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Epidemiology of ventilator-associated tracheobronchitis and ventilator-associated pneumonia caused by multidrug-resistant Gram-negative bacteria at a tertiary care hospital in Thailand

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Objectives: To investigate the epidemiology of MDR Gram-negative bacilli ventilator-associated tracheobronchitis (MDR GNB-VAT) and MDR GNB ventilator-associated pneumonia (MDR GNB-VAP) among mechanically ventilated patients.

Methods: We conducted a retrospective observational study among hospitalized patients who underwent continuous mechanical ventilation for ≥48 h at Siriraj Hospital, Thailand.

Results: During the 18 month study period, 1824 unique patients underwent continuous mechanical ventilation (12 216 ventilator-days). The cumulative incidences of MDR GNB-VAT and -VAP were 8.4% and 8.3%, respectively. The incidence rates of MDR GNB-VAT and -VAP were 12.52 and 12.44 episodes/1000 ventilator-days, respectively. Among those with VAT, the cumulative incidence and incidence rate of subsequent VAP development within 7 days were 11.76% and 2.81 episodes/1000 ventilator-days, respectively. The median durations of mechanical ventilation before having VAP and VAT were 9 and 12 days, respectively. Multivariate analysis identified three independently associated factors for patients having VAP compared with having VAT: underlying cerebrovascular disease [adjusted OR (aOR): 0.46; 95% CI: 0.27–0.78; $P=0.04$], previous surgery (aOR: 0.68; 95% CI: 0.57–0.8; $P<0.001$) and acute renal failure (aOR: 1.75; 95% CI: 1.27–2.40; $P=0.001$).

Conclusions: The study revealed high incidences of MDR GNB-VAT and -VAP among mechanically ventilated patients. The independent risk factors for having VAP can help identify patients at risk for developing VAP and who need early weaning from mechanical ventilation.

Introduction

Ventilator-associated tracheobronchitis (VAT) is inflammation of the trachea and bronchi that develops after use of a ventilator for at least 48 h. This important condition is a common medical problem among mechanically ventilated patients. Previous studies reported that the cumulative incidence of VAT among mechanically ventilated patients in the ICU varied from 1.4% to 18.0%.[1–4]

Previous studies identified VAT as a significant risk factor for developing ventilator-associated pneumonia (VAP).[2,3] In other words, VAT is an early-stage lower respiratory tract infection (LRTI) that may subsequently progress to VAP.[5] The major distinguishing feature between VAT and VAP is infiltration on chest radiography. Pneumonia-compatible pulmonary infiltration is required to diagnose VAP, whereas VAT has no new pulmonary infiltrate. Both of these LRTIs result in increased mortality, prolonged mechanical ventilation, prolonged hospitalization lengths of stay and high healthcare expenditures.[1,6,7] Previous studies showed that the incidence rate of VAP varied from 10 to 16 episodes/1000 ventilator-days and that mortality reached 50%.[8,9]

A recent study reported that approximately 47% of patients with VAT subsequently developed VAP if they did not receive antimicrobial therapy.[10] Both systemic and inhaled antimicrobial therapy reduced the incidence of developing VAP after having VAT to 31.6%[11] and 13.0%,[10] respectively. Therefore, antimicrobial therapy has been associated with a reduced progression of VAT to VAP.[10,11]

The European Network for ICU-Related Respiratory Infections (ENIRRIs) recently published the results of a prospective observational study conducted at 28 ICUs in Europe and Latin America.[12] In this study, the top three causative pathogens of VAT and VAP were similar, including *Pseudomonas aeruginosa*, *Klebsiella* spp, and *Acinetobacter baumannii*. More than one-third of these causative pathogens were MDR strains. High 28 day mortality was observed; 31.8% in patients with VAT and 25.6% in patients with VAP.

