Great example of where risk stratification is important. The highest attributable mortality was in the middle risk APACHE group. Therefore any study looking at intervention to reduce VAP (and mortality) should focus on this sub-group.

Attributable mortality of ventilator-associated pneumonia: a meta-analysis of individual patient data from randomised prevention studies

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Summary

Background Estimating attributable mortality of ventilator-associated pneumonia has been hampered by confounding factors, small sample sizes, and the difficulty of doing relevant subgroup analyses. We estimated the attributable mortality using the individual original patient data of published randomised trials of ventilator-associated pneumonia prevention.

Methods We identified relevant studies through systematic review. We analysed individual patient data in a one-stage meta-analytical approach (in which we defined attributable mortality as the ratio between the relative risk reductions [RRR] of mortality and ventilator-associated pneumonia) and in competing risk analyses. Predefined subgroups included surgical, trauma, and medical patients, and patients with different categories of severity of illness scores.

Findings Individual patient data were available for 6284 patients from 24 trials. The overall attributable mortality was 13%, with higher mortality rates in surgical patients and patients with mid-range severity scores at admission (ie, acute physiology and chronic health evaluation score [APACHE] 20–29 and simplified acute physiology score [SAPS 2] 35–58). Attributable mortality was close to zero in trauma, medical patients, and patients with low or high severity of illness scores. Competing risk analyses could be done for 5162 patients from 19 studies, and the overall daily hazard for intensive care unit (ICU) mortality after ventilator-associated pneumonia was 1·13 (95% CI 0·98–1·31). The overall daily risk of discharge after ventilator-associated pneumonia was 0·74 (0·68–0·80), leading to an overall cumulative risk for dying in the ICU of 2·20 (1·91–2·54). Highest cumulative risks for dying from ventilator-associated pneumonia were noted for surgical patients (2·97, 95% CI 2·24–3·94) and patients with mid-range severity scores at admission (ie, cumulative risks of 2·49 [1·81–3·44] for patients with APACHE scores of 20–29 and 2·72 [1·95–3·78] for those with SAPS 2 scores of 35–58).

Interpretation The overall attributable mortality of ventilator-associated pneumonia is 13%, with higher rates for surgical patients and patients with a mid-range severity score at admission. Attributable mortality is mainly caused by prolonged exposure to the risk of dying due to increased length of ICU stay.

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Introduction

In a 1-day (May 8, 2007) point prevalence survey[1] of 13796 adult patients in 1265 intensive care units (ICUs) in 75 countries, 51% of all patients were infected, of whom 64% (4503 patients) had an infection of the respiratory tract. Many of these episodes could have been classified as ventilator-associated pneumonia, which is one of the most common nosocomial infections with major consequences for patient outcome. Yet, to what extent ventilator-associated pneumonia increases the likelihood of death in ICUs is unknown.

Different methods have been used to calculate the attributable mortality of ventilator-associated pneumonia, yielding estimates ranging from 0 to 60%. Most studies were observational, using cohorts of affected and non-affected patients to calculate relative risks (RRs) or odds ratios (ORs) in univariate and multivariate analyses. Such studies do not include adjustment for confounding, and a meta-analysis of all published observational cohort studies did not allow a reliable estimate of attributable mortality of ventilator-associated pneumonia because of extensive heterogeneity.[2] Quantifying the effects of this disorder on patient outcome is also hampered because of the time-dependent nature of the disease, which might include time-dependent bias, and the fact that ICU mortality and discharge act as competing endpoints. To overcome these issues, innovative techniques such as multistate and competing risks models have been applied to estimate attributable mortality of ventilator-associated pneumonia.[3,4] Although these methods carefully address time effects, adjustment for confounding is still not possible because of the observational nature of the data. Randomisation is the

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only procedure to exclude the effects of confounding, and, therefore, studies in which patients have been randomly assigned to receive a preventive measure would allow a non-confounded estimate of attributable mortality by analysing the preventive effects on ventilator-associated pneumonia and death.

On the basis of a meta-analysis of aggregated data from 53 randomised prevention studies including 58 comparisons, we estimated the attributable mortality of ventilator-associated pneumonia to be 9%.[5] Yet, this approach was limited by the absence of individual patient data, which precluded subgroup analyses as well as applying any of the newer statistical methods that adjust for competing endpoints. We therefore did an individual patient data meta-analysis of studies of ventilator-associated pneumonia prevention, which offered the unique possibility to quantify attributable mortality of ventilator-associated pneumonia in predefined subgroups, while avoiding effects of confounding and adjusting for competing endpoints.

