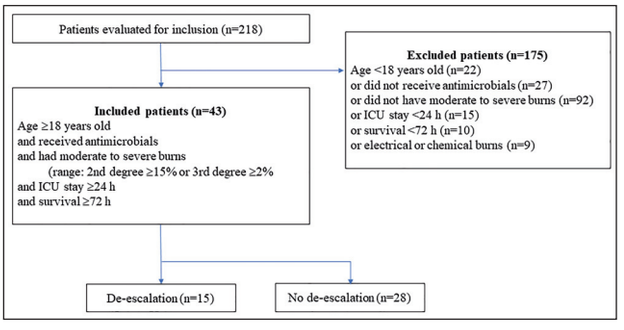

Fig.: Flow chart of the study selection process and classification according to therapeutic strategy. Of the 218 burn patients admitted to the intensive care unit (ICU) between October 1, 2013 and September 30, 2020, a total of 43 patients were enrolled and 175 patients were excluded for the following reasons: age <18 years, no antimicrobial therapy, burn severity less than moderate, ICU stay less than 24 hours, or death within 72 hours of admission. Of the eligible patients, 15 were de-escalated and 28 were not.

The demographic data of Group D and Group ND are shown in Table 1. Mean age on admission was 63.6±14.3 years in Group D and 63.1±19.8 years in Group ND. For Groups D and ND, %TBSAs were 22.5% (20–27%) and 26.3% (15–43%), and mean SOFA scores on ICU admission were 7.2±4.2 and 7.1±3.2, respectively. Sex, medical history, and other patient demographics did not differ significantly between groups.

Table 1: Characteristics on admission to the intensive care unit

	All (n=43)	Group D (n=15)	Group ND (n=28)	*p*
Sex, n (%)				0.502
Male	27 (62.8%)	8 (53.3%)	19 (67.9%)	
Female	16 (37.2%)	7 (46.7%)	9 (32.1%)	
Age, years, mean ± SD	63 ± 16.2	63.1 ± 19.8	63.6 ± 14.3	0.918
Body weight, kg, mean ± SD	61 ± 16.2	59.4 ± 15.2	61.5 ± 16.9	0.682
Height, cm, mean ± SD	163 ± 12.1	162.1 ± 11.9	163.4 ± 12.3	0.729
Body surface area, m^2, mean ± SD	1.6 ± 0.3	1.6 ± 0.3	1.7 ± 0.3	0.693
Beta-lactam allergy, n (%)	2 (4.7%)	1 (6.7%)	1 (3.6%)	1.000
Comorbid conditions, n (%)				
Diabetes disease	7 (16.3%)	3 (20.0%)	4 (14.3%)	0.680
Receiving immunosuppressant	1 (2.3%)	0 (0%)	1 (3.6%)	1.000
Chronic kidney disease	1 (2.3%)	1 (6.7%)	0 (0%)	0.349
RRT	14 (32.6%)	4 (26.7%)	11 (39.3%)	0.512
%TBSA, median	23 (17-35)	22.5 (20-27)	26.3 (15-43)	0.75
Prognostic burn index, mean ± SD	82 ± 18.5	80.5 ± 18.6	83.6 ± 18.6	0.603
Airway burn, n (%)	26 (60.5%)	14 (93.3%)	17 (60.7%)	1.000
GCS, mean ± SD	9 ± 3.6	9.7 ± 3.7	9.0 ± 3.7	0.556
Ventilator, n (%)	41 (95.3%)	14 (93.3%)	27 (96.4%)	1.000
SOFA score, mean ± SD	7 ± 3.5	7.2 ± 4.2	7.1 ± 3.2	0.960
28-day mortality	16.3%	6.7%	21.4%	0.391

Beta-lactam allergy and comorbid conditions were obtained from the medical records.
Values of $p<0.05$ were considered statistically significant.
RRT, renal replacement therapy; %TBSA, percentage of total body surface area; GCS, Glasgow Coma Scale; SOFA, Sequential Organ Failure Assessment.

