Clinical Infectious Diseases

MAJOR ARTICLE

Prophylactic Antibiotics May Improve Outcome in Patients With Severe Burns Requiring Mechanical Ventilation: Propensity Score Analysis of a Japanese Nationwide Database

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(See the Editorial Commentary by Hankovszky et al on pages 67–8.)

Background. The use of prophylactic antibiotics for severe burns in general settings remains controversial and is not suggested by recent guidelines owing to lack of evidence for efficacy. We examined the hypothesis that prophylactic systemic antibiotic therapy may reduce mortality in patients with severe burns.

Methods. We identified 2893 severe burns patients (burn index ≥10) treated at 583 hospitals between July 2010 and March 2013 using the Japanese diagnosis procedure combination inpatient database. We categorized the patients according to whether they received mechanical ventilation within 2 days after admission (n = 692) or not (n = 2201). We further divided the patients into those with and without prophylactic antibiotics and generated 232 and 526 propensity score–matched pairs, respectively. We evaluated 28-day all-cause in-hospital mortality.

Results. Among the mechanically ventilated patients, significant differences in 28-day in-hospital mortality existed between control and prophylaxis groups in both unmatched (control vs prophylaxis; 48.6% vs 38.3%; difference, 10.2%; 95% confidence interval [95% CI], 2.7 to 17.7) and propensity score–matched groups (47.0% vs 36.6%; difference, 10.3%; 95% CI, 1.4 to 19.3). Among patients without mechanical ventilation, there was no significant difference in 28-day in-hospital mortality between the 2 groups in both the unmatched (control vs prophylaxis; 7.0% vs 5.8%; difference, 1.2%; 95% CI, −1.2 to 3.5) and propensity-matched groups (5.1% vs 4.2%; difference, 0.9%; 95% CI, −1.6 to 3.5).

Conclusions. Prophylactic antibiotics use may result in improved 28-day in-hospital mortality in mechanically ventilated patients with severe burns but not in those who do not receive mechanical ventilation.

Keywords. antibiotics; burns; pneumonia; prognosis; sepsis.

Globally, the incidence of burns severe enough to require medical attention was nearly 11 million people (ranked fourth of all injuries), and more than 300 000 persons die each year worldwide because of burn injuries in 2004 [1, 2]. Patients with severe burns are at high risk of developing invasive burn wound infections and sepsis, which often lead to multiorgan dysfunction and death [3]. Although burn wound surfaces are sterile immediately following thermal injury, they eventually become colonized by microorganisms. Gram-positive bacteria that survive the thermal insult, such as staphylococci located deep within sweat glands and hair follicles, colonize the wound surface within the first 48 hours [4, 5]. Several studies have suggested that severe thermal injuries damage the skin barrier; concomitantly, they depress local and systemic host cellular and humoral immune responses, inducing a state of immunosuppression that predisposes burn patients to infectious complications [6–8].

The prophylactic use of antibiotics for patients with severe burns in general settings (ie, not perioperative settings) has been examined in several single-center studies with limited numbers of patients [9–14]. However, no robust conclusions have emerged. Two recent studies of systematic reviews and metaanalyses of trials have produced conflicting results [15, 16]. Avni et al [15] suggested that prophylaxis with systemic antibiotics significantly reduced all-cause mortality by almost 50%; however, Barajas-Nava et al [16] found no statistically significant difference in all-cause mortality. In both studies it was declared that the methodological quality of the data was too weak to draw a firm conclusion [15, 16]. Thus, the role of

Received 26 April 2015; accepted 19 July 2015; published online 24 September 2015.

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Clinical Infectious Diseases® 2016;62(1):60–6

DOI: 10.1093/cid/civ763

prophylactic antibiotics for severe burns is still controversial, and their use has not been advocated in recent guidelines or recommendations owing to a lack of evidence for efficacy and induction of antibiotic resistance [17–20].

We hypothesized that prophylactic systemic antibiotic therapy may reduce mortality in patients with severe burns. The purpose of this study was to evaluate our hypothesis using a large nationwide inpatient database in Japan.

METHODS

The University of Tokyo Institutional Review Board approved this study. The board waived the requirement for informed patient consent because of the anonymous nature of the data.

Data Source and Variables

For this study, we used the Japanese diagnosis procedure combination (DPC) database, which was described in detail previously [21]. In short, the DPC database includes administrative claims and discharge abstract data for all inpatients discharged from more than 1000 participating hospitals; it covers approximately 92% (244/266) of all tertiary-care emergency hospitals in Japan and 90% (90/100) of institutions certified for training burn specialists by the Japanese Society for Burn Injuries [22]. The database includes the following information for each patient: age; sex; primary diagnosis; comorbidities on admission and post-admission complications coded with the International Classification of Diseases, 10th Revision (ICD-10), codes and written in Japanese; medical procedures, including types of surgery, coded with original Japanese codes; daily records of drug administration and devices used; length of stay; and discharge status. The dates of hospital admission, surgery, bedside procedures, drugs administered, and hospital discharge are recorded using a uniform data submission format [21–25].

