Incidence and prognosis of ventilator-associated tracheobronchitis (TAVeM): a multicentre, prospective, observational study

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Summary

Background Ventilator-associated tracheobronchitis has been suggested as an intermediate process between tracheobronchial colonisation and ventilator-associated pneumonia in patients receiving mechanical ventilation. We aimed to establish the incidence and effect of ventilator-associated tracheobronchitis in a large, international patient cohort.

Methods We did a multicentre, prospective, observational study in 114 intensive care units (ICU) in Spain, France, Portugal, Brazil, Argentina, Ecuador, Bolivia, and Colombia over a preplanned time of 10 months. All patients older than 18 years admitted to an ICU who received invasive mechanical ventilation for more than 48 h were eligible. We prospectively obtained data for incidence of ventilator-associated lower respiratory tract infections, defined as ventilator-associated tracheobronchitis or ventilator-associated pneumonia. We grouped patients according to the presence or absence of such infections, and obtained data for the effect of appropriate antibiotics on progression of tracheobronchitis to pneumonia. Patients were followed up until death or discharge from hospital. To account for centre effects with a binary outcome, we fitted a generalised estimating equation model with a logit link, exchangeable correlation structure, and non-robust standard errors. This trial is registered with ClinicalTrials.gov, number NCT01791530.

Findings Between Sept 1, 2013, and July 31, 2014, we obtained data for 2960 eligible patients, of whom 689 (23%) developed ventilator-associated lower respiratory tract infections. The incidence of ventilator-associated tracheobronchitis and that of ventilator-associated pneumonia at baseline were similar (320 [11%; 10·2 of 1000 mechanically ventilated days] *vs* 369 [12%; 8·8 of 1000 mechanically ventilated days], p=0·48). Of the 320 patients with tracheobronchitis, 250 received appropriate antibiotic treatment and 70 received inappropriate antibiotics. 39 patients with tracheobronchitis progressed to pneumonia; however, the use of appropriate antibiotic therapy for tracheobronchitis was associated with significantly lower progression to pneumonia than was inappropriate treatment (19 [8%] of 250 *vs* 20 [29%] of 70, p<0·0001; crude odds ratio 0·21 [95% CI 0·11–0·41]). Significantly more patients with ventilator-associated pneumonia died (146 [40%] of 369) than those with tracheobronchitis (93 [29%] of 320) or absence of ventilator-associated lower respiratory tract infections (673 [30%] of 2271, p<0·0001). Median time to discharge from the ICU for survivors was significantly longer in the tracheobronchitis (21 days [IQR 15–34]) and pneumonia (22 [13–36]) groups than in the group with no ventilator-associated lower respiratory tract infections (12 [8–20]; hazard ratio 1·65 [95% CI 1·38–1·97], p<0·0001).

Interpretation This large database study emphasises that ventilator-associated tracheobronchitis is a major health problem worldwide, associated with high resources consumption in all countries. Our findings also show improved outcomes with use of appropriate antibiotic treatment for both ventilator-associated tracheobronchitis and ventilator-associated pneumonia, underlining the importance of treating both infections, since inappropriate treatment of tracheobronchitis was associated with a higher risk of progression to pneumonia.

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Introduction

Although mechanical ventilation is a potentially life-saving intervention, it is associated with significant risks and complications[1] such as ventilator-associated lower respiratory tract infections, including ventilator-associated pneumonia and ventilator-associated tracheobronchitis.[2] Although ventilator-associated pneumonia is associated with increased morbidity and duration of mechanical ventilation in the intensive care unit (ICU), tracheobronchitis has been proposed to be an intermediate stage between colonisation of the lower respiratory tract and pneumonia, with uncertain effects on clinical outcomes.[3] Other data suggest that ventilator-associated tracheobronchitis might be a separate entity to pneumonia that independently contributes to increased length of stay in the ICU and longer duration of mechanical ventilation.[4]

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Research in context

Evidence before the study

Findings from single-centre studies have identified ventilator-associated tracheobronchitis as an intermediate process between tracheobronchial colonisation and ventilator-associated pneumonia, and suggest a beneficial effect of antibiotic treatment in patients with ventilator-associated tracheobronchitis. Before initiating this study, we searched the scientific literature with the terms "ventilator-associated tracheobronchitis", "mechanical ventilation-associated lower respiratory tract infections", "ventilator-associated pneumonia", "VAT", and "VAP", without any date or language restrictions. We excluded studies of patients not receiving mechanical ventilation and paediatric populations. We did not find any meta-analyses, but we identified observational studies and two randomised controlled trials. The findings from these studies showed no differences in duration of mechanical ventilation or length of stay in an intensive care unit (ICU) between patients who did and did not receive antibiotics for treatment of ventilator-associated tracheobronchitis or ventilator-associated pneumonia. The aim of our study was to establish the incidence of ventilator-associated tracheobronchitis in a large international cohort of mechanically ventilated patients, and its effect on their outcomes.

Added value of this study

This is the first multicentre, first international, and largest study described in the scientific literature focusing specifically on the clinical effect of mechanical ventilation-associated lower respiratory tract infections, including both ventilator-associated tracheobronchitis and ventilator-associated pneumonia. It will add value to the existing evidence because of its prospective design, the consecutive collection of data from patients without exclusion criteria (ie, readmitted patients and patients who had been previously tracheostomised were not included), the strict diagnostic criteria, the detailed description of the microbiological techniques used, and the adjustment of survival for potential confounders.

