

Original Article

Analyzing the impact of duration of ventilation, hospitalization, and ventilation episodes on the risk of pneumonia

Martin Wolkewitz PhD¹, Mercedes Palomar-Martinez MD, PhD², Francisco Alvarez-Lerma MD, PhD³,
Pedro Olaechea-Astiggarraga MD⁴ and Martin Schumacher PhD¹

¹Institute of Medical Biometry and Statistics, Faculty of Medicine and Medical Center, University of Freiburg, Freiburg, Germany, ²Universitat Autònoma de Barcelona, Hospital Vall d'Hebron, Barcelona, Spain, ³Service of Intensive Care Medicine, Parc de Salut Mar, Barcelona, Spain and ⁴Service of Intensive Care Medicine, Hospital de Galdakao-Usansolo, Bizkaia, Spain

Abstract

Objective: To study the impact of duration of mechanical ventilation, hospitalization and multiple ventilation episodes on the development of pneumonia while accounting for extubation as a competing event.

Design: A multicenter data base from a Spanish surveillance network was used to conduct a retrospective analysis of prospectively collected intensive care patients followed from admission to discharge.

Setting: Spanish intensive care units (ICUs).

Patients: Mechanically ventilated adult patients from 158 ICUs with 45,486 admissions, 48,705 ventilation episodes, and 314,196 ventilator days.

Methods: Competing-risk models were applied to account for extubation plus 48 hours as a competing event for acquiring ventilator-associated pneumonia (VAP).

Results: Time in the ICU before mechanical ventilation was associated with an increased VAP hazard rate and with longer intubation time. This indirect prolongation of intubation increased the cumulative risk to eventually acquire VAP. For instance, comparing 3–4 versus 0 days, the adjusted VAP hazard ratio was 1.40 (95% confidence interval [CI], 1.19–1.64) and the adjusted extubation hazard ratio was 0.64 (95% CI, 0.61–0.68), which leads to an adjusted VAP subdistribution hazard ratio (sHR) of 2.13 (95% CI, 1.83–2.50). Similarly, due to prolonged intubation, multiple ventilation episodes increase the risk for VAP; the adjusted sHR is 1.52 (95% CI, 1.35–1.72) for the second episode compared to the first episode, and the adjusted sHR is 1.54 (95% CI, 1.03–2.30) for the third episode compared to the first episode. The Kaplan-Meier method produced an upward biased estimated cumulative risk for VAP.

Conclusions: A competing-risk analysis is necessary to receive unbiased risk estimates and to quantify the indirect effect of intubation time on the cumulative VAP risk. Our findings may guide physicians to improve medical decisions related to the harms and benefits of the duration of ventilation.

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Pneumonia is among the most common and potentially avoidable complications that occur among ventilated patients in intensive care units (ICUs). It is associated with prolonged length of hospital stay and increased hospital mortality, especially if it is caused by multidrug-resistant pathogens.^{1,2} Thus, understanding the risks for ventilator-associated pneumonia (VAP) and identifying high-risk patients is clinically important.

Appropriate statistical models to evaluate the risks for VAP are needed because the definition as well as the occurrence of VAP are closely connected with several time-related issues. First, VAP is defined as pneumonia occurring in a mechanically ventilated

patient after 48 hours of endotracheal intubation.^{1,2} It is common practice in randomized clinical trials³ as well as in epidemiological studies (eg, studies following the protocol of the European Centre for Disease prevention and Control⁴) to consider the at-risk time for VAP as the period between 48 hours after intubation and 48 hours after extubation. This at-risk time is directly linked to 'ventilator-days at risk' as the appropriate denominator in calculating VAP rates.⁵ To account for the at-risk time, commonly used statistical models (eg, Kaplan-Meier techniques and standard Cox proportional hazard models) are applied.³ However, such models fail to account for competing events, which leads to overestimated risks.^{6,7} Second, reintubation (especially after unsuccessful extubation) and multiple ventilation episodes are considered risk factors for VAP.^{8,9} Third, the presence of an endotracheal tube is the principle risk factor for VAP, and the cumulative risk increases