Several lists of scores are also available in the database, including burn index and Japan coma scale (JCS) scores. The burn index takes both the surface area and thickness of the burned area into consideration: burn index = full thickness of total burn surface area + 1/2 partial thickness of total burn surface area [22, 26]. The JCS correlates well with the Glasgow coma scale; consciousness scored at 100 points on the JCS is equivalent to a score of 6–9 on the Glasgow coma scale. We categorized the JCS scores into 4 groups: 0, alert; 1–3, delirium; 10–30, somnolence; and 100–300, coma [21–25]. To quantify the extent of comorbidities, the ICD-10 code for each comorbidity was converted to a score, and the sum was used to calculate the Charlson comorbidity index (CCI) as previously described [22, 27, 28]. Briefly, the CCI is a method of predicting mortality by classifying or weighting comorbidities. It has been widely used by health researchers to measure case mix and the burden of disease [27]. We categorized patients into 1 of 3 groups on the basis of the CCI: low, 0; medium, 1; and high, ≥2 [22].

We categorized the hospital types as academic or nonacademic. We defined teaching hospitals as to whether or not the institution was designated for postgraduate clinical training. We designated hospital volume as the number of eligible patients treated for the current study and categorized into quartiles (very low, low, high, and very high). We defined the use of prophylactic antibiotics as treatment with first-generation cephalosporin and ampicillin/sulbactam (ie, targeted for burn infection) within 2 days after admission without being used for perioperative management.

Patient Selection and Endpoint

We identified all patients with severe burns (burn index ≥10) [22] who were recorded in the database from 1 July 2010 to 31 March 2013. The exclusion criteria for this study were the following types of patients: out-of-hospital cardiac arrest, discharged within 2 days after admission (to avoid immortal time bias), administered nonprophylactic antibiotics within 2 days after admission, and underwent surgery (skin grafting) within 2 days after admission. We thus compared patients who were administered prophylactic antibiotics within 2 days after admission (prophylaxis group) and those who were not administered any antibiotics within that time (control group). Because the DPC is an administrative database with information input as to when patients are discharged, patient follow-up began on the day of admission and ended on the hospital discharge date (to home, transfer to another hospital, or death). We could not follow up patients after discharge from the hospital since the information was not available in this discharge database. Although physicians in charge were obliged to record the burn index, we were unable to evaluate patients for whom these data were missing.

The endpoint used in this study was all-cause 28-day in-hospital mortality. The secondary endpoints were in-hospital mortality and the use of carbapenem, tazobactam/piperacillin, fourth-generation cephalosporins, and drugs for methicillin-resistant *Staphylococcus aureus* (MRSA; eg, vancomycin, teicoplanin, arbekacin sulfate, linezolid daptomycin) started after day 2 or later.

Statistical Analyses

Since inhalation injury that requires mechanical ventilation significantly affects the outcome for burn patients [22, 26, 29–32], we divided the patients into 2 categories: those who had received mechanical ventilation within 2 days after admission and those who had not. We compared categorical variables using the χ^2 or Fisher exact test. To assess the propensity score, we fitted a logistic regression model for prophylactic antibiotic use as a function of patients' demographic and clinical characteristics as well as hospital factors, which included the following: age; sex; burn index; CCI, level of consciousness on admission; hospital type (academic or nonacademic); teaching hospital status and hospital volume; use of catecholamine

(dobutamine, norepinephrine, and/or dopamine); antithrombin use; treatment with recombinant human soluble thrombomodulin; treatment with haptoglobin; and requirement for escharotomy and debridement [1, 21–26, 29–34]. We performed propensity score–adjusted logistic regression analyses to evaluate the effect of prophylactic antibiotics (with and without mechanical ventilation, respectively), fitted with a generalized estimating equation to adjust for institutional clustering [35]. In addition, we also performed a 1-to-1 propensity score–matched analysis (of prophylactic antibiotic and control groups) using nearest-neighbor matching. A match occurred when a patient in the prophylaxis group had an estimated score within 0.2 standard deviations of a patient in the control group. We examined the balance in baseline variables using standardized differences, where >10% was regarded as imbalanced [36]. We performed logistic regression analysis fitted with generalized estimating equations to examine the association between prophylactic antibiotic use and 28-day in-hospital mortality and accounted for the paired nature of the propensity score–matched patients. We used Cox regression analysis to assess differences in in-hospital survival rates between patients with and without prophylactic treatment in the propensity score–matched groups. We performed all statistical analyses using IBM SPSS, version 22 (IBM Corp., Armonk, New York).