Implications of all the available evidence

The future implication for daily clinical practice is that ventilator-associated tracheobronchitis is a very frequent infectious complication of mechanical ventilation and increases the risk of developing pneumonia. Tracheobronchitis has a similar incidence to ventilator-associated pneumonia and also significantly affects patient outcomes, because it increases the duration of mechanical ventilation and length of stay in an ICU similarly to ventilator-associated pneumonia, but with lower mortality. The use of appropriate antibiotic treatment was associated with improved outcomes, both for tracheobronchitis and pneumonia, underlining the importance of treating both infections since inappropriate treatment of tracheobronchitis was associated with a higher risk of progression to pneumonia. Finally, we acknowledge that on the basis of the findings from our study combined with existing evidence, a consensus on the diagnosis and management of ventilator-associated tracheobronchitis is urgently needed.

An improved understanding of ventilator-associated tracheobronchitis could have important implications for early diagnosis, initiation of antimicrobials, and prevention. However, the concept of ventilator-associated tracheobronchitis is controversial, by contrast with ventilator-associated pneumonia, and several important questions remain unanswered, such as its definition, degree of overlap with ventilator-associated pneumonia (if any), diagnostic criteria, and appropriate treatment regimens, amidst a shortage of clinical data.[5]

In the TAVeM study, we aimed to measure the incidence of ventilator-associated tracheobronchitis, and establish its effects on patient outcomes and the effect of appropriate antibiotic treatment on progression from tracheobronchitis to pneumonia.

Methods

Study design and population

We did this prospective international multicentre observational study in 114 ICUs across eight countries in Europe and South America (Spain, France, Portugal, Brazil, Argentina, Ecuador, Bolivia, and Colombia) selected by invitation. Staff from each centre were asked to prospectively obtain data for patients older than 18 years admitted to their ICU who received mechanical ventilation for more than 48 h between the preplanned dates of Sept 1, 2013, and July 31, 2014. Readmitted patients and patients who had been previously tracheostomised were not included.

Participating centres either received ethics approval from their institutions or ethics approval was waived (institutional review board number 2013515). Informed consent was waived because of the observational nature of the study.

Procedures

Patients were followed up for outcome data until death or discharge from hospital. We provided case-report forms electronically using a secure website. Patient demographic characteristics, primary diagnosis, length of stay in the ICU and hospital, the McCabe classification of comorbidities and likelihood of survival[6] (likely to survive 35 years, 1–5 years [ultimately fatal], or <1 year [rapidly fatal]), Simplified Acute Physiology Score II (SAPS II) to predict hospital mortality, and outcome (ICU mortality) were recorded for all patients,[7] and functional status as measured by the Barthel Index.[8] We obtained data about diagnostic procedures for ventilator-associated tracheobronchitis and ventilator-associated

pneumonia including microbiological testing, antibiotic use, appropriate antibiotics given, and outcomes.

A diagnosis of ventilator-associated lower respiratory tract infection was based on the presence of at least two of the following criteria: body temperature of more than 38·5°C or less than 36·5°C, leucocyte count greater than 12 000 cells per µL or less than 4000 cells per µL, and purulent endotracheal aspirate (ETA). Additionally, all episodes of infection had to have a positive microbiological isolation in the ETA of at least 10^5 colony-forming units (CFU) per mL, or with bronchoalveolar lavage (BAL) of at least 10^4 CFU per mL, to be included in the final analysis.[9] Ventilator-associated tracheobronchitis was defined with the aforementioned criteria with no radiographical signs of new pneumonia; ventilator-associated pneumonia was defined by the presence of new or progressive infiltrates on chest radiograph. Anterior-posterior portable radiographs were reviewed either by the attending physicians or radiologist. In case of disagreement, a third physician was asked to interpret the radiograph; however, the final diagnosis and antibiotic treatment were at the discretion of the attending physician. No CT scans or lateral radiographs were done for the diagnosis. We used serial chest radiographs to confirm new or persistent infiltrates as part of the diagnosis, but investigators were not masked to clinical characteristics because of the observational nature of the study. We only included first episodes of microbiologically confirmed ventilator-associated lower respiratory tract infections occurring more than 48 h after starting mechanical ventilation in our analyses. Resolution of either tracheobronchitis or pneumonia was defined as the resolution of all diagnostic criteria.

Ventilator-associated pneumonia was deemed as occurring subsequently to ventilator-associated tracheobronchitis if it was diagnosed in the 96 h period after diagnosis of tracheobronchitis, and the same microorganism caused both infections. We calculated the Sequential Organ Failure Assessment (SOFA) score to assess organ dysfunction or failure when an episode of either tracheobronchitis or pneumonia was diagnosed.[10] We calculated the Clinical Pulmonary Infection Score (CPIS) each day until the time of diagnosis of either infection.[11] We defined empirical antibiotic therapy as that given before microbiological documentation of infection. We deemed treatment as appropriate if it matched the in-vitro susceptibility of the pathogen.[12] We did microbiological identification and susceptibility tests using standard methods.

Outcomes

The primary aim of our study was to measure the incidence of ventilator-associated tracheobronchitis and ventilator-associated pneumonia. For our secondary aims, we clustered patients into groups according to the presence or absence of such infections and recorded the clinical, laboratory, and radiological characteristics, causes, diagnostic techniques, and treatment of both disorders. We also measured the effects of ventilator-associated tracheobronchitis on patient outcomes such as length of stay in the ICU and hospital, days with and without mechanical ventilation, and the effect of appropriate antibiotic treatment on progression from tracheobronchitis to pneumonia.