Author for correspondence: M. Wolkewitz, Email: wolke@imbi.uni-freiburg.de

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Table 1. Description of Study Population

Characteristic	Baseline, No. (%)
No. of ventilated patients in ICU	45,486
No. of ventilation episodes	48,705
No. of ventilator days	314,196
Ventilator-associated pneumonia (VAP)	3,655 (7.45)
APACHE II score	
0–10	9,092 (18.67)
11–20	22,134 (45.45)
21–30	13,277 (27.26)
>30	4,202 (8.63)
Age at ICU admission	
0–40 y	6,061 (12.44)
41–60 y	12,983 (26.66)
61–80 y (reference)	25,043 (51.42)
>80 y	4,618 (9.48)
Time in hospital before ICU admission	
0–3 d (reference)	35,580 (73.05)
4–6 d	3,367 (6.91)
6–10 d	2,901 (5.96)
>10 d	6,857 (14.08)
Time in ICU before mechanical ventilation	
0 d (reference)	39,993 (82.11)
1 d	2,675 (5.49)
2 d	1,465 (3.01)
3–4 d	1,548 (3.18)
>4 d	3,024 (6.21)
Diagnosis	
Cardiovascular (reference)	19,522 (40.08)
Respiratory	7,740 (15.89)
Gastrointestinal	7,936 (16.29)
Central nervous system	10,740 (22.05)
Other diagnoses	2,767 (5.68)
Antibiotic treatment 48 h before and/or after ICU admission	14,424 (29.62)
Male	31,724 (65.13)
Trauma	5,053 (10.37)
Year at ICU admission	
2006	6,447 (13.24)
2007	7,915 (16.25)
2008	10,088 (20.71)
2009	11,547 (23.71)
2010+	12,708 (26.09)
Episode	
First	45,486 (93.39)
Second	2,911 (5.98)
Third	308 (0.63)

Note. ICU, intensive care unit.

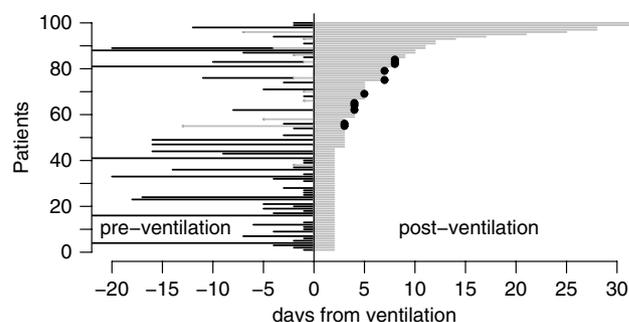


Fig. 1. Graphical visualization of a random sample of 100 patients. Time origin is the start of mechanical ventilation. The corresponding time periods are marked as black (hospitalization before ICU admission) and gray lines (time in ICU before ventilation). The gray line after time 0 shows the duration of ventilation at risk for VAP. The dots show the occurrence of VAP. Extubation without VAP occurs if the gray line ends without a dot.

with the duration of mechanical ventilation.² However, previous studies have found that the VAP hazard rate decreases over ventilation time.¹⁰ Finally, the length of stay in the hospital and intensive care unit (ICU) before intubation might impact the characteristic of VAP because patients who have been in the hospital for ≥ 2 days before intubation are more likely to be colonized with multidrug-resistant pathogens.²

In this study, we aimed to provide and apply an appropriate statistical model to study the risks for VAP. Specifically, we accounted for duration of mechanical ventilation as at-risk time, competing events, preintubation length of hospital or ICU stay, multiple ventilation episodes, and other important and potential confounding factors. We focused on the challenging task of interpreting the results from a competing-risks analyses.