Data on the epidemiology of MDR Gram-negative bacilli ventilator-associated tracheobronchitis (MDR GNB-VAT) and MDR GNB ventilator-associated pneumonia (MDR GNB-VAP among mechanically ventilated patients are limited. Lack of knowledge of the disease incidence, clinical course and treatment response is a great obstacle to preventing and managing MDR GNB-LRTIs in mechanically ventilated patients. Given these considerations, we aimed to determine the epidemiology of MDR GNB-LRTIs in terms of the incidence of MDR GNB-VAT and -VAP among patients requiring mechanical ventilation for ≥48 h and the incidence of and the associated factors for subsequent development of MDR GNB-VAP among patients with MDR GNB-VAT.

Methods

Study settings and design

From October 2016 to March 2018, we conducted a retrospective cohort study of hospitalized patients who required mechanical ventilation for ≥48 h at Siriraj Hospital, Bangkok, Thailand. Siriraj Hospital is the largest university hospital and referral centre in Thailand, with approximately 80 000 hospitalizations and 600 000 inpatient-days annually. The Siriraj Institutional Review Board approved the study protocol (*Si* certificate number: 758/2016) with a waiver of informed consent.

Study population

Eligible patients were all hospitalized adults (age ≥18 years) who met all three of the following inclusion criteria: (i) received mechanical ventilation for ≥48 h; (ii) had clinical symptoms and/or signs of LRTI (VAT or VAP based on the study definitions); and (iii) had at least one bacterial culture from a tracheal aspirate that grew MDR GNB. For patients who met the criteria and had more than one positive tracheal aspiration culture for MDR GNB, we included only the first specimen. Surveillance tracheal aspiration culturing is not routinely performed at our institution.

Study definitions

VAT was defined as an infection in patients with the following four diagnostic criteria: (i) body temperature ≥38°C without other explainable cause of fever or peripheral WBC count of ≥12 000 or ≤4000 cells/mL; (ii) presence of purulent sputum, change in sputum colour, or increased sputum volume; (iii) semi-quantitative bacterial culture of the tracheal aspirate showing moderate to numerous bacterial growth or quantitative bacterial culture of the aspirate showing $\geq 10^5$ cfu/mL of bacteria; and (iv) chest X-ray or chest CT showing no new infiltration compatible with infection.[12,13]

VAP was defined as an infection in patients meeting the first three diagnostic criteria for VAT, together with the presence of new pulmonary infiltration on a chest X-ray or chest CT compatible with pneumonia.[13,14]

MDR GNB were defined as any Gram-negative bacteria that were resistant to ≥1 drug from ≥3 antibiotic classes.[15] Microbiological identification and susceptibility were performed based on CLSI.

Study process and data collection

Potentially eligible patients were identified through the hospital's electronic and microbiology laboratory databases. The hospital's electronic database was used to capture all patients with a 10th revision International Classification of Diseases (ICD-10) code of 9671 (continuous mechanical ventilation for ≥96 consecutive hours) or 9672 (continuous mechanical ventilation for <96 consecutive hours) during the study period. The microbiological database was used to identify patients with at least one sputum culture positive for MDR GNB.

We performed an initial chart review of all potentially eligible patients with ICD-10 codes of 9671 or 9672 having at least one positive tracheal aspiration culture for MDR GNB. We subsequently performed a comprehensive chart review for all study patients meeting the inclusion criteria to obtain data on age, sex, hospital service, hospital location, length of hospital stay, transfer status and comorbidities. Clinical data, including type of intubation (i.e. endotracheal tube, nasotracheal tube, or tracheostomy), reason for hospital admission, antimicrobial therapy details, clinical response, laboratory data, and radiological features were also recorded. The first day that the patient met all three inclusion criteria was considered the index date (Day 1 after enrolment), and the culture obtained on that date was considered the index culture.

Two study physicians independently evaluated the chest radiography (chest X-ray or chest CT) to confirm the presence or absence of pulmonary infiltration compatible with pneumonia. If disagreement occurred between the two physicians, a pulmonary radiologist made the final decision. Only patients meeting the diagnostic criteria for VAT or VAP were enrolled in this study.