RESULTS

Patients

We identified 2893 severe burn patients treated at 583 hospitals during the 33-month study period (Figure 1). We categorized the patients according to whether they received mechanical ventilation within 2 days after admission (n = 692) or not (n = 2201). We further divided the patients into those with and without prophylaxis. From the groups with and without mechanical ventilation, we generated 232 and 526 propensity score–matched pairs, respectively. Overall, 35% (1013/2893) received prophylactic antibiotics: 60% (412/692) with mechanical ventilation and 27.3% (601/2201) without mechanical ventilation. The mean doses and durations of prophylactic first-generation cephalosporin or ampicillin/sulbactam were 2.1 g/day for 6.9 days and 4.6 g/day for 6.7 days, respectively.

Table 1 shows the baseline characteristics of the unmatched and propensity score–matched groups among mechanically ventilated patients. In the unmatched groups, patients were more likely to have received prophylaxis if they were younger, required more norepinephrine or other drugs, or needed escharotomy and debridement. Table 2 shows the baseline characteristics of the unmatched and propensity score–matched groups without mechanical ventilation. Among the unmatched groups, patients were more likely to have received prophylaxis if they were treated at teaching hospitals, required higher doses of catecholamines or other drugs, or required debridement. After propensity score matching, the baseline patient characteristics were well balanced between the groups, as evident in Tables 1 and 2.

Endpoints

Overall 28-day in-hospital mortality among all patients was 15.2% (441/2893). There was a significant 28-day in-hospital mortality difference between patients who were mechanically ventilated and those who were not (42.5%, 294/692 vs 6.7%, 147/2201). Propensity score– adjusted logistic regression analyses adjusted for institutional clustering revealed a significant association between the use of prophylactic antibiotics and lower 28-day in-hospital mortality in 692 mechanically ventilated patients (odds ratio [OR], 0.71; 95% confidence interval [CI], .52 to .96), but there was no significant relationship among the 2201 patients who were not mechanically ventilated (OR, 0.94; 95% CI, .61 to 1.5).

Among the mechanically ventilated patients, significant differences in 28-day in-hospital mortality occurred between the 2

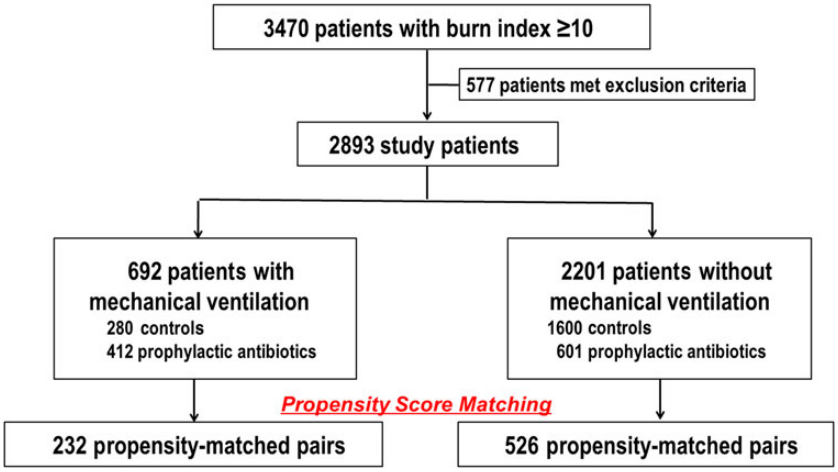

Figure 1. Patient selection.

Table 1. Baseline Patient Characteristics in the Unmatched and Propensity-Matched Groups in Mechanically Ventilated Cases

