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COMMENTARY

Clinical Differences Between Survivors and Non-Survivors of Ventilator-Associated Pneumonia: The Roles of Sulbactam/Ampicillin and Methicillin-Resistant *Staphylococcus aureus*

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Background: Ventilator-associated pneumonia (VAP) is one of the most lethal complications in intensive care unit (ICU) patients. However, critical issues of non-survivors vary and are still unclear in VAP patients.

Methods: The clinical differences between survivors and non-survivors of VAP were retrospectively analyzed in patients hospitalized from April 2023 to March 2024.

Results: Of a total of 42 VAP patients, 22 (52.4%) survived, and 20 died. Survivors were significantly younger (69.1 vs 71.7 years, $p < 0.01$) and received sulbactam/ampicillin (SAM) as the initial antibiotics, significantly more (45.5% vs 10%, $p = 0.006$) than non-survivors. The male/female ratio and wards where they were managed were similar in both groups, but methicillin-resistant *Staphylococcus aureus* (MRSA) was detected significantly more frequently in non-survivors (4/4 = 100%).

Conclusion: These data suggest that VAP patients who survived were younger and received treatment with narrow-spectrum antibiotics, such as SAM. Isolation of MRSA might be critical. These findings could influence antibiotic protocols and ICU management strategies to prevent infection with resistant bacteria to improve the prognosis of patients with VAP.

Keywords: Methicillin-resistant *Staphylococcus aureus*, sulbactam/ampicillin, *Pseudomonas aeruginosa*, vancomycin, ventilator-associated pneumonia

Background

Ventilator-associated pneumonia (VAP) is pneumonia that develops in patients on mechanical ventilation for more than 48 hours, and it is one of the most common hospital-acquired infections affecting patients in the intensive care unit (ICU).[1,2] It has been suggested that VAP is associated with high resource use and prolonged hospital length of stay, and some studies estimated that VAP prolongs the length of mechanical ventilation by 7.6 to 11.5 days and of hospitalization by 11.5 to 13.1 days, compared with patients without VAP.[3,4] In addition, the excess cost related to VAP has been reported to be approximately $40,000 per patient.[1,3]

Although all-cause mortality associated with VAP has been reported to range from 20% to 50%, the direct mortality related to VAP was reported to be 13% in the recent meta-analysis.[1,2] Furthermore, several studies have suggested that a third to a half of VAP-related deaths might be related to the infection, especially in cases caused by *Pseudomonas aeruginosa* (*P. aeruginosa*) and *Acinetobacter* spp, those are known to be antibiotic-resistant pathogens.[1,2,5]

Recently, antimicrobial resistance (AMR) has emerged as an urgent global public health problem, with a forecast of 10 million deaths per year globally by 2050,[6] and some strategies, such as combination therapy and early de-escalation of

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antibiotics, were investigated to reduce resistant bacteria and improve VAP patients' prognosis in the ICU.[7] The usefulness of multidisciplinary approaches, including AMR surveillance, in the treatment of nosocomial infections in critically ill ICU patients has also been suggested.[8] Furthermore, various eco-friendly techniques are being researched to synthesize ZnO-NPs (zinc O-nanoparticles), known for their bioactivity, and an efficient Ka(water-insoluble active compound)-ZnO-NPs nanoemulsion may be a promising solution for resistant Gram-negative pathogenic bacteria because of their antibacterial activity and low toxicity.[9]

In this study, the number and characteristics of VAP patients in our hospital from April 01, 2023 to March 31, 2024, were analyzed, and the clinical differences between those who did and did not survive were investigated.