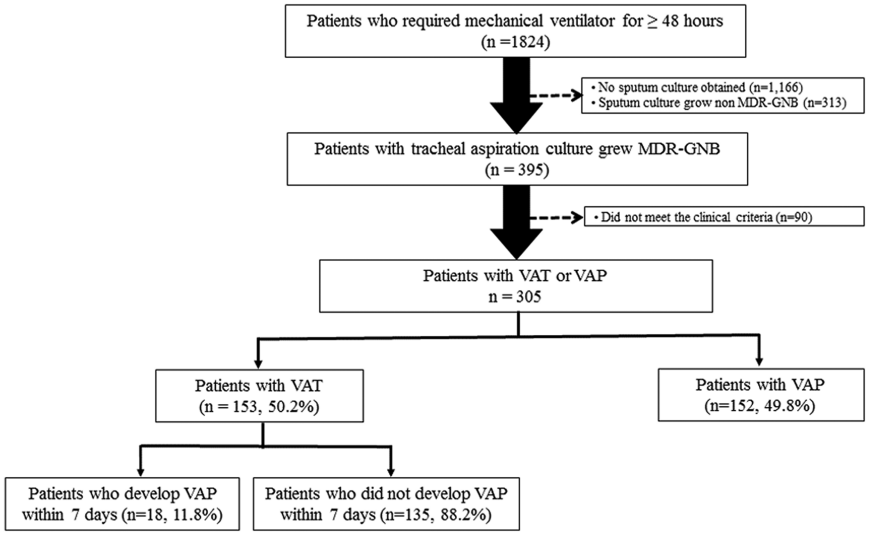
Statistical analysis

Categorical variables are summarized as the frequency and percentage; continuous variables are summarized as the mean ± standard deviation or median (range) as appropriate, according to the distribution. Univariate analysis was performed using chi-squared or Fisher's exact tests for categorical data. *t*-tests or Mann–Whitney *U*-tests were used to compare continuous data. Multivariate analysis was performed to determine independent risk factors for having VAP on Day 1 among patients with MDR GNB-LRTI (model of VAP patients versus VAT patients). Variables were initially selected for inclusion in the model if a given *P* value less than 0.2. For all calculations, a two-tailed $P < 0.05$ was considered statistically significant. All calculations were performed using STATA, version 14.1 (Stata Corp., College Station, TX, USA).

Results

Demographics of study subjects

During the 18 month study period, 1824 unique patients underwent continuous mechanical ventilation for ≥48 h (12 216 ventilator-days). Among these 1824 patients, 395 (21.7%) had at least one tracheal aspiration culture that grew MDR GNB during the hospitalization. Of these 395 patients, 90 had no clinical signs or symptoms of LRTI, 153 met the study definition for VAT, and 152 met the study definition for VAP on the index date (Day 1). The cumulative incidences of MDR GNB-VAT, -VAP and -LRTIs on Day 1 were 8.4%, 8.3% and 16.7%, respectively. The incidence rates of MDR GNB-VAT, -VAP and -LRTI on Day 1 were 12.52, 12.44 and 24.97 episodes per 1000 ventilator-days, respectively. Of the 153 patients with MDR GNB-VAT, the cumulative incidence and the incidence rate of subsequent development of VAP within 7 days (Day 7) were 11.76% and 2.81 episodes per 1000 ventilator-days, respectively. Figure 1 shows the study



Abbreviations: MDR GNB, Multidrug-Resistant Gram Negative Bacilli; SIRS, systemic inflammatory response syndrome; VAT, ventilator-associated tracheobronchitis; VAP, ventilator-associated pneumonia

Figure 1. Study flowchart.

