Effect of Gram Stain–Guided Initial Antibiotic Therapy on Clinical Response in Patients with Ventilator-Associated Pneumonia (GRACE-VAP)

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Background and Purpose

Pneumonia is the second most common nosocomial infection affecting an estimated 27% of all critically ill patients in intensive care units[2]. Ventilator associated pneumonia (VAP), which is defined as pneumonia occurring more than 48 h after patients have been intubated and received mechanical ventilation, accounts for 86% of nosocomial pneumonia[2]. Diagnosing VAP requires a high clinical suspicion combined with bedside examination, radiographic examination, and microbiologic analysis of respiratory secretions. The 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society recommend including coverage for *S. aureus*, *Pseudomonas aeruginosa*, and other gram-negative bacilli in all empiric regimens[1]. This recommendation results in initiation of broad-spectrum antibiotics which could be associated with the accelerated emergence of antimicrobial resistant organisms[2]. The purpose of this study is to compare the clinical response to Gram stain–guided restrictive antibiotic therapy vs guideline-based broad-spectrum antibiotic treatment in patients with ventilator-associated pneumonia (VAP)

Study Overview

Funding

This study was funded by the Public Trust Foundation of Marumo ER Medicine and Research Institute.

Objectives

Primary Outcomes

Clinical response rate at the follow-up or test-of-cure visit which was defined as 7 days after the end of therapy
• Clinical response was defined as meeting the following 4 outcomes
  ○ Completion of antibiotic therapy within 14 days.
  ○ Improvement or lack of progression of baseline radiographic findings at the end of therapy
  ○ Resolution of signs and symptoms of pneumonia at the follow-up or test-of-cure visit
  ○ Lack of antibiotic agent re-administration owing to pneumonia by the follow-up or test-of-cure visit

Secondary Outcomes
• 28-day mortality, ICU-free days, and ventilator free days • Proportions of antipseudomonal agents and anti-MRSA agents as initial antibiotic therapies • Coverage rate of initial antibiotic therapies • De-escalation rate • Duration of therapy • Adverse events

Methods

Design and setting

The study was a multicenter, open label, noninferiority randomized clinical trial conducted in the intensive care units (ICUs) of 12 tertiary referral hospital in Japan.

Population

Inclusion criteria	Exclusion criteria
• 15 years or older • Undergone mechanical ventilation for ≥48 hours • Diagnosed with VAP	• Known allergy to study medication • Pregnancy • Discharge from ICU • Heart failure or atelectasis diagnosis • Receipt of antibiotics for more than 24 hours after meeting the inclusion criteria • Withdrawal or withholding of life support • Covid-19 infection

Interventions

Comparator group

- Guideline based standard treatment: received combination of an antipseudomonal agent and an anti-MRSA agent

Intervention group

- Gram stain–guided antibiotic treatment
  - GPC in chains and/or GNR → nonpseudomonal β-lactam
  - GPC in clusters without GNR → anti-MRSA
  - GNR without GPC in clusters → antipseudomonal
  - GPC in clusters and GNR or no microorganisms on gram stain → antipseudomonal + anti-MRSA

Statistical analysis

- The primary efficacy analysis assessed the noninferiority (20% non-inferiority margin) of the clinical response in the Gram stain– guided group compared with the guideline-based group.
- With a sample size of 86 patients per group, the study would have an 80% power to show non-inferiority of Gram stain–guided antibiotic treatment with a 1-sided α level of 0.025.
- Primary analysis was performed in the per-protocol analysis population.
- Secondary outcomes were analyzed under a superiority assumption, which was based on the intention-to-treat principle
- All P values were 2-sided, and P < .05 was significant except in the noninferiority test for clinical response, for which a 1-sided P < .025 was significant

Enrollment

- The study recruited patients from ICUs of 12 tertiary referral hospitals in Japan.
- Total of 206 subjects underwent randomization (103 of whom were randomized to the Gram stain–guided group and 103 to the guideline-based group).
- Baseline characteristics were similar between the 2 groups (see Figure 2)