2.2. Infection

On average, infection was diagnosed and intravenous antimicrobial therapy was initiated 5 days after admission for Group D and 4 days after admission for Group ND. SOFA scores at the start of infection treatment did not differ significantly between groups (Table 2). The most common site of infection in Group D was the skin and soft tissue (75.0%), followed by the lungs (41.7%), bloodstream in relation to a catheter (37.5%), and urinary tract (20.8%). The most common site of infection in Group ND was the lungs (57.6%), followed by the skin and soft tissue (39.4%), bloodstream in relation to a catheter (27.3%), and urinary tract (9.1%). Reinfection occurred in 2 patients in Group D (8.3%) and 12 patients in Group ND (36.4%), showing a significant difference (p=0.027) (Table 2).

Microbiology testing showed a positive culture result for 23 patients in Group D (95.8%) and 28 patients in Group ND (84.8%). The sampling site was sputum in 26.5% and 30.0% of patients, the wound in 24.7% and 21.7%, blood in 19.8% and 15.6%, a catheter tip in 13.0% and 16.1%, and urine in 8.0% and 8.9%, respectively. None of these differences were significant. The most common causative organism in Group D was *Corynebacterium* spp., followed by MSSA and *P. aeruginosa*. The most common causative organisms in Group ND were *Corynebacterium* spp. and *P. aeruginosa*, followed by *Stenotrophomonas maltophilia*. MSSA was significantly more prevalent in Group D and MRSA was significantly more prevalent in Group ND (Table 3).

Table 2: Characteristics of patients and type of infection at the time of empiric antibiotic prescription

	All (n=57)	Group D (n=24)	Group ND (n=33)	*p*
Re-infections, n (%)	14 (24.6%)	2 (8.3%)	12 (36.7%)	0.027*
Pharmacist interventions, n (%)	23 (53.5%)	13 (46.4%)	10 (66.7%)	0.336
Days in hospital at start of antimicrobial, median	5 (2–10.5)	5 (3.3–9.3)	4 (2–14)	0.752
Days of antibiotic therapy, median	13 (8–13)	14 (9–17.8)	13 (7.5–22)	0.821
Source of infection, n (%)				
Respiratory	29 (50.9%)	10 (41.7%)	19 (57.6%)	0.289
Skin and soft tissue	31 (54.4%)	18 (75.0%)	13 (39.4%)	0.015*
CRBSI	18 (31.6%)	9 (37.5%)	9 (27.3%)	0.565
Urinary tract	8 (14.0%)	5 (20.8%)	3 (9.1%)	0.261
Peritonitis	2 (3.5%)	1 (4.2%)	1 (3.0%)	1.000
Undetermined	3 (5.3%)	1 (4.2%)	2 (6.1%)	1.000
Characteristics of patients				
GCS, median	9 (7.5–10)	9 (8–10)	8 (6.3–10)	0.339
Ventilator, n (%)	54 (94.7%)	22 (91.7%)	32 (97.0%)	0.567
Body temperature, °C, mean ± SD	38.5 ± 1.2	38.8 ± 1.2	38.2 ± 1.1	0.057
Leucocytes, ´10^3/µL, median	8.9 (6.3–14.3)	8.2 (5.5–13.2)	10.3 (8.0–17.1)	0.141
SCr, mg/dL, median	0.8 (0.6–1.4)	0.5 (0.6–1.2)	0.8 (0.5–1.8)	0.686
CRP, mg/dL, median	15.3 (9.0–20.7)	17.8 (12.5–24.6)	12.4 (6.0–18.9)	0.006*
Procalcitonin, ng/mL, median	0.86 (0.3–3.3)	1.0 (0.3–4.0)	0.9 (0.3–3.0)	0.793
SOFA score, mean ± SD	9.0 ± 3.3	9.2 ± 3.6	8.9 ± 3.1	0.772

Number of cases includes re-infections.
GCS, Glasgow Coma Scale; CRP, C-reactive protein; SOFA, Sequential Organ Failure Assessment; CRBSI, catheter-related blood stream infection; SCr, serum creatinine.