Table 1. Detail of the primary outcomes of interest in mechanically ventilated patients

Outcomes of interest	Cumulative incidence, % (95% CI) (*n*/*N* patients)	Incidence rate, per 1000-ventilator days (95% CI) (*n*/*N* ventilator days)
LRTIs (*n* = 305)	16.72 (15.04–18.51) (305/1824)	24.97 (22.27–27.89) (305/12 216)
VAT (*n* = 153)	8.33 (7.11–9.70) (153/1824)	12.52 (10.52–14.66) (153/12 216)
VAP (*n* = 152)	8.39 (7.16–9.76) (152/1824)	12.44 (10.55–14.57) (153/12 216)
Subsequent development of VAP after having VAT on Day 7 (*n* = 18)	11.76 (7.12–17.95) (18/153)	2.81 (1.67–4.45) (18/6411)

flowchart; Table 1 shows the details of the primary outcomes of interest.

Comparison of patients with MDR GNB-VAP versus patients with MDR GNB-VAT on the index date (Day 1)

Table 2 shows the baseline characteristics of patients with MDR GNB-VAP (*n* = 153) and MDR GNB-VAT (*n* = 152) on Day 1. Approximately 60% of both groups (MDR GNB-VAP versus MDR GNB-VAT) were men (58.6% versus 61.4%; *P* = 0.61) with a comparable mean age (67.78 ± 16.92 versus 68.48 ± 17.42 years; *P* = 0.72). The median duration of mechanical ventilation before the index date was significantly shorter in the VAP patients [9 (range, 1–105) versus 12 days (range, 1–104); *P* = 0.01]. Patients with VAP were more likely to be admitted to the medicine department (79.5% versus 66.0%; *P* = 0.008), more likely to have received immunosuppressive agents in the preceding 30 days (11.8% versus 2.6%; *P* = 0.002) and more likely to have acute renal failure at baseline (64.5% versus 44.4%; *P* < 0.001). However, the VAT patients were less likely to have underlying cerebrovascular disease (23.7% versus 38.6%; *P* = 0.005) and less likely to have undergone any operation prior to the index date (21.1% versus 39.9%; *P* = 0.001). Among the patients with an available clinical pulmonary infection score (CPIS), patients with VAP had a significantly higher mean CPIS than did those with VAT (5.61 ± 1.65 versus 3.65 ± 1.72; *P* < 0.001]. *A. baumannii* was the most common causative pathogen in both groups (89.6% versus 92.1%; *P* = 0.36).

Regarding antimicrobial regimens used to treat the index infection, patients with VAP were more likely to receive IV colistin (58.6% versus 38.6%; *P* < 0.001) and less likely to receive carbapenems (23.7% versus 34.0%; *P* = 0.05) than were patients with VAT.

The clinical outcomes of both groups were compared in Table 3. The VAP patients had a significantly higher infection-related hospital mortality (55.3% versus 39.9%; *P* = 0.009), a

Table 2. Baseline characteristics of patients with VAP on Day 1 (A) versus VAT on Day 1 (B), and VAT on Day 1 who did (B 1) versus who did not (B2) develop VAP on Day 7