Methods

Search strategy and selection criteria

We searched for randomised trials assessing ventilator-associated pneumonia prevention measures in PubMed, Embase, the Cochrane library, and Web of Science using the terms and synonyms "ventilator-associated pneumonia" and "randomisation". Eligible trials had to be published between January, 1998, and July, 2010. Inclusion criteria were that the studies had to include only patients who were mechanically ventilated and had to report both ventilator-associated pneumonia and mortality rates during ICU stay. We excluded studies assessing specific populations of patients (appendix) or assessing tracheostomy (since these studies only include patients with prolonged stay in ICU) and circuit changes of mechanical ventilation (since some of these studies are done as cost-saving studies, thus to extend the time of use of a system without increasing the incidence of ventilator-associated pneumonia). We excluded studies that were only published as abstracts, conference summaries, or written in non-English language because thorough quality assessment was not possible.

Procedures

We contacted the original investigators of all selected trials to provide the raw data of their trials. We thoroughly checked the obtained data for consistency, plausibility, and integrity of follow-up. We queried discrepancies with the responsible trial investigator, and, when the data were not complete or if discrepancies could not be resolved, we excluded the database from further analysis.

We classified studies according to the diagnostic methods used for ventilator-associated pneumonia. Studies included in category 1 were those in which the following criteria were used for ventilator-associated pneumonia: radiographic criterion and at least two other criteria (ie, fever, leucocytosis, purulent sputum, isolation of pathogenic bacteria from sputum or blood, or decreased alveolar-arterial oxygenation difference), and substantial growth from samples obtained from lungs by bronchoscopic techniques (protected specimen brush, bronchoalveolar lavage, masked or not masked) or by quantitative cultures of endotracheal aspirates. Studies included in category 2 were those in which the following criteria for leucocytosis were used: radiographic criterion and at least three other criteria (ie, fever, leucocytosis, purulent sputum, isolation of pathogenic bacteria from sputum or blood, or decreased alveolar-arterial oxygenation difference), or clinical pulmonary infection score (CPIS) higher than 6 with quantitative culture.

Statistical analyses

We defined attributable mortality of ventilator-associated pneumonia as the ratio of the RR reductions (RRRs) of mortality and ventilator-associated pneumonia. This implies that if, for instance, the relative attributable mortality due to this disorder would be 100%, a 50% RRR of incidence of ventilator-associated pneumonia due to a randomly applied intervention should lead to a 50% RRR of ICU mortality. We pooled the individual data of the different trials and calculated the RRRs of ventilator-associated pneumonia and mortality and their corresponding 95% CI using a random-effects model, with RRR=1–RR. We used a random-effects model to account for cluster and between study effects. We estimated the 95% CI of the attributable mortality by bootstrapping (n=1000). We did subgroup analyses to examine the effect of trauma, surgical, or medical diagnosis as well as the severity of illness on the association of ventilator-associated pneumonia and mortality. Severity of illness is expressed in acute physiology and chronic health evaluation II (APACHE II) scores or simplified acute physiology score (SAPS) 2 scores measured at admission. To make three categories for APACHE II scores and SAPS 2 scores, we applied previously used cutoff points.[3,6] In the subgroup analyses, we examined the distribution of different covariates (ie, age, sex, severity of illness, and admission diagnosis [trauma, surgical, and medical]) among the intervention and control groups to identify possible confounders. In case of significant differences we provided adjusted RRRs.

Furthermore, we examined direct effects of ventilator-associated pneumonia on outcome in a competing risk analysis, which follows separate Cox models, estimating cause-specific HRs for each possible event (ie, ICU discharge or ICU death). We treated ventilator-associated pneumonia in these models as a time-dependent variable. To directly judge the effect of ventilator-associated pneumonia on death, taking the competing event (ie, discharge) into account, we calculated the subdistribution hazard. We included cluster effects in

the different models to account for possible hospital and between study confounding effects. We combined data of patients in control and intervention groups, since we deemed that each of these interventions affected mortality through prevention of ventilator-associated pneumonia only. We did all statistical tests using SPSS version 17.0 or R 2.8 software.