Table 3: Microbiologic characteristics of infectious episodes

	All	Group D	Group ND	*p*
Detected bacteria, n	342	162	180	
Culture source, n (%)				
Sputum	97 (28.3%)	43 (26.5%)	54 (30.0%)	0.479
Wound swab	79 (23.1%)	40 (24.7%)	39 (21.7%)	0.508
Blood	60 (17.5%)	32 (19.8%)	28 (15.6%)	0.308
Catheter tip	50 (14.6%)	21 (13.0%)	29 (16.1%)	0.411
Urine	29 (8.5%)	13 (8.0%)	16 (8.9%)	0.933
Others	27 (7.9%)	13 (8.0%)	14 (7.8%)	0.775
Pathogens, n (%)				
Corynebacterium spp.	59 (17.3%)	25 (15.4%)	34 (18.9%)	0.398
Pseudomonas aeruginosa	55 (16.1%)	20 (12.3%)	35 (19.4%)	0.074
MSSA	33 (9.6%)	23 (14.2%)	10 (5.6%)	0.006*
Stenotrophomonas maltophilia	19 (5.6%)	7 (4.3%)	12 (6.7%)	0.344
Enterococcus faecalis	15 (4.4%)	9 (5.6%)	6 (3.3%)	0.316
MRSA	14 (4.1%)	3 (1.9%)	11 (6.1%)	0.047*
Klebsiella pneumoniae	13 (3.8%)	9 (5.6%)	4 (2.2%)	0.108
Enterobacter cloacae	12 (3.5%)	6 (3.7%)	6 (3.3%)	0.853
MRSE	10 (2.9%)	5 (3.1%)	5 (2.8%)	0.866
Escherichia coli	9 (2.6%)	6 (3.7%)	3 (1.7%)	0.240
Others	76 (22.2%)	39 (24.1%)	37 (21.0%)	0.960
MDR during ICU stay, n (%)	68 (19.9%)	21 (13.0%)	47 (26.1%)	0.003*

MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*; MRSE, methicillin-resistant *Staphylococcus epidermidis*; MDR, multidrug resistance.

The most common empiric antimicrobial therapy in Group D was anti-MRSA agents (glycopeptides, linezolid, daptomycin) (54.2%) followed by piperacillin/tazobactam (29.2%) and carbapenems (33.3%). In comparison, frequencies of use of these agents in Group ND were 42.4%, 30.3%, and 21.2%, respectively. No significant intergroup differences were noted (Table 4). Significantly more patients used two or more agents as empiric antimicrobial therapy in Group D (75.0%) than in Group ND (33.3%; p=0.003). The groups did not differ significantly in the types of drugs used in antimicrobial regimens, including empiric therapy. The number of days of treatment did not differ significantly between groups, with 14 days in Group D and 13 days in Group ND (p=0.821) (Table 2).

Table 4: Empiric antibiotic treatment

	All (n=57)	Group D (n=24)	Group ND (n=33)	*p*
Broad-spectrum antimicrobial, n (%)	39 (68.4%)	17 (70.8%)	22 (66.7%)	0.781
Glycopeptides, linezolid, daptomycin	27 (47.4%)	13 (54.2%)	14 (42.4%)	0.430
Carbapenems, n (%)	15 (26.3%)	8 (33.3%)	7 (21.2%)	0.369
Fluoroquinolones, n (%)	2 (3.5%)	2 (8.3%)	0 (0%)	0.173
Piperacillin/tazobactam, n (%)	17 (29.8%)	7 (29.2%)	10 (30.3%)	1.000
Cefepime, n (%)	3 (5.3%)	0 (0%)	3 (9.1%)	0.256
Others, n (%)	22 (38.6%)	9 (37.5%)	13 (39.4%)	1.000
Two or more antibiotics, n (%)	29 (50.9%)	18 (75.0%)	11 (33.3%)	0.003*
Inadequate empiric therapy, n (%)	4 (7.0%)	1 (4.2%)	3 (9.1%)	0.631

Broad-spectrum antimicrobials are glycopeptides, linezolid, daptomycin, carbapenems, fluoroquinolones, piperacillin/tazobactam, aminoglycosides and cefepime.

2.3. De-escalation

Of the 24 de-escalated patients, 7 (29.1%) were switched to a narrower-spectrum antimicrobial agent, 6 (25.0%) were given fewer antimicrobial agents, 1 (4.2%) was discontinued early, and 10 (41.7%) were given fewer antimicrobial agents and switched to a narrower-spectrum antimicrobial agent. The antimicrobial agent most commonly discontinued or switched from in de-escalation was an anti-MRSA agent (14 patients, 58.3%), followed by a carbapenem (10 patients, 41.7%) and piperacillin/tazobactam (8 patients, 33.3%).