	A+B	A	B		B1	B2	
Variables	All $N=305$	VAP on Day 1 $N=152$	VAT on Day 1 $N=153$	*P* value (A versus B)	VAP on Day 7 $N=18$	No VAP on Day 7 $N=135$	*P* value (B1 versus B2)
Age (years), mean ± SD	68.12 ± 17.15	67.78 ± 16.92	68.48 ± 17.42	0.72	67.33 ± 18.71	68.63 ± 17.31	0.77
Male, *n* (%)	183 (60.0)	89 (58.6)	94 (61.4)	0.61	10 (55.6)	84 (62.2)	0.59
Body weight (kg), mean ± SD	66.22 ± 20.74	64.74 ± 19.30	67.70 ± 22.03	0.21	68.57 ± 22.15	67.59 ± 22.10	0.86
Duration of MV before the index date (days), median (range)	10 (1–105)	9 (1–105)	12 (1–104)	0.01	11 (2–33)	12 (1–104)	0.52
Department, *n* (%)							
Medicine	221 (72.7)	120 (79.5)	101 (66.0)	0.008	6 (33.3)	46 (34.1)	0.95
Surgery	83 (27.3)	31 (20.5)	52 (33.9)		12 (66.0)	89 (65.9)	
Transfer status, *n* (%)							
Other hospital	61 (20.0)	29 (19.1)	32 (20.9)	0.61[a]	7 (38.9)	25 (19.1)	0.29[a]
Long-term care facilities	6 (2.0)	3 (2.0)	3 (2.0)		0	3 (2.3)	
Previous hospitalization, *n* (%)	70 (23.0)	40 (26.3)	30 (19.6)	0.25	8 (44.4)	22 (16.3)	0.001
Underlying diseases, *n* (%)							
Hypertension	202 (66.2)	95 (62.5)	107 (69.9)	0.17	14 (77.8)	93 (68.9)	0.59
Cerebrovascular accident	95 (31.2)	36 (23.7)	59 (38.6)	0.005	5 (27.8)	54 (40.0)	0.32
Chronic respiratory disease	55 (18.0)	31 (20.4)	24 (15.7)	0.29	2 (11.1)	22 (16.3)	0.74[a]
Cardiovascular disease	111 (36.4)	53 (34.9)	58 (38.0)	0.58	7 (38.9)	51 (37.8)	0.93
Diabetes mellitus	114 (37.4)	54 (35.5)	60 (39.2)	0.51	6 (33.3)	54 (40.0)	0.59
Renal insufficiency	70 (23.0)	33 (21.7)	37 (24.2)	0.61	6 (33.3)	31 (23.0)	0.33
Non-malignant haematological disease	15 (4.9)	11 (7.2)	4 (2.6)	0.07	2 (11.1)	2 (1.5)	0.07[a]
Haematological malignancy	13 (4.3)	8 (5.3)	5 (3.3)	0.39	1 (5.6)	4 (3.0)	0.47[a]
Solid malignancy	20 (6.6)	12 (7.9)	8 (5.2)	0.35	0	8 (5.9)	0.60
Prior organ transplant	6 (2.0)	4 (2.6)	2 (1.3)	0.45[a]	1 (5.6)	1 (0.7)	0.22[a]
Receiving immunosuppressive agents in the preceding 30 days	22 (7.2)	18 (11.8)	4 (2.6)	0.002	0	4 (3.0)	1.00
HIV infections	2 (0.6)	1 (0.7)	1 (0.7)	1.00[a]	0	1 (0.7)	1.00[a]
Surgery in this admission, *n* (%)	104 (34.1)	37 (24.3)	67 (43.8)	<0.001	10 (55.6)	57 (42.2)	0.46
Type of intubation, *n* (%)							
Endotracheal intubation	289 (94.8)	146 (96.1)	143 (93.5)	0.31	18 (100.0)	125 (92.6)	0.61[a]
Tracheotomy	16 (5.3)	6 (4.0)	10 (6.6)		0	10 (7.4)	
Indication of MV, *n* (%)							
Respiratory failure	304 (99.7)	152 (100.0)	152 (99.4)	1.00	18 (100.0)	134 (99.3)	1.00
Airway obstruction	1 (0.3)	0	1 (0.6)		0	1 (0.7)	
Baseline serum creatinine (mg/dL), mean ± SD	2.01 ± 2.09	2.19 ± 2.08	1.83 ± 2.09	0.14	2.06 ± 1.65	1.81 ± 2.14	0.62
Acute renal failure at baseline, *n* (%)	166 (54.4)	98 (64.5)	68 (44.4)	< 0.001	12 (66.7)	56 (41.5)	0.04
Haemodialysis at baseline	63 (20.7)	39 (25.7)	24 (15.7)	0.85	2 (11.1)	22 (16.3)	0.74
CPIS, mean ± SD[b]	4.78 ± 1.94 ($n=174$)	5.61 ± 1.65 ($n=100$)	3.65 ± 1.72 ($n=74$)	<0.001	4.89 ± 1.83 ($n=9$)	3.48 ± 1.65 ($n=65$)	0.02
Causative pathogens, *n* (%)							
A. baumannii	277 (90.8)	140 (92.1)	137 (89.6)	0.36[a]	16 (88.9)	121 (89.6)	0.84[a]
P. aeruginosa	13 (4.3)	4 (2.6)	9 (5.9)		1 (5.6)	8 (5.9)	
Klebsiella pneumoniae	14 (4.6)	8 (5.3)	6 (3.9)		1 (5.6)	5 (3.7)	
A. baumannii and *P. aeruginosa*	1 (0.3)	0	1 (0.7)		0	1 (0.7)	