Role of the funding source

The study was unfunded and was investigator-driven and thus independent of any pharmaceutical company. 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

Through our systematic search we identified 45 trials of ventilator-associated pneumonia prevention that were eligible for inclusion, and all corresponding authors were contacted. Individual patient data were provided from 26 studies (appendix). After screening of the individual patient data, 24 studies remained for further analyses yielding 6284 patients, of whom 3384 had been randomly assigned to a preventive measure (table 1).[6–29] Overall, 1061 patients had developed ventilator-associated pneumonia and 1683 had died in ICUs. 17 trials (71%) were rated to category 1 in accordance with the diagnostic criteria for ventilator-associated pneumonia (see appendix for the diagnostic criteria per study).

Pooling the results of all studies yielded a significant RRR of ventilator-associated pneumonia in the total population (0·30, 95% CI 0·21–0·38), as well as in all three subgroups of trauma, medical, and surgical patients, and in all subgroups based on APACHE II scores (table 2).

RRRs of mortality, though, were substantially lower than those of ventilator-associated pneumonia, and in none of these analyses reached significance. Pooling the data of all studies resulted in an RRR of mortality of 0·04 (95% CI –0·06 to 0·12) and highest relative mortality reductions were noted in surgical patients and patients with mid-range severity of illness scores (ie, APACHE II 20–29 and SAPS 2 35–58; table 2).

The overall estimate of attributable mortality due to ventilator-associated pneumonia was 13% (95% CI –0·14 to 0·38), with highest estimates for surgical patients and

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See **Online** for appendix

	Year	Prevention method	Total number of patients		VAP		Mortality		Subgroup analysis
			Prevention	Control	Prevention	Control	Prevention	Control	
Bergmans et al[7]	2001	Oral decontamination	87	139	13	42	25	53	Trauma/medical/surgical/APACHE II
Camus et al[8]	2005	Oral decontamination	389	126	24	19	103	41	Trauma/medical/surgical/SAPS 2
Cook et al[9]	1998	Stress ulcer prophylaxis	604	596	98	114	138	140	Trauma/medical/surgical
Drakulovic et al[10]	1999	Body positioning	39	47	2	11	7	13	Trauma/medical/surgical/APACHE II
Hanisch et al[11]	1998	Stress ulcer prophylaxis	101	57	20	12	19	12	Trauma/surgical/APACHE II
Klarin et al[12]	2008	Probiotics	23	21	1	3	5	4	Trauma/medical/surgical/APACHE II
Koeman et al[13]	2006	Chlorhexidine	255	130	29	23	95	38	Trauma/medical/surgical/APACHE II
Krueger et al[6]	2002	Oral decontamination with ciprofloxacin IV	265	262	6	29	52	75	Trauma/medical/surgical/APACHE II
Lacherade et al[14]	2005	Humidification system	185	184	47	53	60	63	Medical/surgical/SAPS 2
Lacherade et al[15]	2010	Subglottic drainage	169	164	25	42	71	65	Trauma/medical/surgical/SAPS 2
Lorente et al[16]	2005	Suctioning system	210	233	43	42	52	50	Trauma/medical/surgical/APACHE II
Lorente et al[17]	2006	Humdification system	53	51	21	8	13	12	Trauma/APACHE II
Lorente et al[18]	2007	Polyurethane cuff and subglottic drainage	140	140	11	31	26	32	Trauma/medical/surgical/APACHE II
Memish et al[19]	2001	Humidification system	123	120	14	19	40	30	Trauma/medical/surgical
Morrow et al[20]	2010	Probiotic prophylaxis	73	73	14	28	15	12	Trauma/APACHE II
Nardi et al[21]	2001	Selective digestive decontamination	119	104	9	20	25	26	Trauma/medical/surgical
Van Nieuwenhoven et al[29]	2006	Body positioning	112	109	13	8	33	33	Trauma/medical/surgical/APACHE II
O'Keefe et al[22]	1998	Stress ulcer prophylaxis	47	49	10	14	6	11	Trauma
Pneumatikos et al[23]	2002	Decontamination subglottic area	31	30	5	16	5	7	Trauma/APACHE II
Scannapieco et al[24]	2009	Chlorhexidine	103	53	14	12	18	8	Trauma/medical/surgical/APACHE II
Seguin et al[25]	2006	Oral decontamination	67	31	15	13	16	6	Trauma/SAPS 2
Staudinger et al[26]	2010	Continuous lateral rotation therapy	75	75	8	17	22	18	Medical/APACHE II/SAPS 2
Topeli et al[27]	2004	Suctioning system	41	37	13	9	27	25	APACHE II
Valencia et al[28]	2007	Automatic control cuff pressure	73	69	11	10	20	16	Trauma/medical/surgical/APACHE II

VAP=ventilator-associated pneumonia. APACHE=acute physiology and chronic health evaluation. SAPS 2=simplified acute physiology score. IV=intravenously.