Statistical analysis

We based our study sample size on the nature of the study and the preplanned dates; we did not do any formal size calculations. We used SPSS (version 20) for data analysis. All p values were two-tailed. We judged differences as significant if p was less than 0·05. We described categorical variables as numbers and frequencies (%), normally distributed continuous variables as means (SD), and skewed continuous variables as medians (IQR). We used χ^2 tests or Fischer's exact test to compare qualitative variables, and Student's *t* tests and ANOVAs or Mann-Whitney *U* and non-parametric Kruskal-Wallis tests to compare normally distributed and skewed continuous variables, as appropriate. We incorporated all variables from univariate analysis with p values that were less than 0·1 or were clinically relevant into the regression analyses as potential predictor variables (age, SAPS II score, appropriate antibiotics, multidrug-resistant [MDR] isolates, transition of ventilator-associated tracheobronchitis to ventilator-associated pneumonia, presence of either infection, and type of patient [ie, medical, surgical, trauma]). We included all these variables, plus chronic respiratory failure, in the model used to calculate mortality risks.

We adjusted for other mortality risk factors and possible confounders in two ways. For all primary endpoints, we first calculated unadjusted and adjusted estimates of the effect size and corresponding 95% CIs using linear, logistic, or Cox proportional hazards regression (as appropriate). Second, we created a propensity score and then adjusted for this score in a regression model. To account for centre effects in this multicentre trial with a binary outcome, we fitted a generalised estimating equation model with a logit

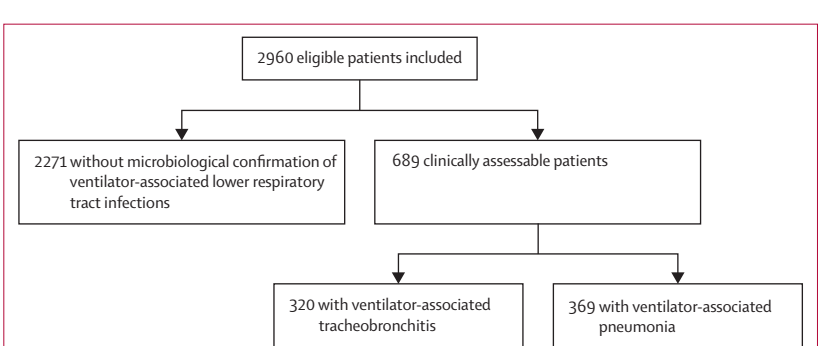


Figure 1: **Participant flow**

	VAT (n=320)	VAP (n=369)	No VA-LRTI (n=2271)	p value
Sex				
Male	199 (62%)	264 (72%)	1386 (61%)	0·001
Female	121 (38%)	105 (28%)	885 (39%)	..
Age (years)	61·20 (16·25)	57·74 (18·46)	62·46 (16·50)	0·0001*
SAPS II	48·85 (18·12)	49·89 (17·80)	51·10 (18·79)	0·088*
Barthel score	75·02 (36·11)	85·76 (28·96)	83·00 (30·09)	<0·0001*
SOFA score	7·64 (3·79)	8·07 (3·63)	8·23 (3·86)	0·032*
Medical disorders	175 (55%)	218 (59%)	1495 (66%)	0·0001
Surgical disorders	49 (15%)	52 (14%)	443 (20%)	0·015
Trauma	96 (30%)	99 (27%)	333 (15%)	0·0001
COPD	64 (20%)	61 (17%)	369 (16%)	0·24
Chronic kidney disease	35 (11%)	34 (9%)	224 (10%)	0·74
Haematological disorders	11 (3%)	10 (3%)	102 (4%)	0·22
Diabetes mellitus	66 (21%)	69 (19%)	433 (19%)	0·77
Alcohol abuse	34 (11%)	49 (13%)	275 (12%)	0·56
Bone-marrow transplantation	2 (1%)	5 (1%)	18 (1%)	0·49
Solid-organ transplantation	2 (1%)	2 (1%)	24 (1%)	0·54
Immunocompromised patients	24 (8%)	31 (8%)	241 (11%)	0·12
Non-metastatic cancer	25 (8%)	29 (8%)	242 (11%)	0·097
Metastatic cancer	4 (1%)	9 (2%)	99 (4%)	0·008
AIDS	3 (1%)	10 (3%)	36 (2%)	0·18
Intravenous drug abuse	6 (2%)	5 (1%)	42 (2%)	0·79
Homeless	3 (1%)	2 (1%)	25 (1%)	0·60
Chronic respiratory failure	35 (11%)	27 (7%)	224 (10%)	0·22
Previous antibiotic use	210 (66%)	232 (63%)	170 (7%)	<0·0001

Data are n (%) or mean (SD), unless otherwise specified. We computed column percentages by dividing each count by the total. p values are for comparison between the three groups. ··=data not available. VAT=ventilator-associated tracheobronchitis. VAP=ventilator-associated pneumonia. VA-LRTI=ventilator-associated lower respiratory tract infection. SAPS II=Simplified Acute Physiology Score II. SOFA=Sequential Organ Failure Assessment. COPD=chronic obstructive pulmonary disease. *ANOVA parametric tests were used.

Table 1: **Baseline characteristics of patients**

	VAT (n=320)	VAP (n=369)	p value
Endotracheal aspirate	278 (87%)	253 (69%)	<0·0001
Blind protected specimen brush	32 (10%)	51 (14%)	0·12
Bronchoscopy	17 (5%)	56 (15%)	<0·0001
Bronchoalveolar lavage	12 (4%)	59 (16%)	<0·001
Mini bronchoalveolar lavage	16 (5%)	45 (12%)	<0·0001
Blood cultures	186 (58%)	275 (75%)	<0·0001
Tested for *Streptococcus pneumoniae* antigen	14 (4%)	21 (6%)	0·43
Tested for *Legionella pneumophila* antigen	14 (4%)	16 (4%)	0·98

Data are n (%) unless otherwise specified. VAT=ventilator-associated tracheobronchitis. VAP=ventilator-associated pneumonia.