	Unmatched Groups			Matched Groups		
Variable	Control (n = 280)	Prophylaxis (n = 412)	Standardized Differences, %	Control (n = 232)	Prophylaxis (n = 232)	Standardized Differences, %
Age, y (SD)	61.0 (22.1)	58.5 (22.1)	11.3	59.1 (21.8)	60.4 (20.7)	−6.0
Adult (age >15 y)	268 (95.7)	396 (96.1)	−2.0	222 (95.7)	222 (95.7)	0.0
Sex (male)	167 (59.6)	266 (64.6)	−10.3	141 (60.8)	143 (61.6)	−1.8
Burn index, mean (SD)	37.2 (23.7)	36.6 (22.9)	2.6	37.2 (22.8)	35.9 (22.3)	5.6
Charlson comorbidity index				214 (92.2)	214 (92.2)	0.0
0	256 (91.4)	385 (93.4)	−7.6	8 (3.4)	6 (2.6)	5.0
1	8 (2.9)	12 (2.9)	−0.3	10 (4.3)	12 (5.2)	−4.1
≥2	16 (5.7)	15 (3.6)	9.8	133 (57.3)	127 (54.7)	5.2
Academic hospital	166 (59.3)	230 (55.8)	7.1	225 (97.0)	225 (97.0)	0.0
Teaching hospital	272 (97.1)	396 (96.1)	5.5	214 (92.2)	214 (92.2)	0.0
Hospital volume, cases						
Very low, <3	35 (12.5)	73 (17.7)	−14.6	32 (13.8)	34 (14.7)	−2.5
Low, 3–6	77 (27.5)	112 (27.2)	0.7	67 (28.9)	64 (27.6)	2.9
High, 7–12	139 (49.6)	169 (41.0)	17.3	105 (45.3)	104 (44.8)	0.9
Very high, >13	29 (10.4)	58 (14.1)	−11.3	28 (12.1)	30 (12.9)	−2.6
Consciousness level						
Alert	113 (40.4)	140 (34.0)	13.3	88 (37.9)	91 (39.2)	−2.7
Delirium	69 (24.6)	115 (27.9)	−7.5	63 (27.2)	56 (24.1)	6.9
Somnolence	18 (6.4)	48 (11.7)	−18.6	16 (6.9)	19 (8.2)	−4.9
Coma	80 (28.6)	109 (26.5)	4.7	65 (28.0)	66 (28.4)	−1.0
Catecholamines						
Dopamine use	78 (27.9)	101 (24.5)	7.7	66 (28.4)	65 (28.0)	1.0
Dobutamine use	15 (5.4)	29 (7.0)	−6.6	15 (6.5)	15 (6.5)	0.0
Noradrenaline use	45 (16.1)	83 (20.1)	−10.4	42 (18.1)	39 (16.8)	3.4
Antithrombin use	29 (10.4)	70 (17.0)	−19.3	28 (12.1)	24 (10.3)	5.5
Recombinant human soluble thrombomodulin use	22 (7.9)	35 (8.5)	−2.2	10 (4.3)	11 (4.7)	−2.1
Haptoglobin use	68 (24.3)	126 (30.6)	−14.2	64 (27.6)	62 (26.7)	1.9
Escharotomy performed	29 (10.4)	66 (16.0)	−16.6	29 (12.5)	29 (12.5)	0.0
Debridement performed	6 (2.1)	35 (8.5)	−28.6	6 (2.6)	6 (2.6)	0.0

Abbreviation: SD, standard deviation.

groups for both the unmatched (control vs prophylaxis, 48.6% vs 38.3%; difference, 10.2%; 95% CI, 2.7 to 17.7) and propensity-matched groups (47.0% vs 36.6%; difference, 10.3%; 95% CI, 1.4 to 19.3; Table 3). Logistic regression analyses showed a significant association between the use of prophylactic antibiotics and lower 28-day in-hospital mortality in the propensity-matched groups (OR, 0.65; 95% CI, .45 to .95). There was a significant in-hospital mortality difference between the 2 groups for both the unmatched (56.8% vs 48.5%; difference, 8.2%; 95% CI, .6 to 15.8) and propensity-matched groups (55.6% vs 45.6%; difference, 9.9%; 95% CI, .8 to 19.0). Cox regression analysis showed a significant in-hospital mortality difference between the control and prophylaxis groups in the propensity-matched groups (hazard ratio, 0.70; 95% CI, .54 to .91; Figure 2). In the propensity-matched groups, after day 2, there were no significant differences in the proportion administered anti-MRSA drugs (43.1% vs. 38.8%; difference, 4.3%; 95% CI, −4.6 to 13.2), carbapenem (34.1% vs. 37.9%; difference, −3.9%; 95% CI, −12.6 to 4.9), tazobactam/piperacillin (31.0% vs. 29.3%; difference, 2.0%; 95% CI, −7.8 to 12.0), or fourth-generation cephalosporins (12.5% vs. 14.2%; difference, −1.7%; 95% CI, −7.9 to 9.6).

Among the patients who did not receive mechanical ventilation, there was no significant difference in 28-day in-hospital mortality between the 2 groups for both the unmatched and propensity-matched groups (Table 3). Logistic regression analyses showed that there was no significant association between the use of prophylactic antibiotics and lower 28-day in-hospital mortality in the propensity score–matched groups (OR, 0.81; 95% CI, .45 to 1.4). There were no significant in-hospital mortality differences between the 2 groups for both the unmatched (control vs prophylaxis; 11.3% vs 10.1%; difference, 1.1%; 95% CI, −1.8 to 4.0) and propensity-matched groups (8.6% vs 8.4%; difference, 0.2%; 95% CI, −3.2 to 3.6). Cox regression analysis did not indicate significant in-hospital mortality differences between the control and prophylaxis groups for the propensity-matched groups (hazard ratio, 0.94; 95% CI, .61 to 1.5).