Table 1: **Characteristics of included studies**

patients with mid-range severity scores (APACHE II 20–29 and SAPS2 35–58). We noted no evidence for attributable mortality due to ventilator-associated pneumonia in trauma and medical patients and patients with low (ie, APACHE scores <20 or SAPS2 score <35) or high (APACHE >30 or SAPS2 score >58) severity of illness scores.

In the competing risk analyses, only patients with information on length of stay in the ICU, duration of mechanical ventilation until the occurrence of ventilator-associated pneumonia, and ICU mortality could be included. Therefore, in five studies,[11,16,19,22,24] all patients were excluded, as were 26 patients because of missing data from other studies. Eventually 5162 patients were available for these analyses, and their baseline characteristics are shown in table 3.

	Total number of patients	RRR VAP (95% CI)	RRR mortality (95% CI)	Attributable mortality (95% CI*)
All studies	6284	0·30 (0·21 to 0·38)	0·04 (–0·06 to 0·12)	13% (–0·14 to 0·38)
Trauma	1159	0·40 (0·25 to 0·52)	–0·08 (–0·45 to 0·19)	0% (–1·06 to 0·45)
Medical	3314	0·32 (0·17 to 0·43)	–0·01 (–0·14 to 0·11)	0% (–0·41 to 0·29)
Surgical	1560	0·26 (0·04 to 0·43)	0·18 (–0·01 to 0·33)	69% (0·08 to 3·60)
APACHE <20				
Unadjusted	1588	0·31 (0·10 to 0·47)	0·00 (–0·26 to 0·20)	0% (–0·94 to 0·72)
Adjusted†	1521	0·34 (0·14 to 0·49)	–0·03 (–0·31 to 0·18)	0% (–0·97 to 0·77)
APACHE 20–29	1176	0·28 (0·05 to 0·45)	0·10 (–0·12 to 0·27)	36% (–0·29 to 1·51)
APACHE ≥30	359	0·47 (0·08 to 0·70)	–0·03 (–0·39 to 0·23)	0% (–0·95 to 0·37)
SAPS 2 <35	364	0·45 (0·08 to 0·67)	–0·23 (–1·18 to 0·30)	0% (–4·48 to 0·82)
SAPS 2 35–58	723	0·38 (0·11 to 0·56)	0·18 (–0·07 to 0·38)	47% (–0·13 to 1·08)
SAPS 2 ≥58	377	0·35 (–0·05 to 0·60)	–0·12 (–0·50 to 0·16)	0% (–2·27 to 0·60)

RRR=relative risk reduction. VAP=ventilator-associated pneumonia. APACHE=acute physiology and chronic health evaluation. SAPS 2=simplified acute physiology score. *95% CI attributable mortality as estimated with bootstrap analyses. †Adjusted for trauma .

Table 2: **Results of primary analysis (random effects model)**

Compared with patients not developing ventilator-associated pneumonia, the cause-specific hazard ratio (CSHR) of dying in the ICU was 1·13 (95% CI 0·98–1·31; table 4), and after development of the disorder, patients had a lower risk per day for ICU discharge, as represented by the CSHR of discharge of 0·74 (0·68–0·80; table 4). As a result, these patients were exposed longer to a daily risk of dying in the ICU. When combining the direct effects of ventilator-associated pneumonia on the hazard of ICU mortality with the indirect effects imposed by a decreased risk of ICU discharge, the combined hazard for mortality (ie, subdistribution hazard) for patients with the disorder was 2·20 (95% CI 1·91–2·54). These findings imply that the increased risk of dying in the ICU after ventilator-associated pneumonia is merely the result of prolonged stay in the ICU rather than the direct effect of ventilator-associated pneumonia on mortality. Results were similar for patients randomly assigned to preventive measures or to control strategies.

In subgroup analyses, surgical patients and patients with SAPS 2 score of 35–58 had a higher mortality risk per day after ventilator-associated pneumonia and a lower risk of ICU discharge after ventilator-associated pneumonia (table 4). This resulted in higher combined hazards for mortality for surgical patients and for patients with SAPS 2 score of 35–58 (table 4).