Table 2: **Diagnostic procedures used in study**

link, exchangeable correlation structure, and non-robust standard errors. In addition to the potential confounders, we included a country variable into the model to take into account potential country effects.[13] We also analysed the effects of the presence or absence of ventilator-associated lower respiratory tract infections (tracheobronchitis and pneumonia). Additionally, we used a propensity score regression approach: first, we estimated the propensity scores by fitting a logistic regression for the variable appropriate treatment. The covariates we included in the model were age, SAPS II score, appropriate antibiotics, MDR isolates, transition of tracheobronchitis to pneumonia, presence of tracheobronchitis or pneumonia, type of patient, and comorbidities. Next, we fitted a regression model using logistic regression models for ICU mortality, adjusting for the variable of appropriate treatment and the propensity scores (as a continuous variable) that we obtained in the previous regression model. To assess associations between pneumonia or tracheobronchitis and mortality, duration of mechanical ventilation, and length of stay, we calculated an unadjusted hazard ratio (HR) and 95% CI using a Cox proportional hazards regression based on a binary outcome of being taken off mechanical ventilation, and discharged from ICU, and from hospital, respectively. In a further sensitivity analysis, we fitted a multivariable Cox proportional hazards model with appropriateness of treatment and potential confounders for patients, including severity, as independent variables.[14] We tested potential interactions and calculated the Hosmer-Lemeshow goodness-of-fit. This trial is registered with ClinicalTrials.gov, number NCT01791530.

Role of the funding source

There was no funding source for this study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Sept 1, 2013, and July 31, 2014, we obtained data for 2960 eligible patients (figure 1). Their mean age was 62 years (SD 17), 1849 (62%) were male, mean SAPS II score was 50·7 points (SD 18·6), and mean Barthel score was 89·4 points (30·7). Medical patients represented most of the admissions (1888 [64%]), followed by surgical (544 [18%]), and trauma (528 [18%]).

689 (23%) patients with positive microbiological confirmation subsequently developed ventilator-associated lower respiratory tract infections. The incidence of ventilator-associated tracheobronchitis and ventilator-associated pneumonia were similar (320 [11%] patients [10·2 of 1000 mechanically ventilated days] *vs* 369 [12%; 8·8 of 1000 mechanically ventilated days], p=0·48). Patients who developed ventilator-associated pneumonia were younger, had a worse functional status on admission as assessed by the Barthel Index, a similar SAPS II score, but a higher SOFA score, than those with ventilator-associated tracheobronchitis (table 1). A greater proportion of trauma patients developed ventilator-associated tracheobronchitis (96 [18%] of 528 patients) and ventilator-associated pneumonia (99 [19%] of 528 patients) than did

medical patients (175 [9%] and 218 [12%] of 1888 patients, respectively) and surgical patients (49 [9%] and 52 [10%] of 544 patients, respectively). More than a half of the patients who developed ventilator-associated lower respiratory tract infections had received previous antibiotics before developing these infections (table 1). Additionally, previous antibiotic use was significantly higher in patients who developed these infections than in patients who did not (p<0·0001; table 1). No significant differences in previous antibiotic use were noted between patients with tracheobronchitis and patients with pneumonia.

On the day of diagnosis, patients with ventilator-associated pneumonia were sicker than those with ventilator-associated tracheobronchitis according to the mean maximum SOFA score (8·4 points [SD 5·5] *vs* 6·4 points [4·7], p=0·0001). Mean CPIS for the day before diagnosis (3·7 points [SD 1·8] *vs* 4·8 points [2·1], p<0·0001) and on the day of diagnosis (4·5 points [1·8] *vs* 6·4 points [1·9], p<0·0001) were significantly lower in patients with tracheobronchitis than in those with pneumonia. Mean number of days on mechanical ventilation until development of either disorder was similar in both sets of patients (8·3 days [SD 6·9] in the ventilator-associated tracheobronchitis group *vs* 8·7 days [7·1] in the ventilator-associated pneumonia group, p=0·5). A higher proportion of patients with ventilator-associated pneumonia had invasive microbiological diagnostic tests than did those with ventilator-associated tracheobronchitis (table 2). Significantly more patients with ventilator-associated pneumonia had an episode of worsening gas exchange than did those with tracheobronchitis (255 [69%] *vs* 98 [31%], p<0·0001; odds ratio [OR] 5·06 [95% CI 3·6–7·1]). Patients with either disorder had no difference in the presence of purulent secretion for diagnosis of ventilator-associated lower respiratory tract infections (322 [87%] with pneumonia *vs* 275 [86%] with tracheobronchitis, p=0·65). 45 (14%) patients with tracheobronchitis and 47 (13%) patients with pneumonia did not present with macroscopic purulent secretions but did show substantial microbiological growth (table 3).

294 (92%) patients with ventilator-associated tracheobronchitis received antibiotic treatment. The number of episodes of ventilator-associated tracheobronchitis and pneumonia with resolution of the diagnostic criteria was similar in both groups (260 [81%] with tracheobronchitis *vs* 292 [79%] with pneumonia, p=0·48); however, the resolution of diagnostic criteria at 72 h with appropriate antibiotic therapy was significantly higher in patients with tracheobronchitis than in those with pneumonia (278 [75%] *vs* 231 [72%], p=0·01). Appropriate initial antibiotic therapy was given to a significantly higher proportion of patients with ventilator-associated pneumonia than those with tracheobronchitis (337 [91%] *vs* 250 [78%], p<0·0001). 39 (12%) of 320 patients progressed from ventilator-associated tracheobronchitis to ventilator-associated pneumonia. The use of appropriate antibiotic therapy in the ventilator-associated tracheobronchitis group was associated with a significantly lower progression to pneumonia than use of inappropriate treatment (19 [8%] of 250 patients *vs* 20 [29%] of 70, p<0·0001; crude OR 0·21 [95% CI 0·11–0·41]). More patients with tracheobronchitis who did not receive antibiotic treatment progressed to pneumonia than those who did receive antibiotics (eight [31%] of 26 *vs* 31 [11%] of 294, p=0·007; OR 3·7 [95% CI 1·37–10·16]). Repeat microbiological data were obtained from all patients who progressed from tracheobronchitis to pneumonia. In accordance with the definition used in