Table 2. Baseline Patient Characteristics in the Unmatched and Propensity-Matched Groups Without Mechanically Ventilation

	Unmatched Groups			Matched Groups		
Variable	Control (n = 1600)	Prophylaxis (n = 601)	Standardized Differences, %	Control (n = 526)	Prophylaxis (n = 526)	Standardized Differences, %
Age, y (SD)	54.7 (26.6)	55.7 (29.2)	−3.6	53.2 (29.5)	54.1 (29.5)	−3.0
Adult (age >15 y)	1427 (89.2)	507 (84.4)	14.2	428 (81.4)	428 (81.4)	0.0
Sex (male)	1014 (63.4)	341 (56.7)	13.7	317 (60.3)	303 (57.6)	5.4
Burn index, mean (SD)	19.1 (14.5)	16.2 (9.8)	23.4	15.8 (10.0)	16.1 (9.7)	−3.6
Charlson comorbidity index						
0	1362 (85.1)	529 (88.0)	−8.5	460 (87.5)	465 (88.4)	−2.9
1	76 (4.8)	17 (2.8)	10.1	18 (3.4)	15 (2.9)	3.3
≥2	162 (10.1)	55 (9.2)	3.3	48 (9.1)	46 (8.7)	1.3
Academic hospital	506 (31.6)	187 (31.1)	1.1	159 (30.2)	162 (30.8)	−1.2
Teaching hospital	883 (55.2)	551 (91.7)	−90.8	473 (89.9)	476 (90.5)	−1.9
Hospital volume, cases						
Very low, <3	687 (42.9)	253 (42.1)	1.6	239 (45.4)	229 (43.5)	3.8
Low, 3–6	356 (22.3)	162 (27.0)	−10.9	124 (23.6)	131 (24.9)	−3.1
High, 7–12	441 (27.6)	153 (25.5)	4.8	142 (27.0)	140 (26.6)	0.9
Very high, >13	116 (7.3)	33 (5.5)	7.4	21 (4.0)	26 (4.9)	−4.6
Consciousness level						
Alert	1313 (82.1)	487 (81.0)	2.8	447 (85.0)	442 (84.0)	2.6
Delirium	180 (11.3)	84 (14.0)	−8.1	53 (10.1)	64 (12.2)	−6.7
Somnolence	43 (2.7)	19 (3.2)	−3.0	16 (3.0)	10 (1.9)	7.4
Coma	64 (4.0)	11 (1.8)	13.1	10 (1.9)	10 (1.9)	0.0
Catecholamines						
Dopamine use	26 (1.6)	27 (4.5)	−16.9	11 (2.1)	11 (2.1)	0.0
Dobutamine use	4 (0.3)	3 (0.5)	−3.2	2 (0.4)	1 (0.2)	3.6
Noradrenaline use	5 (0.3)	8 (1.3)	−11.2	1 (0.2)	1 (0.2)	0.0
Antithrombin use	9 (0.6)	10 (1.7)	−10.3	3 (0.6)	3 (0.6)	0.0
Recombinant human soluble thrombomodulin use	19 (1.2)	12 (2.0)	−6.4	1 (0.2)	2 (0.4)	−3.6
Haptoglobin use	16 (1.0)	21 (3.5)	−16.9	5 (1.0)	4 (0.8)	2.1
Escharotomy performed	33 (2.1)	10 (1.7)	2.9	6 (1.1)	8 (1.5)	−3.3
Debridement performed	25 (1.6)	40 (6.7)	−25.9	10 (1.9)	7 (1.3)	4.5

Abbreviation: SD, standard deviation.

Although more patients received carbapenem and tazobactam/piperacillin after day 2 in the prophylaxis group than the control group (10.5% vs 18.1%; difference, −7.6%; 95% CI, −8.4 to −3.4 and 8.7% vs 13.3%; difference, −4.6%; 95% CI, −8.9 to −.8, respectively), there was no significant difference between the proportion administered anti-MRSA drugs (14.8% vs 18.4%; difference, −3.6%; 95% CI, −8.1 to 1.6) or fourth-generation cephalosporins (4.2% vs 5.3%; difference, −1.1%; 95% CI, −3.7 to 1.4) after day 2 in the prophylaxis and control groups.