VAP patients were those who had pneumonia at 48 hours or more after bronchial intubation and ventilator management based on the National Healthcare Safety Network criteria.[1,10] Patients who were admitted within 48 hours, were on non-invasive positive-pressure ventilators, and who received ventilator management for less than 48 hours were excluded. Patients aged 18 years and younger and those with viral/fungal pneumonia were also excluded. Usually, the patients had some severe underlying disease, including cancers, and were diagnosed from a combination of clinical, radiographic, and microbiological data, such as fever, increased leukocyte count, purulent sputum/bronchial specimens, worsening gas exchange, appearance of shadows on the chest X-ray, and isolation of pathogenic bacteria from respiratory specimens according to ventilator-associated event criteria.[11]

The minimum inhibitor concentrations (MICs) of isolated bacteria were determined by a Phoenix M-50 system (Becton Dickinson, Franklin Lakes, NJ, USA) and Lysys@S4 (Shimazu Diagnostics, Tokyo, Japan) based on the broth microdilution method.

This study and related analyses were approved by the Institutional Review Board of Saitama Medical University International Medical Center on September 07, 2022, as #2022-072 and registered as UMIN000047992. The patients whose specimens were analyzed provided written, informed consent to have any accompanying images and their case details published. This study was performed in accordance with the Declaration of Helsinki.

Although the sample size was small, and there were potential confounders or biases in the retrospective design, statistical analyses were performed in consultation with a statistician. The chi-squared test and the Mann–Whitney *U*-test were used to compare continuous variables between two groups. A significant difference was defined as a p-value less than 0.05. All analyses were performed using Stat View software (Abacus Concepts, Cary, NC, USA).

A total of 42 VAP patients were identified, of whom 22 (52.4%) survived, and 20 did not (Table 1). Those who survived were significantly younger (69.1 vs 71.7 years, $p < 0.01$), but the male/female ratio was almost identical between those who did and did not survive (59.1% vs 70.0%, $p = 0.46$), although males tended to predominate in those who did not survive. All VAP patients were managed in emergency, cardiovascular surgery, brain surgery, cardiology, otolaryngology, and neurology wards, and there were no significant differences between those who did and did not survive. Underlying diseases, such as chronic heart/lung diseases, diabetes mellitus, and brain strokes were also not significantly different between the two groups (data not shown).

Table 1 Clinical Characteristics of Ventilator-Associated Pneumonia Patients Compared Between Survivors and Non-Survivors

		Survive (n=22)	Non-Survive (n=20)	p value
Age (y.o.)		69.1 (37–88)	71.7 (42–86)	p<0.01***
Male/ Female		13 / 9 (59.1)	14 / 6 (70.0%)	p=0.46
Ward	Emergency	10 (45.5%)	6 (30%)	p=0.30
	Cardiosurgery	7 (31.8%)	6 (30%)	p=0.65
	Brain surgery	3 (13.6%)	2 (10%)	p=0.71
	Cardiology	1 (4.5%)	4 (20%)	p=0.12
	Otolaryngology	1 (4.5%)	0	p=0.33
	Neurology	0	2 (10%)	p=0.13

Bacteria, such as *P. aeruginosa, Enterococcus faecalis* (*E. faecalis)*, methicillin-susceptible/resistant *Staphylococcus aureus* (MSSA/MRSA), *Acinetobacter baumannii (A. baumannii), Enterobacter cloacae* (*E. cloacae), Escherichia coli* (*E. coli), Serratia marcescens* (*S. marcescens), Klebsiella pneumoniae* (*K. pneumoniae*), and other pathogenic bacteria were isolated from the patients' specimens, including sputum, bronchial aspirations, and blood cultures, and MRSA was significantly more frequent in patients who did not survive, with no MRSA detected in patients who survived (survived: 0% vs did not survive: 20%, P = 0.035, Figure 1A). In two of four non-surviving cases in which *P. aeruginosa* was isolated, the bacteria showed reduced susceptibility to either meropenem (MEM) or tazobactam/piperacillin (TZP), but all three *Acinetobacter* species from patients who did not survive were not resistant to either MEM or TZP (data not shown).

For these patients, several kind of antibiotics were given, but those who survived were initially treated significantly more often with sulbactam/ampicillin (SAM) than those who did not survive (survived: 45.5% vs did not survive: 10%, p = 0.006, Figure 1B), although the use of broad-spectrum antibiotics, including MEM, TZP, and vancomycin (VAN), was almost the same between the two groups.