	Total VA-LRTI cohort			Patients who progressed from VAT to VAP		
	VAT (N=320)	VAP (N=369)	p value	Inappropriate treatment (N=20)	Appropriate treatment (N=19)	p value
Streptococcus pneumoniae	16 (5%)	24 (7%)	0·41	2 (62%)	0	0·48
Stenotrophomonas maltophilia	19 (6%)	12 (3%)	0·09	1 (5%)	1 (5%)	0·99
MRSA	8 (2%)	8 (2%)	0·77	0	1 (5%)	0·48
MSSA	66 (21%)	80 (22%)	0·73	3 (15%)	3 (16%)	0·99
Serratia marcescens	12 (4%)	16 (4%)	0·69	0	0	..
Pseudomonas aeruginosa	79 (25%)	89 (24%)	0·86	2 (10%)	2 (11%)	0·99
Proteus mirabilis	15 (5%)	14 (4%)	0·56	0	0	..
Klebsiella pneumoniae	48 (15%)	53 (14%)	0·81	2 (10%)	1 (5%)	0·99
Haemophilus influenzae	32 (10%)	25 (7%)	0·12	2 (10%)	2 (11%)	0·99
Escherichia coli	37 (12%)	40 (11%)	0·76	6 (30%)	6 (32%)	0·55
Enterobacter spp	35 (11%)	46 (12%)	0·53	4 (20%)	4 (21%)	0·99
Citrobacter fruendii	7 (2%)	6 (2%)	0·58	0	1 (5%)	0·48
Acinetobacter baumannii	14 (4%)	27 (7%)	0·10	0	0	..
MDR	195 (61%)	225 (61%)	0·96	7 (35%)	8 (42%)	0·48

Data are n/N (%). VA-LRTI=ventilator-associated lower respiratory tract infection. VAT=ventilator-associated tracheobronchitis. VAP=ventilator-associated pneumonia. MRSA=meticillin-resistant *Staphylococcus aureus*. MSSA=meticillin-sensitive *Staphylococcus aureus*. MDR=multidrug-resistant isolates.

Table 3: **Microbiological findings**

See Online for appendix

	Adjusted OR (95% CI) for associated mortality risk	p value
Age (per year)	1·04 (1·01–1·06)	<0·0001
SAPS II (per point)	1·02 (1·01–1·04)	0·01
Appropriate antibiotic (yes *vs* no)	0·63 (0·42–0·83)	0·02
MDR (yes *vs* no)	1·41 (1·28–2·23)	0·02
Transition of VAT to VAP (yes *vs* no)	2·12 (1·05–5·02)	0·04
VAT (yes *vs* no)	0·74 (0·45–3·42)	0·56
VAP (yes *vs* no)	2·23 (1·62–3·34)	0·001

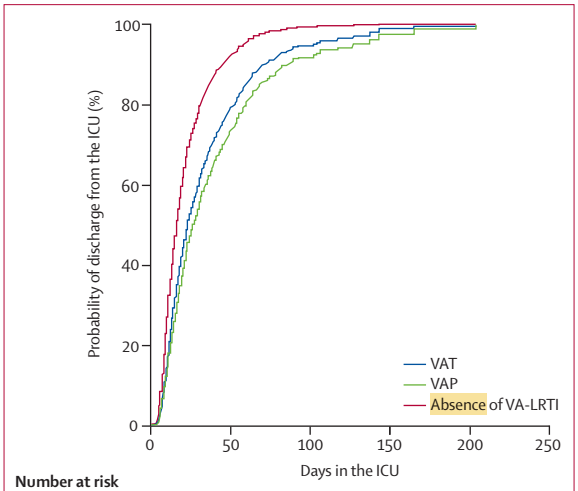
Data are for patients with ventilator-associated pneumonia and ventilator-associated tracheobronchitis. OR=odds ratio. SAPS II=Simplified Acute Physiology Score. MDR=multidrug-resistant isolates. VAT=ventilator-associated tracheobronchitis. VAP=ventilator-associated pneumonia.

Table 4: **Assessment of mortality risk in the intensive care unit**

	VAT (n=320)	VAP (n=369)	No VA-LRTI (n=2271)	p value for the difference between all three groups
Days on mechanical ventilation	13 (8–20)	13 (8–26)	7 (4–7)	<0·0001
Days in the ICU	21 (15–34)	22 (13–36)	12 (8–20)	<0·0001
Days in the hospital	42 (26–61)	38 (23–62)	28 (17–47)	<0·0001
Ventilator-free days	16 (11–20)	17 (10–21)	21 (17–24)	<0·0001

Data are median (IQR). VAT=ventilator-associated tracheobronchitis. VAP=ventilator-associated pneumonia. ICU=intensive care unit. VA-LRTI=ventilator-associated lower respiratory tract infections.

Table 5: **Clinical effects of ventilator-associated pneumonia and ventilator-associated tracheobronchitis**



Number at risk of being discharged from the ICU						
VAT	..	284	301	319	320	320
VAP	..	324	352	368	368	369
No VA-LRTI	..	2204	2263	2271	2271	2271

Figure 2: **Kaplan-Meier curves of discharge from the ICU**
Estimates of the probability of being discharged from the ICU (adjusted hazard ratio 1·65 [95% CI 1·38–1·97] p<0·0001) among survivors according to the presence or absence of ventilator-associated lower respiratory tract infections. ICU=intensive care unit. VAT=ventilator-associated tracheobronchitis. VAP=ventilator-associated pneumonia. VA-LRTI=ventilator-associated lower respiratory tract infections.

this study, the causative pathogens were similar in tracheobronchitis and subsequent pneumonia (table 3). No differences regarding the causative pathogen were noted between patients who received appropriate treatment and those who received inappropriate treatment (antibiotic prescriptions are in the appendix).