Antimicrobial use for the index infection, *n* (%)							
Any antimicrobial	266 (87.2)	135 (88.8)	131 (85.6)	0.40	17 (94.4)	114 (84.4)	0.47
Colistin (any route)	151 (49.5)	90 (59.2)	61 (39.9)	0.001	13 (72.2)	48 (35.6)	0.003
IV colistin	148 (48.5)	89 (58.6)	59 (38.6)	<0.001	13 (72.2)	46 (34.1)	0.002
Nebulized colistin	5 (1.6)	3 (2.0)	2 (1.3)	0.68[a]	0	2 (1.5)	1.00[a]
β-Lactamase inhibitor	82 (26.9)	43 (28.3)	39 (25.5)	0.58	7 (38.9)	32 (23.7)	0.17
Piperacillin/tazobactam	63 (20.7)	33 (21.7)	30 (19.6)	0.65	6 (33.3)	24 (17.8)	0.12
Cephalosporins	19 (6.2)	8 (5.3)	11 (7.2)	0.49	2 (11.1)	9 (6.7)	0.62[a]
Carbapenems	88 (28.9)	36 (23.7)	52 (34.0)	0.05	6 (33.3)	46 (34.1)	0.95
Fluoroquinolones	31 (10.2)	20 (13.2)	11 (7.2)	0.09	0	11 (8.2)	0.36[a]
Other antimicrobial	21 (6.9)	13 (8.6)	8 (5.2)	0.25	0	8 (5.9)	0.60[a]
Days of antimicrobial therapy, mean ± SD	14.29 ± 12.72	14.53 ± 12.20	14.05 ± 13.25	0.75	13.94 ± 7.02	14.07 ± 13.89	0.97

MV, mechanical ventilation.
[a]*P* value from a non-parametric test.
[b]CPIS was not available in some patients without arterial blood gas results.

significantly higher prevalence of acute renal failure on Day 7 after enrolment (60.5% versus 47.1%; $P=0.02$) and a significantly shorter median hospital stay length [34.5 (range, 5–277) versus 45 days (range, 5–255); $P=0.03$] than did those with VAT. The VAP patients also had a slightly but not significantly higher 28 day mortality than those with VAT (30.3% versus 21.6%; $P=0.08$). Surprisingly, patients with VAP had a higher microbiological cure rate on Day 28 after enrolment (18.4% versus 8.5%; $P=0.03$) than did the VAT patients.

Multivariate analysis identified three independently associated factors for having MDR GNB-VAP compared with having MDR GNB-VAT at the time of enrolment: having underlying cerebrovascular disease [adjusted OR (aOR): 0.46; 95% CI: 0.27–0.78; $P=0.04$], having had prior surgery (aOR: 0.68; 95% CI: 0.57–0.81; $P<0.001$) and having acute renal failure at baseline (aOR: 1.75; 95% CI: 1.27–2.40; $P=0.001$).