Factors related to de-escalation were investigated. Univariate analysis revealed that Group D showed a longer time from admission to infection onset and more often used two or more antimicrobials as empiric antimicrobial therapy than Group ND. Of these factors, only the use of two or more antimicrobials as empiric antimicrobial therapy correlated with de-escalation in multivariate analysis (odds ratio 9.45, 95% confidence interval [CI] 2.50–35.77; p=0.001) (Table 5).

Table 5: Multivariate logistic regression analysis for factors associated with de-escalation therapy

	Odds ratio (95%CI)	*p*
Number of days in hospital at start of antimicrobial	0.92 (0.84–1.00)	0.060
Two or more antibiotics as empiric therapy	9.45 (2.50–35.77)	0.001*

CI, confidence interval.

De-escalation was not undertaken in Group ND because a narrower-spectrum antimicrobial agent was used (17 patients, 51.5%), the antimicrobial regimen selected was appropriate (4 patients, 12.1%), the condition of the patient did not improve (4 patients, 12.1%), or a resistant strain was detected (5 patients, 15.2%), while the reason remained unknown in 3 patients (9.1%). Four (12.1%) of these patients could have undergone de-escalation.

2.4. Outcome

Seven patients (16.3%) died within 28 days of ICU admission, 9 (21.0%) died while in the ICU, and 12 (27.9%) died while hospitalised. The 28-day mortality rate was 6.7% in Group D and 21.4% in Group ND, which tended to be lower in Group D but not statistically significant (Table 1). Neither duration of ICU stays (Group D: 19 days (9–26 days); Group ND: 25 days (9–34 days) nor number of days of antimicrobial use (Group D: 14 days; Group ND: 13 days) were impacted by de-escalation. MDR detection as analysed using culture data showed a significant difference between group D (13.0%) and group ND (26.1%; p = 0.003) (Table 3).

3. Discussion

This retrospective observational study was conducted to assess infection treatment strategies used for patients admitted to the ICU with burns. Our findings suggest that de-escalation can be safely used when treating infections in patients with moderate or greater burns without increasing mortality and may help suppress the appearance of resistant strains. No consensus has been reached regarding the definition of de-escalation. For the purposes of this study, we defined de-escalation as a switch to a narrower-spectrum antimicrobial, a reduction in the number of antimicrobials used, or early discontinuation of antimicrobial treatment, as in previous research (Morel et al. 2010; Tabah et al. 2016). As inappropriate use of antimicrobials is associated with the acquisition of drug resistance by bacteria (Geissler et al. 2003), the approaches in these three definitions represent ways to more appropriately use antimicrobials.

Ventilator-associated pneumonia and other respiratory infections are common in ICU settings and accounted for about half of the infections in this study. As skin and soft-tissue infections also accounted for about half of the infections, evaluating de-escalation without consideration of the site of infection appears appropriate. We evaluated de-escalation in patients with second-degree burns covering 15% or more of the body or third-degree burns covering 2% or more of the body to limit the scope to patients requiring admission for the treatment of burns. We established criteria for determining %TBSA in reference to the criteria of Artz, which are used as criteria for admission under Japanese burn management guidelines (Hiroto et al. 2021). A total of 42% of patients in the study underwent de-escalation, compared to 8–50% of ICU patients in other studies (Morel et al. 2010; De Waele et al. 2010; Heenen et al. 2012; Montravers et al. 2011). This suggests that, similar to patients with other conditions, patients with moderate or greater burns are eligible for de-escalation and thus supports our findings.

Studies have found that de-escalation as an approach for treating infections in ICU patients is associated with a reduction in 28-day mortality (Routsi et al.2020; Granacho-Montero et al. 2014). Although we found no such reduction in 28-day mortality, our study did not identify any clear deleterious effects from de-escalation. %TBSA has been used as a prognostic factor (Saffle et al.1995). %TBSA did not differ between groups in this study and therefore did not likely impact whether de-escalation was performed. This also suggests that, as is the case with patients with other conditions, patients with moderate or greater burns can undergo de-escalation regardless of the extent of their burns.