Materials and methods

Spanish ICU data

We used a multicenter database from the Spanish surveillance network HELICS-ENVIN (<http://hws.vhebron.net/envin-helics/>), embedded in the HELICS project (Hospitals in Europe Link for Infection Control through Surveillance).¹¹ We included ICUs that contributed to the registry between January 2006 and June 2011, and we included only ventilated adult patients who stayed at least 2 days in an ICU, due to the definition of hospital-acquired infections. Up to 3 ventilation episodes were considered. Ventilation episodes following a VAP were excluded for the following reasons: (1) because VAP was not specified as the reason for ventilation; (2) to avoid noncausal artefacts; and (3) to ensure a true incident VAP outcome. The study population contained 158 ICUs with 45,486 admissions, 48,705 ventilation episodes, and 314,196 ventilator days. This Deutsche Forschungsgemeinschaft (DFG) research project was approved by the Ethics committee of University Medical Center Freiburg, Germany.

Statistical methods

The time from 48 hours after first intubation until the occurrence of VAP (event of interest) or 48 hours after extubation (competing event) was studied using a competing-risks analysis, without administrative censoring. We estimated the actual hazard rates for VAP and 48 hours after extubation (hereafter termed extubation) in dependency of duration of ventilation as the at-risk time. The cumulative incidences of both events were estimated using the Aalen-Johansen method.¹²

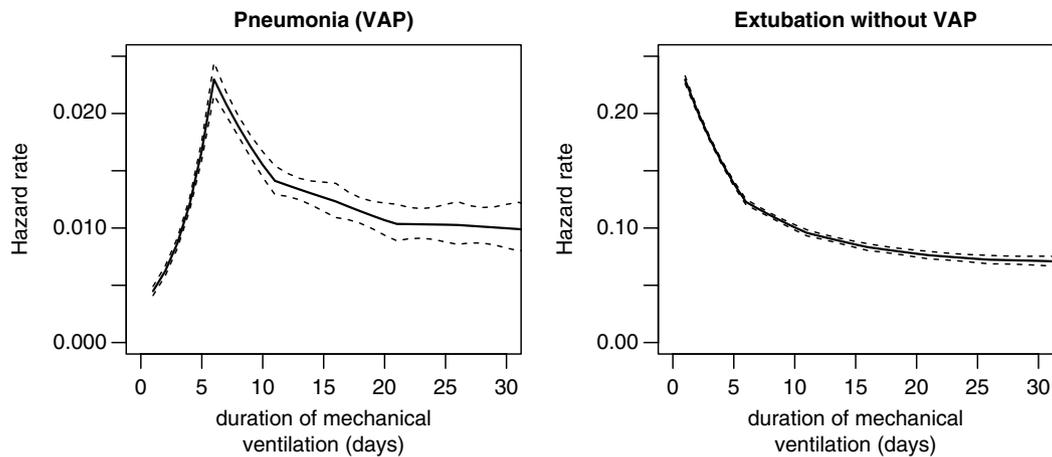


Fig. 2. Hazard rates for ventilator-associated pneumonia (VAP) and extubation without VAP.