We obtained one of the lowest subdistribution hazards for trauma patients (1·48, 95% CI 0·93–2·36; table 4), with no evidence that the disorder increased the daily risk of death (CSHR 0·73, 95% CI 0·43–1·23), although it seemed to reduce the likelihood of discharge (CSHR 0·65, 0·54–0·78). Furthermore, the overall effects of ventilator-associated pneumonia on mortality were lower in the extremes of the SAPS 2 scores (<35 and >58). This trend was less obvious for the three categories of the APACHE scores—the direct effect of the disorder on death was one of the lowest for patients with APACHE

	VAP				Others		
	Number of patients	Onset	Mortality	LOS	Number of patients	Mortality	LOS
All patients	848 (16%)	7·0 (7·0)	257 (30%)	21·0 (20·0)	4314 (84%)	1176 (27%)	9·0 (11·0)
Control	488 (21%)	7·0 (6·0)	149 (31%)	20·0 (19·8)	1888 (79%)	527 (28%)	9·0 (11·0)
Prevention	360 (13%)	7·0 (7·0)	108 (30%)	22·5 (21·0)	2426 (87%)	649 (27%)	9·0 (12·0)
Trauma	198 (27%)	6·0 (6·0)	26 (13%)	21·0 (16·0)	538 (73%)	91 (17%)	10·0 (10·0)
Surgery	196 (15%)	7·0 (6·0)	65 (33%)	22·0 (22·0)	1116 (85%)	259 (23%)	9·0 (11·0)
Medical	395 (14%)	7·0 (7·0)	138 (35%)	21·0 (20·0)	2481 (86%)	765 (31%)	9·0 (12·0)
APACHE II <20	145 (14%)	6·0 (5·5)	37 (26%)	22·0 (19·0)	922 (86%)	153 (17%)	8·0 (10·0)
APACHE II 20–29	165 (18%)	8·0 (8·5)	56 (34%)	23·0 (26·0)	776 (82%)	234 (30%)	9·0 (13·0)
APACHE II ≥30	51 (15%)	6·0 (5·0)	24 (47%)	17·0 (17·0)	287 (85%)	149 (52%)	8·0 (11·0)
SAPS 2 <35	61 (17%)	6·0 (5·0)	12 (20%)	23·0 (20·0)	303 (83%)	47 (16%)	13·0 (15·0)
SAPS 2 35–58	128 (18%)	8·0 (7·0)	52 (41%)	23·0 (23·8)	593 (82%)	167 (28%)	12·0 (14·0)
SAPS 2 ≥58	73 (19%)	7·0 (4·5)	28 (38%)	23·0 (18·5)	304 (81%)	159 (52%)	11·0 (13·0)

Data are number of patients (%) or median (IQR). VAP=ventilator-associated pneumonia. LOS=length of stay on the intensive-care unit (days). APACHE=acute physiology and chronic health evaluation. SAPS 2=simplified acute physiology score. Onset and LOS are expressed in days.

Table 3: **Baseline characteristics of patients included in the competing risk analysis**

less than 20, but the effect on length of stay was highest in this category. Almost the opposite was recorded for patients with APACHE greater than 30.

Discussion

On the basis of a meta-analysis of 6284 individual patient's data from 24 trials of ventilator-associated-pneumonia prevention, we estimate that the attributable mortality of the disorder is 13%. Yet, there are large differences between subgroups of patients, with attributable mortality rates of 69% in surgical patients and 36% in patients with an intermediate severity of illness score (ie, APACHE 20–29). The attributable mortality was close to zero in trauma and medical patients and in patients with a low (ie, APACHE scores <20 or SAPS 2 score <35) or high (APACHE >30 or SAPS 2 score >58) severity of illness scores. These findings were confirmed by competing risk analyses. Our findings elucidate that attributable mortality mainly results from longer stay in the ICU. This prolonged stay increases the risk of dying; possible reasons are increased risk of ICU-related complications such as other nosocomial infections and complications related to invasive procedures. For trauma patients and patients with low severity of illness scores, this prolonged stay due to ventilator-associated pneumonia does not increase mortality, which could be explained by the better clinical condition to cope with these complications. Severely ill patients (ie, APACHE II >30, SAPS 2 >58) are the ones likely to have prolonged ICU stays already, so the presence of ventilator-associated pneumonia does not contribute to additional ICU days with the attendant mortality. The observed differences in mortality between surgical and medical patients corroborate with previous findings,[3] and remain unexplained. Possible explanations include differences in severity of illness, comorbidity, and other differences in casemix, but more detailed information on individual patients is needed to elucidate this matter.