Multivariate analysis conducted to evaluate factors related to de-escalation revealed that the use of two or more antimicrobials as empiric antimicrobial therapy was independently associated with de-escalation. *S. aureus*, *P. aeruginosa*, *Enterobacter*, and *Klebsiella* are often responsible for infections in burn patients, and particular care is warranted when *S. aureus* or *P. aeruginosa* is involved (Mentzelopoulos et al. 2007). Broad-spectrum therapy combining a carbapenem and piperacillin/tazobactam or other agent with activity against *P. aeruginosa* with an anti-MRSA agent is therefore often used as empiric antimicrobial therapy. Vancomycin is a widely used anti-MRSA agent in Japan and was widely used in this study. Vancomycin necessitates therapeutic drug monitoring. Clearance of vancomycin is elevated in burn patients due to factors including increased glomerular filtration rate and higher renal tubular secretion (Dolton et al. 2009; Elligsen et al. 2010). Elevated clearance results in lower-than-expected blood levels, meaning that a therapeutically effective blood level may not be reached. On the other hand, acute kidney injury (AKI) occurs in 38% of burn patients (Folkestad et al. 2020), and the combination of vancomycin and piperacillin/tazobactam has been reported as a risk factor for AKI (Hundeshagen et al. 2017). AKI results in increased blood levels of vancomycin as a renally excreted drug, and these higher levels can often further worsen renal function. Physicians may therefore be likely to actively discontinue vancomycin when MRSA is not detected in culture. MRSA was detected in the wounds of only 4 patients in this study, leading to early discontinuation of anti-MRSA agents, potentially representing a factor underlying the prevalence of skin and soft tissue infections in Group D.

Skin and soft tissue infections, pneumonia, and catheter infections were the most common infections in the present study. Disruption of the skin barrier reduced immune function, and prolonged catheter placement under ICU management left study patients prone to these infections. The finding that burn patients with a %TBSA

exceeding 25–30% are at increased risk of wound infection, pneumonia, and bacillaemia (Rafla and Tredget 2009; Church et al. 2006) is compatible with our results.

MDR was identified in 19.9% of samples collected during the ICU stay of these burn patients with infections. MDR was less prevalent in Group D. Although de-escalation would be expected to protect against MDR, evidence in the literature is lacking. Thus, while de-escalation may have impacted the emergence of resistant strains, this study was not able to reveal whether de-escalation suppressed the emergence of MDR or whether the lack of MDR allowed de-escalation.

This study had several limitations. The single-centre design and small sample size resulted in weak statistical power. The retrospective observational design prevented determination of the effects of the number of days of treatment. However, the assessment of de-escalation therapy with a focus on burn patients provides a snapshot of routine clinical practice. Further cases must be examined to better inform best infection treatment practices.

In conclusion, de-escalation of antimicrobial therapy did not affect the mortality rate of burn patients treated for infections. This suggests that de-escalation, as a component of appropriate antimicrobial use, can be safely performed in patients with moderate or greater burns.

4. Experimental

4.1. Study design and patients

This single-centre, retrospective study included patients admitted to the 12-bed ICU of Yokohama City University (YCU) Medical Center, a tertiary hospital and the only advanced emergency and critical care medical centre in the city of Yokohama. The study population comprised burn patients 18 or more years old who were admitted to the ICU between October 1, 2013, and September 30, 2020, had moderate or greater injury in the form of second-degree burns covering 15% or more of the body or third-degree burns covering 2% or more of the body, arrived within 24 h of injury, and were started on antimicrobial therapy for a diagnosed infection while in the ICU. Patients with chemical or electrical burns, age <18 years, patients whose stay in the ICU was <24 h, and patients who died within 72 h of admission to YCU Medical Center were excluded.

4.2. Data collection, definitions and outcomes

Data were collected from the electronic medical records. Collected data were stored on a password-protected computer not connected to the internet.