Results and Authors Conclusion

Figure 1: Primary and secondary outcomes

Outcome	No. (%)		*P* value
	Gram stain-guided group (n = 103)	Guideline-based group (n = 103)	
Primary outcome			
Clinical response rate	79 (76.7)	74 (71.8)	<.001[a]
Completion of antibiotic therapy within 14 d[b]	98 (95.1)	94 (91.3)	NA
Improvement or lack of progression of baseline radiographic findings[b]	85 (82.5)	78 (75.7)	NA
Resolution of signs and symptoms of pneumonia[b]	87 (84.5)	85 (82.5)	NA
Lack of antibiotic agent readministration[b]	85 (82.5)	85 (82.5)	NA
Secondary outcomes			
28-d mortality	14 (13.6)	18 (17.5)	.44
28-d ventilator-free days, median (IQR)	21 (0-24)	21 (4-25)	.63
28-d ICU-free days, median (IQR)	18 (11-22)	17 (5-22)	.61
Administration of antibiotic therapy			
Antipseudomonal agents	72 (69.9)	103 (100)	<.001
Anti-MRSA agents	63 (61.2)	103 (100)	<.001
Coverage rate of initial antibiotic therapy	89 (86.4)	95 (92.2)	.18
Escalation[b]	7 (6.8)	1 (1.0)	.03
De-escalation	67 (65.0)	79 (76.7)	.07
Antibiotic therapy days until de-escalation, median (IQR)	3 (2-4)	3 (2-4)	.22
Antibiotic therapy days, median (IQR)	8 (7-11)	8 (7-11)	.09

Authors conclusion

Gram stain–guided restrictive antibiotic therapy was noninferior to guideline-based broad-spectrum antibiotic therapy in patients with VAP in terms of the clinical response rate. Gram staining of endotracheal aspirates optimized the use of broad-spectrum antibiotic agents for VAP without detrimental effects on patient outcomes

Critique

Study strengths

- The study was randomized and multicenter
- The study reached a statistically significant endpoint
- Informed consent provided to all participants
- Outcomes evaluated by a blinded independent adjudication committee
- Baseline characteristics in both arms were identical

Study Limitation

- Per protocol analysis of primary analysis
- Open-label design may have influenced the behavior of the site investigator in charge
- Narrow sample size limits generalizability to other patient populations
- Frequency of multidrug resistant (MDR) GNR was low (<10%) and *P. aeruginosa* susceptibility to antipseudomonal β-lactam was high (80%-90%) in the participating ICUs limiting generalizability to ICUs with high rates of MDR GNR.

Reviewer's opinion

The guidelines for management of adult VAP published by the Infectious Diseases Society of America (IDSA) have emphasized the importance of reducing the unnecessary use of broad-spectrum antimicrobials to minimize patient harm and reduce the development of antimicrobial resistance. The results of this study indicate that Gram stain–guided antibiotic therapy could help safely reduce the use of broad-spectrum antibiotics in patients who have VAP. However, due to the limitations of this study, decisions on which empiric therapy to initiate in patients diagnosed with VAP should be based on individual patient risk factors for MDR organisms as well as resistance rates and local susceptibility in each ICU setting. In the GRACE-VAP study, it is notable that there was a statistically significant number of patients that needed escalation of antibiotics in the Gram-stain guided to cover for all pathogens isolated. This finding highlights the potential for suboptimal or inappropriate therapy when using Gram-stain results to select empiric therapy. Additionally, participants in this study were relatively healthy and had low-to-moderate severity of illness based on median APACHE II score and percentage of patients classified as having sepsis or septic shock. Therefore, these results may not be generalizable in clinical practice in patients with severe VAP.

References

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Figure 2: Baseline characteristics

Characteristic	No. (%)	
	Gram stain–guided group (n = 103)	Guideline-based group (n = 103)
Age, median (IQR), y	69 (54-78)	69 (54-78)
Female sex	37 (35.9)	28 (27.2)
Male sex	66 (64.1)	75 (72.8)
Diagnosis on ICU admission		
Trauma	28 (27.2)	27 (26.2)
Postcardiopulmonary arrest syndrome	25 (24.3)	24 (23.3)
Stroke	11 (10.7)	10 (9.7)
Other	39 (37.9)	42 (40.8)
mCPIS, median (IQR)[b]		
Overall	6 (5-7)	6 (5-7)
Temperature	1 (0-2)	1 (0-2)
Leukocytes	0 (0-1)	0 (0-2)
Pao_2/Fio_2	0 (0-2)	0 (0-2)
Chest radiograph	2 (2-2)	2 (2-2)
Tracheal secretions	2 (2-2)	2 (2-2)
Comorbidities		
Diabetes	27 (26.2)	26 (25.2)
Chronic		
Heart failure	22 (21.4)	16 (15.5)
Respiratory disorder	6 (5.8)	6 (5.8)
Hemodialysis	5 (4.9)	5 (4.9)
Liver cirrhosis	4 (3.9)	1 (1.0)
Immunocompromised	3 (2.9)	4 (3.9)
Previous antibiotic therapy	30 (29.1)	27 (26.2)
Length of ICU stay before randomization, d		
≥5	53 (51.5)	49 (47.6)
<5	50 (48.5)	54 (52.4)
Sepsis	36 (35.0)	33 (32.0)
Septic shock	6 (5.8)	3 (2.9)
Acute kidney injury[c]	20 (19.4)	13 (12.6)
APACHE II score, median (IQR)[d]	18 (14-24)	19 (15-23)
SOFA score, median, (IQR)[e]	7 (5-9)	7 (5-9)