Significantly more patients with ventilator-associated pneumonia died (146 [40%]) than those with ventilator-associated tracheobronchitis (93 [29%]) or no ventilator-associated lower respiratory tract infections (673 [30%], p<0·0001 for the difference between all three groups). Ventilator-associated pneumonia, but not tracheobronchitis, was an independent risk factor associated with significantly higher ICU mortality (p=0·001; table 4). The variable included in the statistical model to take into account potential country effects was not significant (p=0·18). A similar proportion of patients with tracheobronchitis who received no treatment died as did those who received antibiotic treatment (eight [31%] of 26 *vs* 85 [29%] of 294, p=0·82; appendix). A propensity score analysis resulted in a similar association between appropriate antibiotic use and mortality in both the ventilator-associated tracheobronchitis and pneumonia groups (OR 0·81 [95% CI 0·66–0·97], p=0·02).

Duration of length of stay in the ICU and hospital, and the number of days on and off mechanical ventilation, are shown in table 5. Median time to discharge from the ICU for survivors was significantly longer in the ventilator-associated tracheobronchitis and ventilator-associated pneumonia groups (28 days [IQR 25·73–30·26]) than in the group without ventilator-associated lower respiratory tract infections (15 days [IQR 14·32–15·67]; HR 1·65 [95% CI 1·38–1·97], p<0·0001; figure 2).

Discussion

Our TAVeM study showed that ventilator-associated tracheobronchitis is a frequent and clinically relevant infectious complication in patients undergoing mechanical ventilation for more than 48 h, with a similar incidence to ventilator-associated pneumonia. Although associated with a significantly lower mortality than ventilator-associated pneumonia, survivors who had tracheobronchitis had a similar duration of mechanical ventilation and length of stay in the ICU. Finally, we showed that almost all patients with tracheobronchitis were given antibiotics, and whereas an absence of antibiotic treatment was associated with a greater risk of development of pneumonia, appropriate antibiotic treatment was associated with a decrease in progression to pneumonia.

To our knowledge, the TAVeM study is the largest prospective, multicentre, international observational study of the natural history and incidence of ventilator-associated lower respiratory tract infections—namely, ventilator-associated tracheobronchitis and ventilator-associated pneumonia. The study included 2960 patients from 114 ICUs in different geographical areas and generated robust and reproducible results. In a large

survey by the TAVeM work group,[4] almost all responders thought that ventilated patients are at risk of tracheobronchitis, especially those with a medical diagnosis; most make the diagnosis on the basis of clinical and microbiological criteria and half agree to give antibiotics by using the time that the patient has spent on mechanical ventilation as the basis for such decisions. In this study, we showed that more patients with ventilator-associated pneumonia had invasive microbiological diagnostic tests than those with tracheobronchitis. In our previous survey,[4] surprisingly, almost 80% of physicians diagnosed ventilator-associated tracheobronchitis with the assistance of microbiological studies, and only 14% used only clinical assessments as proposed by the US Centers of Disease Control and the Prevention/National Healthcare Safety Network[15] and the task force from the European Respiratory Society, the European Society of Clinical Microbiology and Infectious Diseases, and the European Society of Intensive Care Medicine.[16]

To achieve microbiological confirmation, as expected, non-invasive techniques were most frequently preferred to obtain microbiological samples. In our study, we used a range of samples for the microbiological diagnosis (eg, ETA, blind protected brush specimen, bronchoscopy, BAL). Some studies[17] have reported no difference between bacteriological results with ETA and other methods, but which procedure is the best? The difference between diagnostic procedures could have affected our main results. Because no diagnostic criteria of ventilator-associated tracheobronchitis is widely accepted, the prevalence can vary from almost 0% to 15% in patients who are mechanically ventilated.[18,19] For this reason, we predefined the presence of a pathogen at high concentration in respiratory tract samples, in addition to clinical criteria, to avoid overestimating the incidence. In doing so, we used the same diagnostic criteria for ventilator-associated tracheobronchitis and ventilator-associated pneumonia with the exception of the absence or presence of new or progressive pulmonary infiltrates, respectively. With these strict clinical, radiological, and microbiological criteria, we noted a similar incidence of both disorders (11% and 13%, respectively). Importantly, the definition used for both disorders included two of the following three criteria: fever, very high or low leucocyte count, or purulent secretions plus positive microbiology. To diagnose tracheobronchitis in the absence of purulent secretions would be counterintuitive, and therefore the presence of purulent secretions (according to quantitative Gram-staining criteria) and pathogenic culture data will identify the patient as having ventilator-associated pneumonia or tracheobronchitis. As previously reported,[1,2] the Gram stain can provide crucial initial clues to the type of organism or organisms present, and whether or not the material is purulent (defined as ≥25 neutrophils and ten or less squamous epithelial cells per low power field). Our results show that almost a quarter of patients undergoing mechanical ventilation for more than 48 h develop a ventilator-associated lower respiratory tract infection. Likewise, using very similar diagnostic criteria, Craven and colleagues[20] reported a prevalence of 22% (in 41 of 188 ventilated patients) for ventilator-associated lower respiratory tract infection. 21 (11%) patients developed tracheobronchitis, which progressed to pneumonia in six (29%) of these patients. 28 (15%) of all study patients, including these six, developed pneumonia).