Comparison of patients with MDR GNB-VAT who subsequently developed MDR GNB-VAP and those who did not within 7 days after index date (Day 7)

Table 2 shows the baseline characteristics and clinical outcomes of patients with MDR GNB-VAT who subsequently developed MDR GNB-VAP ($n=18$) and those who did not ($n=135$) within 7 days after the index date. Of the 153 patients with MDR GNB-VAT, those with VAP had a comparable mean age to that of patients without VAP (67.33 ± 18.71 versus 68.63 ± 17.31 years; $P=0.77$). VAP patients were more likely to have histories of previous hospitalization (44.4% versus 16.3%; $P=0.001$) and acute renal failure at baseline (66.7% versus 41.5%; $P=0.04$). *A. baumannii* was the most common causative pathogen in both groups (88.9% versus 89.6%; $P=0.84$). IV colistin was more frequently prescribed to VAP patients (72.2% versus 35.6%; $P=0.002$). Several negative clinical outcomes were more prevalent in the VAP group: 7 day mortality (27.8% versus 10.4%; $P=0.04$), infection-related hospital mortality (66.7% versus 36.3%; $P=0.05$) and acute renal failure on Day 7 (72.2% versus 43.7%; $P=0.02$). The median hospital stay length was shorter in patients with VAP but not significantly [31 (range, 5–84) versus 46 days (range, 7–255); $P=0.07$]. We could not perform multivariate analysis to identify associated factors for developing MDR GNB-VAP owing to the small number of patients with VAP.

Discussion

Our results showed a lower incidence of VAT but a similar incidence of VAP among mechanically ventilated patients compared with those of previous studies.[1–4] However, the infection-related hospital mortality of patients with MDR GNB-VAP on Day 1 of our study was similar to that of previous studies.[8,9,12] These findings may be the result of difficulties in diagnosing VAT. Because some mechanically ventilated patients at our institute are hospitalized in non-ICU wards, they may not be monitored as closely as those who are hospitalized in ICU wards. Therefore, patients with mild LRTIs such as VAT may be underdiagnosed, whereas those with more severe LTRIs such as VAP may be less likely to be missed. Furthermore, the incidence of patients with VAT and subsequent development of VAP was 11.8%, which was similar to that of a recent meta-analysis of five observational studies (11.5%),[16] but

Table 3. Clinical outcomes of patients with VAP on Day 1 (A) versus VAT on Day 1 (B), and VAT on Day 1 who did (B1) versus who did not (B2) develop VAP on Day 7

	A+B	A	B		B1	B2	
Variables	All *N*=305	VAP on Day 1 *N*=152	VAT on Day 1 *N*=153	*P* value (A versus B)	VAP on Day 7 *N*=18	No VAP on Day 7 *N*=135	*P* value (B1 versus B2)
Subsequent development of VAP, *n* (%)							
Day 7	NA	NA	NA	NA	18 (100.0)	0	<0.001[a]
Day 28	NA	NA	NA	NA	0	4 (3.0)	0.001[a]
Mortality, *n* (%)							
7 day mortality	39 (12.8)	20 (13.2)	19 (12.4)	0.85	5 (27.8)	14 (10.4)	0.04
28 day mortality	79 (25.9)	46 (30.3)	33 (21.6)	0.08	8 (44.4)	25 (18.5)	0.06
Infection-related hospital mortality	145 (47.5)	84 (55.3)	61 (39.9)	0.009	12 (66.7)	49 (36.3)	0.05
Microbiological eradication, *n* (%)							
Day 7	126 (41.3)	68 (44.7)	58 (37.9)	0.07	11 (61.1)	47 (34.8)	0.04
Day 28	41 (13.4)	28 (18.4)	13 (8.5)	0.03	1 (5.6)	12 (8.9)	0.67[a]
Renal adverse events, *n* (%)							
Acute renal failure on Day 7	164 (53.8)	92 (60.5)	72 (47.1)	0.02	13 (72.2)	59 (43.7)	0.02
Haemodialysis on Day 7	60 (19.7)	36 (23.7)	24 (15.7)	0.08	3 (16.7)	21 (15.6)	1.00[a]
Acute renal failure on Day 28	68 (22.3)	39 (25.7)	29 (19.0)	0.16	3 (16.7)	26 (19.3)	1.00[a]
Haemodialysis on Day 28	24 (7.9)	15 (9.9)	9 (7.9)	0.20	1 (5.6)	8 (5.9)	1.00[a]
Other outcomes							
Length of hospital stay (days), median (range)	38 (5–277)	34.5 (5–277)	45 (5–255)	0.03[a]	31 (5–84)	46 (7–255)	0.07[a]
Duration of MV (days), median (range)	28 (4–205)	25 (4–193)	30 (5–205)	0.20[a]	22.5 (5–98)	30 (6–205)	0.33[a]
Prior to the index date (days), median (range)	10 (1–105)	9 (1–105)	12 (1–104)	0.01[a]	11 (2–33)	12 (1–104)	0.52[a]
After the index date (days), median (range)	13 (0–170)	14 (1–144)	13 (0–170)	0.87[a]	11 (3–75)	13 (0–170)	0.72[a]