In this study, a total of 42 VAP patients were identified, and their clinical features were compared between those who did and did not survive. Mortality was estimated at 47.6% (20/42 patients), and non-survivors were older and showed a tendency for males to predominate compared with those who survived. These data were generally similar to previous studies,[1,2,4] and suggested consideration of risk factors, such as elderly and male patients, to prevent the development of severe and lethal VAP in patients who are intubated and started on ventilator management. In contrast, no significant

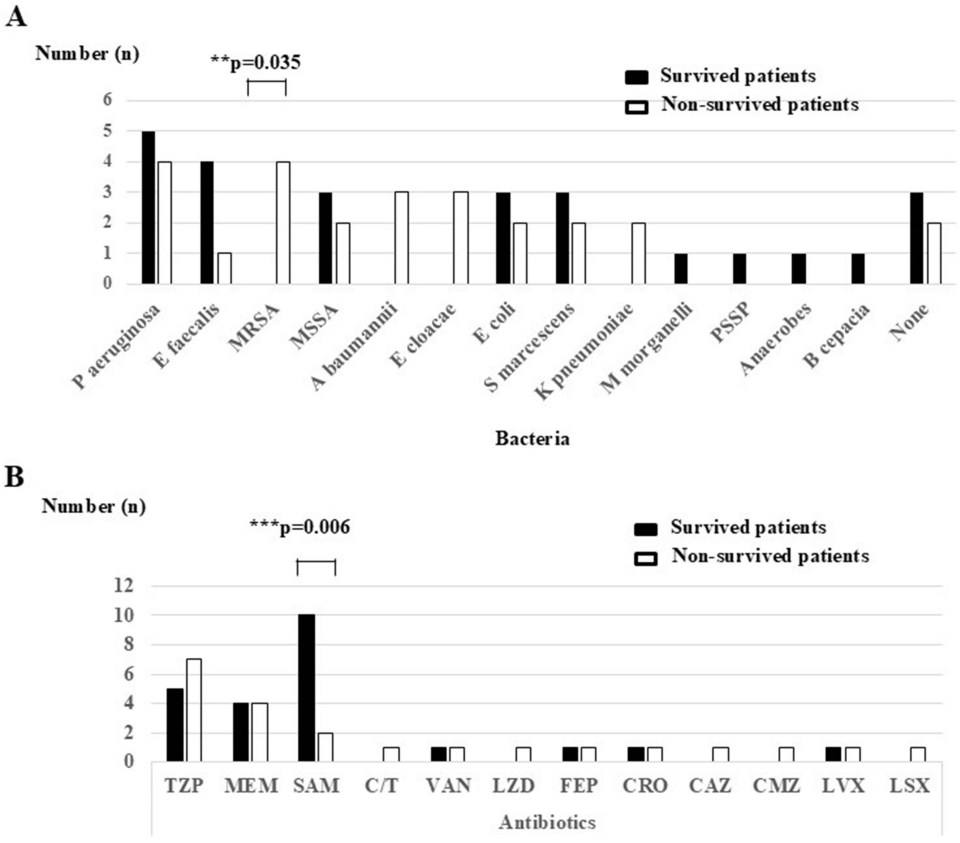

Figure 1 (**A**) Isolated bacteria and (**B**) antibiotics use of ventilator-associated pneumonia patients compared between survivors and non-survivors. (**A**) MRSA isolation was more prevalent in non-survivors, and (**B**) use of SAM was associated with higher survival rates. *** indicates p<0.01, and **indicates P<0.05, respectively. Black bars: Survived patients, and White bars: Non-survived patients, respectively.