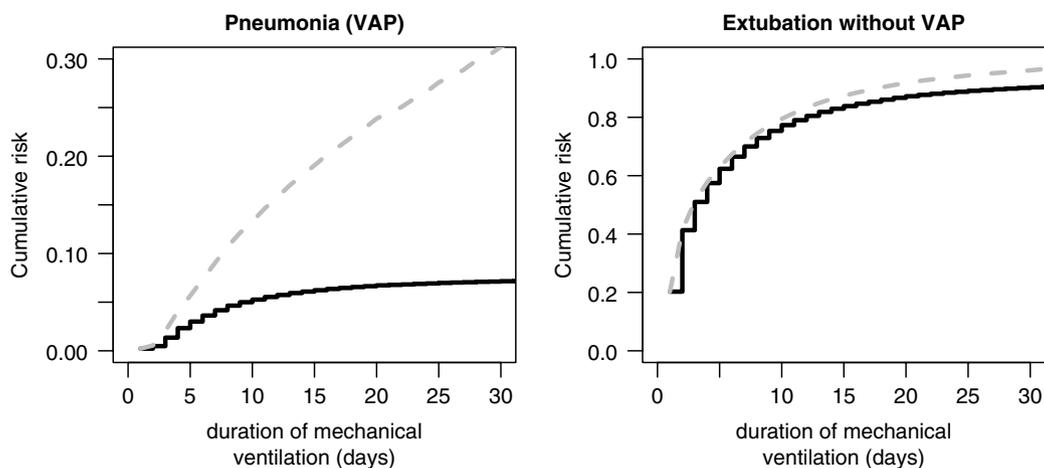


Fig. 3. Cumulative risk (incidence) of ventilator-associated pneumonia (VAP) and extubation without VAP, accounting for competing events (black) versus treated as censored (gray).

For each event (ie, VAP occurrence or extubation), a separate cause-specific hazard analysis was performed via Cox proportional hazards models to explore etiological associations. For VAP as the event of interest, an adapted Cox regression analysis (the Fine and Gray model¹³) was performed to calculate subdistribution hazard ratios (sHRs) and to study the summary effects on the cumulative incidence of VAP. All regression models were stratified by ICU. For multiple ventilation episodes, the time in ICU before ventilation was updated. Because the update led to a correlation between the episode variable and time in the ICU before ventilation, only 3 main variables of interest were included: ie, time in ICU before mechanical ventilation, time in hospital before ICU admission, and multiple episodes. However, the following variables were further included to adjust for confounding: APACHE II score measured at ICU admission, age, gender, trauma, diagnosis (eg, respiratory, gastrointestinal, central nervous system, cardiovascular, and other diagnoses), antibiotic treatment 48 hours before and/or after ICU admission, and calendar year of admission. In all regression models, we used robust variance estimation to account for data clustering regarding multiple ventilation episodes.

Results

Among all 48,705 ventilation episodes in the ICU, 3,655 patients (7.45%) developed a VAP during their stay (Table 1). Figure 1

illustrates the time-dependent data structure of 100 randomly sampled patients. Time origin is the start of mechanical ventilation. The corresponding time periods, marked as black lines for hospitalization before ICU admission and as gray lines for time in ICU before ventilation were entered into the Cox regression models as covariates. The gray line after time 0 shows the duration of ventilation at risk for VAP; this time is modeled as an outcome variable in the Cox regression models.

Hazard rates

Figure 2 shows the duration-dependent hazard rates of VAP and extubation, which are interpreted as the instantaneous daily risk of experiencing the corresponding event VAP or extubation without VAP. Interestingly, the hazard rate of VAP is low but increasing for earlier duration days, and after 5 duration days the hazard rate is decreasing. In contrast, the extubation rate only decreases, which means that most ventilated patients received short-term ventilation (2–4 days) without acquiring VAP.

Cumulative risks

The cumulative risk for VAP (Fig. 3, left, black line) depends on both hazard rates. The duration-dependent proportion of ventilated patients have acquired a VAP by duration day t . Analogously, the

Table 2. Time-Related Factors Associated With Ventilator-Associated Pneumonia (VAP) and Extubation^a