We did not take into account worsening oxygenation in our definition of ventilator-associated tracheobronchitis. In our population, patients with ventilator-associated pneumonia had significantly more episodes of worsening gas exchange than those with tracheobronchitis but no significant differences were noted in the presence of purulent secretion for diagnosis. Nseir and colleagues[21] reported a slightly lower incidence of tracheobronchitis (122 [8%] of 1501 patients), but they used different diagnostic criteria. Additionally, we noted that the incidence of ventilator-associated lower respiratory tract infections depends also on the type of admission—ie, medical, surgical, or trauma. Contrary to the responders' perceptions assessed in our previous survey,[4] medical patients were not at higher risk of ventilator-associated tracheobronchitis. In this study,[4] the proportion of patients with a ventilator-associated lower respiratory tract infection was similar in medical and surgical patients, at roughly 20%.[4] However, nearly twice as many patients admitted for trauma developed one of these infections, with an overall incidence of 37%.[4] Trauma patients are known to be at an increased risk for ventilator-associated lower respiratory tract infections.[22,23] In two studies of trauma that used the same criteria for diagnosis of pneumonia that we used in our study,[24,25] the incidence of ventilator-associated lower respiratory tract infections was 44%[24] and 49%,[25] respectively. However, only one study assessed the incidence of tracheobronchitis,[24] but the diagnostic criteria were not described and, additionally, the incidence was very low—only 5%. Because the diagnostic accuracy of chest radiographs is very low,[26] we could speculate that some of these patients who were diagnosed as having pneumonia in fact had tracheobronchitis; additionally, because all these episodes of tracheobronchitis were left untreated, many would have developed into pneumonia. This could be a possible reason for the discrepancies between incidences of tracheobronchitis and pneumonia in comparison with our data, but a similar incidence of ventilator-associated lower respiratory tract infections.[27]

The finding of a higher rate of such infections in trauma patients is not surprising, because these patients frequently presented at hospital admission with low levels of consciousness, and as a result they were at increased risk of microaspiration of oropharyngeal content—namely, the subgroup of traumatic brain injury with a low Glasgow Coma Score.[24,25] In that sense, results of these two studies lend support to the concept that ventilator-associated tracheobronchitis could be an intermediate stage between colonisation of the lower respiratory tract

and pneumonia, especially if tracheobronchitis is left untreated, with high bacterial load and inflammation.

However, contrary to what would be expected from this hypothesis, in our current study, the number of days on mechanical ventilation until diagnosis of tracheobronchitis was almost the same as that until diagnosis of pneumonia (roughly 8 days). Patients who developed ventilator-associated pneumonia, however, were younger, presented with a worse functional status on admission, and had a higher SOFA score than did those with tracheobronchitis who did not develop pneumonia. Craven and colleagues[20] also reported similar cumulative incidences between ventilator-associated tracheobronchitis and pneumonia in the first 7 days after initiation of mechanical ventilation and those with ventilator-associated pneumonia were also slightly younger and had fewer comorbidities than did those with ventilator-associated tracheobronchitis. These findings raise the question of whether these infections are a continuum of bacterial burden and inflammation or whether they represent two distinct but related clinical entities. Surprisingly in our study, patients with tracheobronchitis had lower Barthel and SOFA scores than patients without ventilator-associated lower respiratory tract infections. Perhaps with tracheobronchitis, a compartmentalisation of the inflammatory and infectious process occurs that does not occur in ventilator-associated pneumonia.[28] This theory needs further confirmation and validation; however, patients who develop ventilator-associated tracheobronchitis might have a better immune response to bacterial burden, suggesting that immunosuppression might play a part.

Our study was probably underpowered to determine the effect of appropriate antibiotic treatment on duration of stay in the ICU and duration of mechanical ventilation in patients with ventilator-associated tracheobronchitis, and large randomised studies are needed to clarify these issues.

Data about the microbiology of ventilator-associated tracheobronchitis and pneumonia are scarce. Findings from the study by Craven and colleagues[20] pointed to a similar microbiological cause of both types of infection. With a larger sample size, we clearly showed that the microorganisms associated with ventilator-associated tracheobronchitis and pneumonia were almost the same, and that *Pseudomonas aeruginosa* and *Staphylococcus aureus* are the most frequently isolated. CPIS values, manifested by worse oxygenation, were higher in patients with ventilator-associated pneumonia than in patients with tracheobronchitis. Patients with pneumonia also received appropriate treatment more frequently than those with tracheobronchitis. A possible explanation could be that because tracheobronchitis is a less severe infection, physicians were probably less aggressive in their choices of treatment.

The true effect of tracheobronchitis on patient outcomes is still under discussion. Nseir and colleagues[29] showed in a cohort of 1241 patients with chronic obstructive pulmonary disease undergoing mechanical ventilation that patients with ventilator-associated pneumonia and tracheobronchitis had a similar duration of mechanical ventilation and stay in the ICU; however, patients with tracheobronchitis had a significantly lower risk of mortality in the ICU than patients with pneumonia. Similar findings have been shown by other studies[27]—namely, increased duration of mechanical ventilation, increased length of stay, and variable mortality in patients with ventilator-associated pneumonia versus those with tracheobronchitis. Similarly, Nseir and colleagues[30] showed that ventilator-associated tracheobronchitis was associated with longer durations of mechanical ventilation and stay in the ICU for patients without chronic respiratory failure. In our study, we show the clinically relevant effect of tracheobronchitis, because patients with this disorder had a significantly longer duration of mechanical ventilation and length of stay in the ICU than patients undergoing mechanical ventilation for at least 48 h without ventilator-associated lower respiratory tract infections. Additionally, these outcome variables were similar to those in patients with ventilator-associated pneumonia. However, tracheobronchitis, if treated, had no significant effect on mortality compared with patients without ventilator-associated lower respiratory tract infections, and mortality was significantly lower than that of patients with pneumonia. As a result, unsurprisingly ventilator-associated pneumonia, but not tracheobronchitis, was independently associated with mortality (OR 2·23 [95% CI 1·62–3·34], p=0·001).