Abbreviations: (**A**) *P aeruginosa, Pseudomonas aeruginosa*; *E faecalis, Enterococcus faecalis*; MRSA, methicillin resistance *Staphylococcus aureus* ATCC43300; MSSA, methicillin susceptible *Staphylococcus aureus* ATCC25923; *A baumannii, Acinetobacter baumannii; E cloacae, Enterobacter cloacae; E coli, Escherichia coli* ATCC25922; *S marcescens, Serratia marcescens; K pneumoniae, Klebsiella pneumoniae*; PSSP, penicillin susceptible *Streptococcus pneumoniae; M morganelli, Morganella morganii; B cepacia, Burkholderia cepacia;* (**B**) TZP; tazobactam/piperacillin; MEM; meropenem; SAM, sulbactam/ampicillin; T/C; tazobactam/ ceftolozane; VAN, vancomycin; LZD, linezolid; FEP, cefepim; CRO, ceftriaxone; CAZ, ceftadizime; CMZ, cefmetazole; LFX, levofloxacin; LSX, lascufloxacin; respectively.

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differences were observed in the management wards, but underlying diseases, such as cardiac, pulmonary, and neurological diseases, usually affected the prognosis of these patients.[4] These data suggested that factors other than underlying diseases might be more significant in the development of severe/lethal VAP.[1,2,4,12]

Furthermore, MRSA isolation significantly affected the prognosis of VAP patients in this study, though isolation of *P. aeruginosa*, which was frequently isolated and considered as one of the most important pathogens of VAP,[1,13] was not different between patients who did and did not survive. MRSA was usually isolated from patients who received ventilator management but considered just colonization,[14] and it was reported that patients treated using anti-MRSA drugs showed worse outcomes than patients who did not receive anti-MRSA treatment.[12,15] The present data suggested that the MRSA isolates might be possible pathogens, and they matched with our recent data that MRSA-alone isolated pneumonia cases should be treated as real "MRSA pneumonia" and might have a better outcome.[16]

In addition, patients who received SAM initially showed better outcomes. SAM has been considered a relatively narrow-spectrum antibiotic combination, but it could cover the anaerobes without inducing resistance in high-risk pathogens, including *P. aeruginosa* and the enterobacteriae.[17] These data suggest that patients with suspected aspiration pneumonia might have better outcomes, and resistant pathogens including MRSA and patients who received broad-spectrum antibiotics might have a poor prognosis, as previously reported.[1,2,13] De-escalation strategies, such as switching from broad- to narrow-spectrum antibiotics, have been reported to be effective in preventing the emergence of resistant bacteria and a poor prognosis,[1,2] and recently, monotherapy with trimethoprim-sulfamethoxazole (TMP-SMX) as de-escalation from broad-spectrum empirical regimens was reported as a β-lactam-sparing strategy worthy of being further investigated in either multicenter, cohort studies or randomized, clinical trials.[18] The VAP study that showed that MRSA was the most common isolated pathogen showed that de-escalation therapy did not lead to recurrence of pneumonia or increased mortality in critically ill surgical patients with VAP.[19] In this report, the most commonly used initial antibiotic choice was VAN/TZP (16%), and the final choice was TZP (20%).[19] De-escalation therapy was also shown to be safe in patients with septic shock.[19] Because of its acknowledged benefits and lack of demonstrable risks, de-escalation therapy might be used whenever possible in critically ill patients with VAP.

Regarding the limitations of the present study, it was performed in one tertiary hospital and had a small sample size. Therefore, further multicenter studies are needed to validate the findings and confirm the effectiveness of SAM as a targeted treatment. A quick analysis of monthly or any periodic assessments of hospital data may also be useful.

In conclusion, there were 42 VAP cases in our hospital during this one-year period; the 52.4% who survived were younger and received SAM, because aspiration-type pneumonia might have been suspected. MRSA might be a key pathogen that affects patient prognosis, although not all MRSA isolates of patients treated using anti-MRSA drugs are the real pathogens. We should attempt to prevent transmission of MRSA to patients on ventilators without consideration of their underlying diseases, and the present results might lead to changes in hospital protocols for managing VAP, particularly in terms of antibiotic selection and infection control measures for MRSA. The study's results have the potential to shift practice from the current reliance on broad-spectrum antibiotics to more targeted treatments such as SAM in a more aggressive manner.

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Disclosure

The authors reported no conflicts of interest in this work.

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