Variable	VAP Rate HR (95% CI)	Extubation (w/o VAP) Rate HR (95% CI)	VAP Risk sHR (95% CI)
Time in ICU before mechanical ventilation			
1 vs 0 d	1.17 (1.04–1.32)	0.74 (0.71–0.77)	1.60 (1.42–1.81)
2 vs 0 d	1.21 (1.02–1.42)	0.65 (0.61–0.68)	1.92 (1.64–2.24)
3–4 vs 0 d	1.39 (1.20–1.62)	0.63 (0.60–0.66)	2.17 (1.87–2.51)
>4 vs 0 d	0.89 (0.78–1.01)	0.61 (0.59–0.63)	1.49 (1.31–1.69)
Time in hospital before ICU admission			
4–6 vs 0–3 d	0.94 (0.81–1.09)	0.95 (0.92–0.99)	0.98 (0.84–1.14)
6–10 vs 0–3 d	1.02 (0.87–1.19)	0.94 (0.91–0.98)	1.06 (0.91–1.25)
> 10 vs 0–3 d	0.85 (0.75–0.96)	0.95 (0.92–0.97)	0.89 (0.79–1.00)
Ventilation episode			
Second vs first	0.99 (0.87–1.12)	0.66 (0.64–0.68)	1.52 (1.35–1.72)
Third vs first	0.87 (0.58–1.30)	0.54 (0.49–0.59)	1.54 (1.03–2.30)

Note. HR, hazard ratio; sHR, subdistribution hazard ratio; ICU, intensive care unit.

^aAll (subdistribution) hazard ratios are adjusted for APACHE II score, age, diagnosis (respiratory, gastrointestinal, central nervous system, cardiovascular and other diagnoses), antibiotic treatment 48 h before and/or after ICU admission, gender and trauma; stratified for intensive care units. Analysis is based on 48,705 ventilation episodes of 45,486 patients.

cumulative risk of extubation is estimated (Fig. 3, right, black line), and the duration-dependent proportion of ventilated patients have been extubated by duration day t . For instance, after duration day 15, ~6% of ventilated patients have acquired a VAP whereas ~80% have been extubated without VAP. The sum of the 2 black curves in Figure 3 do not exceed 100%; thus, the remaining ~14% is the proportion of ventilated patients who are still ventilated after 15 days. In contrast, the 1-Kaplan-Meier estimates predicts a biased VAP risk of ~20% at day 15 (Fig. 3, left, gray line) and ~85% for extubation (Fig. 3, right, gray line); thus, the sum already exceeds 100%. This commonly used approach handles extubated patients as noninformative censored observations. The estimated cumulative risk for VAP is biased upward because the underlying model of noninformative censoring assumes that extubated patients have the same VAP hazard as intubated patients. This assumption is contradicted by the definition of VAP.

Regression models

The event-specific Cox regression models provide hazard ratios (HRs) for VAP and extubation (Table 2). Regarding the VAP event, the time in ICU before mechanical ventilation is associated with an increased VAP hazard rate. For instance, the hazard for VAP increased by 39% for patients who stayed 3–4 days in the ICU before ventilation compared to patients who received ventilation at the day of ICU admission (adjusted HR, 1.39; 95% CI, 1.20–1.62). In other words, the longer a patient has stayed in ICU before tube insertion the higher the daily risk to acquire a VAP (direct effect). Furthermore, the competing-risk analysis for the other event shows that the time in ICU before ventilation is also associated with an decreased extubation rate. For instance, patients who stayed 3–4 days in ICU before ventilation have a 37% lower discharge hazard compared to patients who received ventilation at the day of ICU admission (adjusted HR, 0.63; 95% CI, 0.60–0.66). Thus, patients with long stays before tube insertion require longer intubations. Hence, this indirect prolongation of intubation increases the at-risk time to eventually acquire VAP. Therefore, the effect is more pronounced in

terms of cumulative risk for VAP (see sHRs in Table 2). Thus, the cumulative risk for VAP increased by 117% for patients who stayed 3–4 days in the ICU before ventilation compared to the reference (adjusted sHR, 2.17; 95% CI, 1.87–2.51). In contrast, such a trend is not observed for the time spent in the hospital before ICU admission, even though patients with longer hospitalizations before ICU admission tend to stay intubated longer without VAP development (Table 2).

Figure 4 (left) shows the cumulative risks for VAP stratified by time in the ICU before mechanical ventilation. These effects correspond to the unadjusted sHR. For instance, for patients who stayed 3–4 days in the ICU before ventilation, the sHR is 2.03 (95% CI, 1.76–2.33) compared to reference.