The following basic information was collected: age, sex, height, body weight, body surface area, use of immunosuppressants, presence of chronic kidney disease/diabetes mellitus, allergy to beta-lactam agents, severity of burn, %total body surface area (%TBSA), presence of airway burns, and duration of ICU stay. The following infection-related information was also collected: Sequential Organ Failure Assessment (SOFA) score just before starting antimicrobial therapy, antimicrobial regimen, sites of infection, and culture results. Information collected on the antimicrobial regimen included the types of antimicrobials administered, dosage, start date, and date of discontinuation. Sites of infection were inferred from the diagnosis stated in the medical records. Information collected on culture results included the sampling date, sampling site, microorganism name, and drug sensitivity.

As our medical institution had no defined protocol for empiric antimicrobial therapy, the attending physician prescribed antimicrobials on the basis of the medical history, condition, and supposed site of infection for the patient. Every morning, physicians, nurses, pharmacists, and physical therapists held a conference to discuss the approaches being used for infection and other treatment. As there was also no protocol for de-escalation, this process was carried out by individual physicians as needed in light of the clinical course of the patient, the bacteria identified, and drug sensitivity information.

For the purposes of the study, patients who underwent de-escalation during their stay in the ICU were classified as the de-escalation group (Group D) and those not undergoing de-escalation were classified as the non-de-escalation group (Group ND). The primary outcome of the study was 28-day mortality. The secondary outcome was the emergence of resistant strains.

De-escalation was defined as a reduction in the types of antimicrobials used, a switch to a narrower-spectrum antimicrobial, or early discontinuation of antimicrobial treatment. Switching to a narrower-spectrum antimicrobial constituted switching from a drug with anti-methicillin-resistant *Staphylococcus aureus* (MRSA) activity to a drug with anti-methicillin-susceptible *S. aureus* (MSSA) activity or switching from an antipseudomonal agent to a non-antipseudomonal agent. A reduction in the types of antimicrobials used constituted discontinuing a drug within 5 days of the start of infection treatment or based on the results of culture. Early discontinuation of antimicrobial treatment constituted discontinuation of an antimicrobial three or less days after the start of use because the patient was found not to be infected or antimicrobial therapy was found to be unnecessary.

Multidrug-resistant (MDR) strains were defined as MRSA, methicillin-resistant coagulase-negative staphylococci, beta-lactamase-producing *Enterobacterales*, and piperacillin/tazobactam-resistant, ceftazidime-resistant, carbapenem-resistant, quinolone-resistant, or aminoglycoside-resistant non-fermenting Gram-negative rods (*Pseudomonas aeruginosa*, *Acinetobacter*, *Maltophilia*, *Burkholderia cepacia*, Genus *Chryseobacterium*, and *Achromobacter xylosoxidans*).

Empiric antimicrobial therapy was considered appropriate if the responsible organism was sensitive to at least one of the antimicrobials used. Re-escalation was defined as the resumption of broad-spectrum antimicrobial agents after de-escalation for clinical worsening, including cases unrelated to the initial infection. Escalation was defined as the addition of an antimicrobial or switching to a broader-spectrum agent when clinical worsening occurred after empiric antimicrobial therapy or when the therapy used did not cover the organism detected as indicated by culture results. Reinfection was defined as the occurrence of another infection after the conclusion of antimicrobial treatment.

4.3. Statistical analysis

Categorical variables were summarised as percentages or frequencies, and continuous variables were summarised as median values and interquartile ranges. Continuous variables were statistically analysed using a t-test, and categorical variables were analysed with the chi-square test. In both cases, values of $p < 0.05$ were taken to indicate statistical significance. Univariate regression analysis was performed to assess variables associated with de-escalation. All variables showing a value of $p < 0.2$ in univariate regression modelling were plugged into a multivariate logistic regression model. JMP Pro version 15 (SAS Institute Inc., Cary, NC, USA) was used to conduct all statistical analyses.

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Data availability: Data supporting the findings of this study are available from the corresponding author upon reasonable request.

Ethics approval: The study was conducted in compliance with the Declaration of Helsinki and the "Ethical Guidelines for Medical and Health Research Involving Human Subjects". All study protocols were approved by the Yokohama City University Certified Institutional Review Board (approval no. B191200052).

Consent to participate: Not applicable due to the retrospective study design.

Consent to publish: Not applicable due to the retrospective study design.

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