DISCUSSION

The results of this study, which used a nationwide database, suggest that there may be a significant association between the use of prophylactic antibiotics and lower mortality in

Table 3. Comparisons of 28-Day In-Hospital Mortality Rates Between the Groups

Groups	Control	Prophylaxis	Difference (95% Confidence Interval)
Mechanically ventilated patients			
Unmatched groups	48.6% (136/280)	38.3% (158/412)	10.2% (2.7 to 17.7)
Propensity-matched groups	47.0% (109/ 232)	36.6% (85/232)	10.3% (1.4 to 19.3)
Patients without mechanical ventilation			
Unmatched groups	7.0% (112/1600)	5.8% (35/601)	1.2% (–1.2 to 3.5)
Propensity-matched groups	5.1% (27/526)	4.2% (22/526)	0.9% (–1.6 to 3.5)

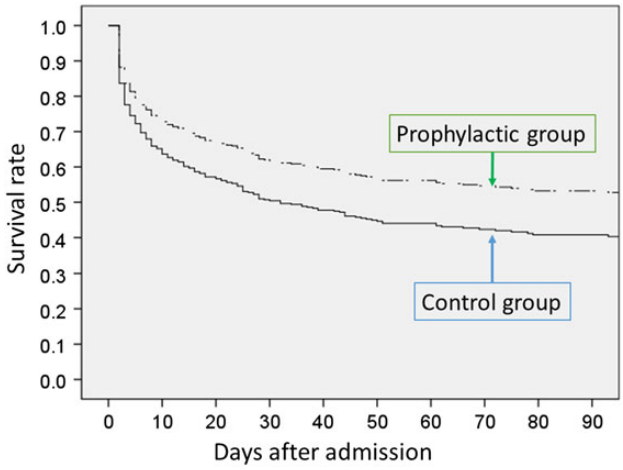

Figure 2. Survival plots for mechanically ventilated patients with severe burns treated with (dashed line) or without (solid line) prophylactic antibiotics in propensity score-matched groups.

mechanically ventilated patients with severe burns. However, this association was not found in patients with severe burns who did not receive mechanical ventilation. There were no significant differences in the proportion administered anti-MRSA drugs, carbapenem, tazobactam/piperacillin, or fourth-generation cephalosporins after day 2 in the propensity-matched groups undergoing mechanical ventilation.

Several recommendations and guidelines for the initial management of severe burns [17, 18, 20], including Japanese guidelines (Japanese Society for Burn Injuries) [19], do not address systemic antibiotic prophylaxis or explicitly state that prophylactic antibiotics are not recommended. The use of prophylactic antibiotics may not be safe because they could also promote the emergence of resistant strains of microorganisms, further impeding the treatment of infections. However, in terms of actual clinical practice in a general setting (ie, not for perioperative management) across Japan, the present study found that prophylactic antibiotics were administered to approximately 35% of all patients with severe burns and to 60% of those receiving mechanical ventilation.

These results are consistent with the findings of the systematic review study by Avni et al [15]. They analyzed 136 paired cases from 5 studies that did not take the use of mechanical ventilation into consideration and determined that systemic antibiotic prophylaxis significantly reduces all-cause mortality. The methodological strength of our study lies in the evaluation of a large sample of patients across Japan with severe burns. We conducted robust adjustment for measured confounders using propensity-matched analyses and focused on patients who did or did not receive prophylaxis within 2 days after admission. In our study, the prophylactic antibiotics mainly targeted microorganisms, which in general heavily colonize the wound surface within the first 48 hours. In severe burn patients, coagulase-negative staphylococci and methicillin-sensitive *S. aureus* have been found to be the most prevalent isolates in admission cultures [4]. A gradual decrease in the number of isolates of coagulase-negative staphylococci and a marked increase in the numbers of *S. aureus* and *Pseudomonas aeruginosa* have been observed from admission to day 21 [4]. There was subsequently a constant increase in MRSA [4]. Accordingly, as the secondary outcome, we compared the incidence of patients who required anti-MRSA drug administration with the prophylaxis group and controls. We found that the use of prophylactic antibiotics did not lead to an increase in the proportion of anti-MRSA drug administration.

Several small sample studies [10, 11] and systematic reviews [15, 16] have found reduced incidence of pneumonia in burn patients to be associated with systemic antibiotic regimens. Several studies have indicated the presence of immune defects in the early phase following thermal injury among patients with severe burns. The defects include impaired cytotoxic T-lymphocyte response, myeloid maturation arrest causing neutropenia, impaired neutrophil function, and decreased macrophage production [6–8] .The results of the current propensity score–matched analysis suggest that mechanically ventilated patients with severe burns who received prophylactic antibiotics were more likely to survive than similar patients who did not receive the antibiotics. These findings were robust, as demonstrated by the results obtained by the logistic regression and Cox regression analyses. Although in the present study we were unable to determine the indications for mechanical ventilation for each patient, mechanically ventilated patients were apparently in a more severe condition (higher burn index and mortality rate) than those who did not undergo the procedure. Although we cannot infer a robust cause-and-effect relationship from this study, we can speculate that severe burn patients who required mechanical ventilation could have (severe enough to) had immune defects and may have suffered from sepsis (including pneumonia) in the early phase after burn injury.