Figure 5 shows the cumulative risks for VAP stratified by first, second, and third ventilation episodes and indicate the increased risk of the second and third episodes. The corresponding unadjusted sHR was 1.52 (95% CI, 1.35–1.72) comparing the second episode versus the first episode and the sHR was 1.47 (95% CI, 0.99–2.18) comparing the third episode versus the first episode. These effects remained stable after adjusting for the potential confounders APACHE II score, age, gender, trauma, diagnosis, antibiotic treatment, and calendar year of admission. The corresponding adjusted sHRs in Table 2 are 1.52 (95% CI, 1.35–1.72) for the second versus the first episode and 1.54 (95% CI, 1.03–2.30) for the third versus the first episode.

Finally, we emphasize that it is a common practice to interpret the HRs for VAP as risk ratios. However, as demonstrated here, risk factors have often strong indirect effects on extubation; thus, VAP hazard ratios usually differ from the sHRs, which do actually compare risks.

Discussion

To our knowledge, this is the first competing-risk analysis for VAP to study the impact of hospitalization/ICU stay, duration of ventilation, and multiple episodes in a large intensive care population. In competing-risks settings, the summary effect of a risk factor can be decomposed into 2 effects: a direct effect regarding the event of interest (ie, VAP) and an indirect effect regarding the competing event (ie, extubation).¹⁴ Thus, a competing-risk analysis is necessary to quantify the indirect effect of intubation time on the cumulative VAP risk. We found that time in ICU before mechanical ventilation is directly associated with an increased VAP hazard as well as indirectly with a decreased extubation hazard. No such effects have been detected for the time spent in hospital before ICU admission. We also found that multiple episodes have an indirect effect on the risk for VAP due to prolonged ventilation. Accounting for extubation as a competing event for VAP is also necessary to estimate cumulative risk of VAP depending on duration of ventilation. In contrast, treating extubation as censored leads to values that could be interpreted as the hypothetical ‘probability of VAP by duration of ventilation if the possibility of extubation could be removed.’ This is a highly controversial approach with a debatable assumption.¹⁵

We estimated the hazard rate for VAP depending on duration of ventilation. Our findings coincide with some published results. For instance, Cook¹⁰ found that the hazard rate for VAP decreased over time: VAP rates were ~3% per day in the first week of ventilation, 2% per day in the second week, and 1% per day in the third week and thereafter. In their study, early-onset VAP accounted for as many as 50% of cases of VAP. We estimated a similar shape of the VAP hazard rate. However, we emphasize that the estimation

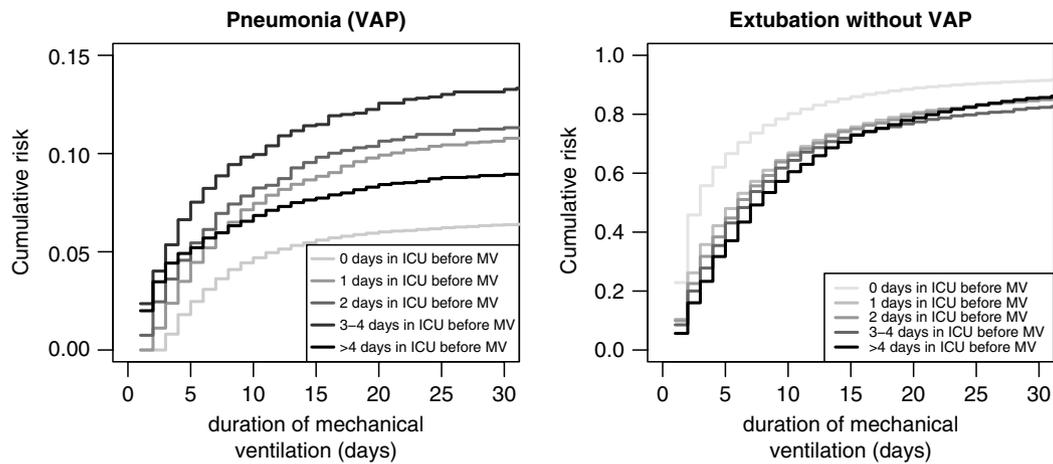


Fig. 4. Cumulative risk (incidence) of ventilator-associated pneumonia (VAP) and extubation without VAP, stratified by days in ICU before mechanical ventilation.