NA, not applicable; MV, mechanical ventilation.
[a]*P* value from a non-parametric test.

slightly lower than the incidence from a previous study conducted in mixed ICUs (32.1%).[2]

The median duration of mechanical ventilation before exhibiting symptoms was significantly shorter in patients with MDR GNB-VAP than in those with MDR GNB-VAT (9 versus 12 days; $P=0.01$). These durations were similar to those reported in previous studies.[4,17] Because most study patients developed VAT or VAP after the first week of mechanical ventilation, early weaning of mechanical ventilation, especially within 1 week, is crucial.

Our results revealed three independently associated factors for having VAP compared with VAT at the first presentation: having cerebrovascular disease, having had elective surgery and having acute renal failure at baseline. These three independent factors are well-known risk factors for VAP according to previous reports.[17–19]

Our study had some strengths. First, to our knowledge, this was the largest observational study focused on MDR GNB-VAT and -VAP. We screened nearly 2000 patients and finally enrolled 305 patients with MDR GNB-VAT or -VAP. Second, the chest X-ray and chest CT were carefully reviewed by at least two study physicians. When the results were inconclusive, final conclusions were drawn by an experienced chest radiologist.

This study had several limitations. First, this was an observational study, and we captured all eligible study patients based on existing information. Our institute does not actively survey sputum cultures among mechanically ventilated patients. Therefore, selection bias may have been a factor. Some mild cases of VAT or VAP may not be further investigated (i.e. tracheal aspiration culture, chest X-ray or chest CT findings) and may go unidentified. Second, we did not collect data on antimicrobial agent use prior to the index infection. This may have affected treatment outcomes. Finally, we excluded mechanically ventilated patients who did not meet the study definitions of VAT or VAP. Therefore, we could not determine risk factors for developing MDR GNB-LRTIs among patients requiring mechanical ventilation.

In conclusion, the study results revealed high incidences of MDR GNB-VAT and -VAP among mechanically ventilated patients. However, the cumulative incidence of subsequent development of VAP among patients with VAT was comparable to that of previous studies. The independent risk factors for having VAP compared with VAT on Day 1 in our study can help identify patients at risk for poor clinical outcomes. Further studies with larger sample sizes should be conducted to explore how antimicrobial use affects subsequent development of VAP after having VAT.

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Transparency declarations

All authors declare no personal or professional conflicts of interest relating to any aspect of this study.

Author contributions

P.R. and V.T. conceptualized the study design. R.K., S.W. and P.R. performed data collection, data cleaning and analysis. All authors participated in drafting the manuscript. All authors read and approved the final version of the manuscript.

Data availability

The study dataset is available from the corresponding author upon reasonable request.

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