This study has some limitations. First, although it used a nationwide database, it was retrospective and observational, without randomization. Even though we adopted propensity score matching to adjust for differences in baseline characteristics and disease severity, there may still have been bias in the form of confounders that were not measured. However, we were able to identify the major factors that potentially affect mortality in patients with severe burns, such as age, sex, burn index, comorbidities, and use of mechanical ventilation [5, 20, 22, 26, 28, 33], and the baseline characteristics of selected patients with severe burns were well balanced in the propensity score–matched groups. Although large randomized trials are necessary to confirm these results, it may be not easy to perform such trials in a large number of patients for this life-threatening condition, especially for mechanically ventilated patients with

severe burns (mortality rate of 42.5%). Thus, the present nationwide study may provide the best attainable level of evidence on this issue. Second, the database does not include data on microorganisms, the actual incidence of infection, or the cause of death, that is, death caused by sepsis due to burn site infection or pneumonia. Third, we did not consider topical antibiotics when we analyzed the data. However, recent studies have suggested that topical antibiotic prophylaxis confers no beneficial effects on outcome [15, 16]. Finally, we evaluated only severe burn patients in a general setting (ie, not in a perioperative setting), as defined in previous studies [15, 16]. Thus, our results cannot be generalized to the use of prophylactic antibiotics for severe burns in perioperative settings.

CONCLUSIONS

The current nationwide database study using propensity score analyses found that the use of systemic prophylactic antibiotics in general settings may result in improved 28-day in-hospital mortality in mechanically ventilated patients with severe burns but not in patients who do not receive mechanical ventilation. Future multination studies are required to validate our results.

Notes

Author contributions. All authors assisted with study conception and design and with data acquisition. T. T., H. M., and H. Y. were responsible for the statistical analyses and the first draft of the manuscript. All authors amended and commented on the manuscript and approved the final version.

Financial support. This work was supported by grants for Research on Policy Planning and Evaluation from the Ministry of Health, Labour and Welfare, Japan (grant numbers H27-Policy-Designated-009 to K. F. and H. Y. and H27-Policy-Strategy-011 to H. Y.) and Grants-in-Aid for Scientific Research, Japan (grant number KAKENHI-15H05685 to T. T.). The funders had no role in the execution of this study or interpretation of the results.