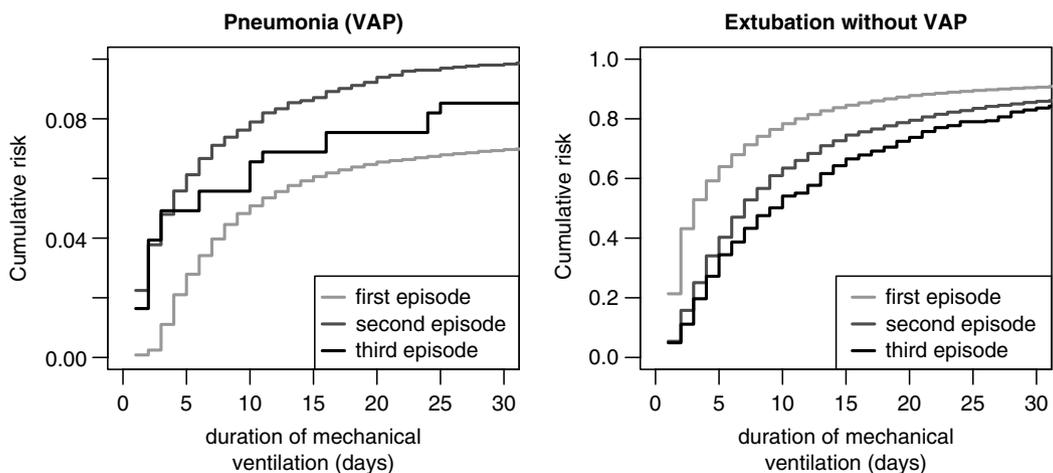


Fig. 5. Cumulative risk (incidence) of ventilator-associated pneumonia (VAP) and extubation without VAP, stratified by episode.

of the extubation hazard rate is also of importance because it indirectly determines the cumulative VAP risk.

Patients who have been in the hospital for 2 or more days before intubation have a higher VAP risk regardless of the duration of ventilation.² We distinguished the preintubation time between general hospital and intensive care and found that it is rather the time in ICU than the time in the general ward. In addition, our results indicate that the risk for VAP is higher during the second and third episodes of ventilation. Such effects, even though much less pronounced, have been reported in previous studies.^{8,9}

The study had following limitations. First, extubation documentation did not indicate whether it was a planned or unplanned extubation. Such a distinction would have been interesting for studying the effect of reintubation in more detail. Second, we included only adults in this analysis. Thus, the results cannot be generalized to pediatric populations. In this study, we did not distinguish between early or late onset of VAP. To investigate late-onset VAP occurring after 4 days of intubation and mechanical ventilation,² conditional models should be used.¹⁶ Therefore, for late-onset VAP, a statistical analysis must account for the fact that patients have to be ventilated at least 4 days without acquiring a VAP; patients who acquire an early-onset VAP or were extubated within four days are not at-risk for late-onset VAP.¹⁶ Many patients receive short-term ventilation

(Fig. 1) and are therefore excluded from the risk set, and the cumulative risk of late-onset VAP is greater than that for early- and late-onset VAP combined (data not shown).

In conclusion, we hope that our approach leads to a better risk understanding of VAP. This information may guide physicians to improve medical decisions related to the harms and benefits of the duration of ventilation.

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Conflicts of interest. All authors report no conflicts of interest relevant to this article.

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