Discussions are in progress about the need and indication for antibiotic therapy for patients with ventilator-associated tracheobronchitis. Two small randomised trials[31,32] showed a marked positive effect of antibiotic treatment for this disorder, assessed by a significant decrease in subsequent incidence of ventilator-associated pneumonia. Additionally, a prospective observational study[21] showed that appropriate antibiotic therapy was the only identified factor associated with reducing the transition of tracheobronchitis to pneumonia. In our study, appropriate initial antibiotic therapy was given more frequently to patients with ventilator-associated pneumonia than tracheobronchitis. Despite these differences, the rate of clinical response was similar for either disorder; however, the resolution of diagnostic criteria at 72 h with appropriate antibiotic therapy was higher in patients with tracheobronchitis than in those with pneumonia. Additionally, we showed that the progression of tracheobronchitis to pneumonia was significantly higher in patients with tracheobronchitis given inappropriate antibiotics—ie, without resolution of the infectious process. Even though these disorders could occur independently, some evidence suggests that they are somewhat related and that, if left untreated or inappropriately treated, ventilator-associated tracheobronchitis is highly likely to progress to pneumonia.

Our study has several strengths—namely, the prospective design, obtaining consecutive data from patients without exclusion criteria, the strict diagnostic criteria, the detailed description of microbiology, the adjustment of survival for potential confounders, and that this is the first multicentre, international, and largest study in the scientific literature focusing specifically on the effect of ventilator-associated lower respiratory tract infections, including both pneumonia and tracheobronchitis.

However, we acknowledge some limitations. First, this observational study was undertaken in selected units by invitation. Surprisingly, almost all patients with ventilator-associated tracheobronchitis received antibiotic treatment (92%). This amount is much higher than expected and higher than the previous TAVeM survey suggested.[4] These findings might suggest some predilection in the choice of participating units towards investigators who already have strong beliefs about the clinical importance of ventilator-associated tracheobronchitis and the value of treatment, and therefore extrapolation of these findings to other settings should be done very cautiously. All ICUs that participated in the TAVeM survey[4] were invited to participate in this study, including those where physicians declared that they do not treat ventilator-associated tracheobronchitis. Although we could not exclude a higher participation of ICUs where tracheobronchitis is routinely treated, the TAVeM survey was only based on what physicians think is best for patients, and not on what is really done in their ICUs. Therefore, another potential explanation would be that the proportion of patients with tracheobronchitis given antibiotics is probably high, including in ICUs where physicians are not enthusiastic about this treatment.

Second, microbiological examination was only repeated in patients who progressed from ventilator-associated tracheobronchitis to pneumonia, and no microbiological documentation occurred in 239 (26%) of patients. Some cases for which we did not diagnose the cause might possibly have been caused by colonisation or other non-infectious ventilator-associated complications, such as increased bronchial secretions, pulmonary oedema, pleural effusions, or atelectasis; however, this finding is unusual in clinical practice and the incidence of microbiological diagnosis in our study was similar to ancillary reports regarding this disorder.[21,23,33,34]

Third, the use of either microbiological diagnostic techniques or treatments was not adjusted by guidelines, but in accordance with the attending physician. We reiterate that this was a non-interventional study and our aim was mostly to describe international clinical practice.

The final limitations of our study were that the strategies for prevention of ventilator-associated tracheobronchitis or pneumonia were not standardised (including selective digestive tract decontamination or automatic tracheal cuff pressure), no information about any antibiotics given before diagnosis could be provided, and chest radiographs were reviewed by either the attending physicians or radiologist. In case of disagreement, a third physician was asked to interpret the radiograph; however, the final diagnosis and antibiotic treatment were at the discretion of the attending physician. A diagnosis of ventilator-associated tracheobronchitis required the absence of consolidation or a new infiltrate on the day of the diagnosis. Neither CT scans or lateral films were done to correctly assess posterior-inferior lung fields. However, despite the low sensitivity of chest radiographs in patients who were mechanically ventilated, our strict definition criteria probably allowed a good distinction between patients with tracheobronchitis and pneumonia, as suggested by the higher CPIS, SOFA scores, and greater oxygenation deterioration in patients with pneumonia than in patients with tracheobronchitis.

In conclusion, ventilator-associated tracheobronchitis is definitely a frequent infectious complication of mechanical ventilation with an incidence similar to ventilator-associated pneumonia. Additionally, tracheobronchitis significantly affects patient outcomes because it increases duration of mechanical ventilation and length of stay in the ICU similarly to pneumonia, but with a lower mortality rate. The use of appropriate antibiotic treatment was associated with less progression to pneumonia, and an improved outcome for both disorders, underlining the importance of treating both infections. Finally, we acknowledge the urgent need for a consensus in the diagnosis and management of ventilator-associated tracheobronchitis. Our study has given us the opportunity to show the incidence and clinical characteristics of this disorder, but the question of treatment is still unanswered. Further large randomised studies are needed to clarify the effect of appropriate antibiotic treatment on duration of stay in the ICU and mechanical ventilation in these patients.

Contributors

IM-L, SN, AR, JS, and PP assisted in the design of the study, coordinated patient recruitment, analysed and interpreted the data, and assisted in the writing of the report. DCu, DCo, J-PM, MLC, RL, CG, CC, PS, CP, JM, AGC, JV, LC, LR, and TL made important contributions to the acquisition and analysis of data. IM-L, AT, and DS revised the report critically for important intellectual content. DS made important contributions to the statistical analysis. IM-L, SN, AR, JS, and PP made substantial contributions to the concept, design, analysis, and interpretation of the data, and revised the final version of the report. All authors read and approved the final manuscript.

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Declaration of interests

We declare no competing interests.

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