Potential conflicts of interest. All authors: No potential conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Torpy JM, Lynm C, Glass RM. JAMA patient page. Burn injuries. JAMA **2009**; 302:1828.
2. Peck MD. Epidemiology of burns throughout the world. Part I: Distribution and risk factors. Burns **2011**; 37:1087–100.
3. Fitzwater J, Purdue GF, Hunt JL, O'Keefe GE. The risk factors and time course of sepsis and organ dysfunction after burn trauma. J Trauma **2003**; 54:959–66.
4. Erol S, Altoparlak U, Akcay MN, Celebi F, Parlak M. Changes of microbial flora and wound colonization in burned patients. Burns **2004**; 30:357–61.
5. Church D, Elsayed S, Reid O, Winston B, Lindsay R. Burn wound infections. Clin Microbiol Rev **2006**; 19:403–34.
6. Sharma BR. Infection in patients with severe burns: causes and prevention thereof. Infect Dis Clin North Am **2007**; 21:745–59, ix.
7. Gamelli RL, He LK, Liu LH. Macrophage mediated suppression of granulocyte and macrophage growth after burn wound infection reversal by means of anti-PGE2. J Burn Care Rehabil **2000**; 21:64–9.
8. Hunt JP, Hunter CT, Brownstein MR, et al. The effector component of the cytotoxic T-lymphocyte response has a biphasic pattern after burn injury. J Surg Res **1998**; 80:243–51.
9. Durtschi MB, Orgain C, Counts GW, Heimbach DM. A prospective study of prophylactic penicillin in acutely burned hospitalized patients. J Trauma **1982**; 22:11–4.
10. de La Cal MA, Cerda E, Garcia-Hierro P, et al. Survival benefit in critically ill burned patients receiving selective decontamination of the digestive tract: a randomized, placebo-controlled, double-blind trial. Ann Surg **2005**; 241:424–30.
11. Kimura A, Mochizuki T, Nishizawa K, et al. Trimethoprim-sulfamethoxazole for the prevention of methicillin-resistant *Staphylococcus aureus* pneumonia in severely burned patients. J Trauma **1998**; 45:383–7.
12. Munster AM, Xiao GX, Guo Y, Wong LA, Winchurch RA. Control of endotoxemia in burn patients by use of polymyxin B. J Burn Care Rehabil **1989**; 10:327–30.
13. Ugburo AO, Atoyebi OA, Oyeneyin JO, Sowemimo GO. An evaluation of the role of systemic antibiotic prophylaxis in the control of burn wound infection at the Lagos University Teaching Hospital. Burns **2004**; 30:43–8.
14. Deutsch DH, Miller SF, Finley RK Jr. The use of intestinal antibiotics to delay or prevent infections in patients with burns. J Burn Care Rehabil **1990**; 11:436–42.
15. Avni T, Levcovich A, Ad-El DD, Leibovici L, Paul M. Prophylactic antibiotics for burns patients: systematic review and meta-analysis. BMJ **2010**; 340:c241.
16. Barajas-Nava LA, Lopez-Alcalde J, Roque i Figuls M, Sola I, Bonfill Cosp X. Antibiotic prophylaxis for preventing burn wound infection. Cochrane Database Syst Rev **2013**; 6:CD008738.
17. Hettiaratchy S, Papini R. Initial management of a major burn: I–overview. BMJ **2004**; 328:1555–7.
18. Latenser BA. Critical care of the burn patient: the first 48 hours. Crit Care Med **2009**; 37:2819–26.
19. Japanese Society for Burn Injuries. Guidelines for the management of burn patients (in Japanese). Japanese_Society_for_Burn_Injuries, **2009**. Available at: http://www.jsbi-burn.org/members/guideline/pdf/guideline.pdf. Accessed 2 September 2015.
20. Snell JA, Loh NH, Mahambrey T, Shokrollahi K. Clinical review: the critical care management of the burn patient. Crit Care **2013**; 17:241.
21. Tagami T, Matsui H, Fushimi K, Yasunaga H. Intravenous immunoglobulin and mortality in pneumonia patients with septic shock: an observational nationwide study. Clin Infect Dis **2015**; 61:385–92.
22. Tagami T, Matsui H, Fushimi K, Yasunaga H. Validation of the prognostic burn index: a nationwide retrospective study. Burns **2015**; 41:1169–75.
23. Tagami T, Matsui H, Horiguchi H, Fushimi K, Yasunaga H. Low-dose corticosteroid use and mortality in severe community-acquired pneumonia patients. Eur Respir J **2015**; 45:463–72.
24. Tagami T, Matsui H, Horiguchi H, Fushimi K, Yasunaga H. Antithrombin and mortality in severe pneumonia patients with sepsis-associated disseminated intravascular coagulation: an observational nationwide study. J Thromb Haemost **2014**; 12:1470–9.
25. Tagami T, Matsui H, Fushimi K, Yasunaga H. Use of recombinant human soluble thrombomodulin in patients with sepsis-induced disseminated intravascular coagulation after intestinal perforation. Front Med **2015**; 2:7.
26. Sheppard NN, Hemington-Gorse S, Shelley OP, Philp B, Dziewulski P. Prognostic scoring systems in burns: a review. Burns **2011**; 37:1288–95.
27. Quan H, Li B, Couris CM, et al. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. Am J Epidemiol **2011**; 173:676–82.
28. Lundgren RS, Kramer CB, Rivara FP, et al. Influence of comorbidities and age on outcome following burn injury in older adults. J Burn Care Res **2009**; 30:307–14.
29. Belgian Outcome in Burn Injury Study G. Development and validation of a model for prediction of mortality in patients with acute burn injury. Br J Surg **2009**; 96:111–7.
30. O'Keefe GE, Hunt JL, Purdue GF. An evaluation of risk factors for mortality after burn trauma and the identification of gender-dependent differences in outcomes. J Am Coll Surg **2001**; 192:153–60.
31. Osler T, Glance LG, Hosmer DW. Simplified estimates of the probability of death after burn injuries: extending and updating the Baux score. J Trauma **2010**; 68:690–7.
32. Smith DL, Cairns BA, Ramadan F, et al. Effect of inhalation injury, burn size, and age on mortality: a study of 1447 consecutive burn patients. J Trauma **1994**; 37:655–9.
33. Ryan CM, Schoenfeld DA, Thorpe WP, et al. Objective estimates of the probability of death from burn injuries. N Engl J Med **1998**; 338:362–6.
34. Kraft R, Herndon DN, Al-Mousawi AM, et al. Burn size and survival probability in paediatric patients in modern burn care: a prospective observational cohort study. The Lancet **2012**; 379:1013–21.
35. Hubbard AE, Ahern J, Fleischer NL, et al. To GEE or not to GEE: comparing population average and mixed models for estimating the associations between neighborhood risk factors and health. Epidemiology **2010**; 21:467–74.
36. Austin PC. The use of propensity score methods with survival or time-to-event outcomes: reporting measures of effect similar to those used in randomized experiments. Stat Med **2014**; 33:1242–58.