Our estimate of attributable mortality is consistent with estimates from other studies. Nguile-Makao and colleagues[3] estimated attributable mortality in a cohort of 2873 patients, with 434 of them developing ventilator-associated pneumonia, using three statistical methods. On the basis of unadjusted logistic regression and a progressive disability model, attributable mortality of the disorder was estimated to be 8·1% (95% CI 3·1–13·1). In conditional logistic regression on a matched population (matching on duration of mechanical ventilation) attributable mortality was estimated to be 10·4% (95% CI 5·6–24·5). Schumacher and colleagues[4] estimated attributable mortality of nosocomial pneumonia (not only ventilator-associated pneumonia, because not all patients were mechanically ventilated) to be 10·6% using multistate models in a cohort of 1876 patients with a duration of ICU stay of at least 48 h.

Our finding that surgical patients and patients with mid-range severity of illness had the highest attributable mortality due to ventilator-associated pneumonia corroborates with findings from Nguile-Makao and colleagues' study.[3] Moreover, our finding of absence of attributable mortality in trauma patients corroborates with findings from another study by Magret and colleagues.[30] In a prospective observational survey of 2436 patients from 27 ICUs in nine European countries, mortality was 73% lower in trauma patients with ventilator-associated pneumonia compared with non-trauma patients with the disorder (adjusted OR of 0·37, 95% CI 0·21–0·65).

We have used an innovative approach by doing a meta-analysis of studies assessing different intervention methods. This implies that this study did not aim (and should not be used) to determine the preventive effects of individual measures. However, this approach offers a unique opportunity to estimate attributable mortality of ventilator-associated pneumonia, as long as the preventive measures only affect mortality through reducing the risk of developing ventilator-associated pneumonia. The main strengths of our analyses are the reliability of the data as they were prospectively obtained during randomised controlled trials, the size of the study population increasing the power to assess the effects of ventilator-associated pneumonia in subgroups of patients, and the absence of confounding due to randomisation in the calculation of attributable mortality. Moreover, we included adjustments for cluster effects to account for hospital effects and between study effects in all statistical analyses, and did sensitivity analyses to assess the effect of the diagnostic methods for the disorder. This did not change conclusions (data not shown).

Some limitations should also be discussed. First, our analyses were restricted to trials of ventilator-associated pneumonia prevention published after 1998, mainly because of feasibility reasons. We expected in the study design phase that the availability of the original datasets of randomised trials published before 1998 would be limited. Furthermore, treatment of ICU patients in these

	CSHR mortality (95% CI)	CSHR discharge (95% CI)	SHR mortality (95% CI)
All patients	1·13 (0·98–1·31)	0·74 (0·68–0·80)	2·20 (1·91–2·54)
Control	1·13 (0·93–1·38)	0·75 (0·67–0·84)	2·15 (1·77–2·61)
Prevention	1·12 (0·90–1·39)	0·72 (0·64–0·81)	2·24 (1·81–2·77)
Trauma	0·73 (0·43–1·23)	0·65 (0·54–0·78)	1·48 (0·93–2·36)
Medical	1·20 (0·99–1·46)	0·75 (0·67–0·84)	2·23 (1·84–2·70)
Surgical	1·37 (1·03–1·83)	0·69 (0·58–0·82)	2·97 (2·24–3·94)
APACHE <20	1·03 (0·70–1·52)	0·54 (0·44–0·66)	2·66 (1·84–3·84)
APACHE 20–29	1·31 (0·94–1·83)	0·73 (0·60–0·88)	2·49 (1·81–3·44)
APACHE ≥30	1·22 (0·79–1·89)	1·04 (0·71–1·52)	1·72 (1·09–2·71)
SAPS 2 <35	1·31 (0·65–2·62)	0·92 (0·72–1·17)	1·88 (0·96–3·70)
SAPS 2 35–58	1·49 (1·05–2·11)	0·62 (0·50–0·77)	2·72 (1·95–3·78)
SAPS 2 ≥58	0·81 (0·53–1·22)	0·76 (0·55–1·03)	1·16 (0·77–1·76)

CSHR=cause-specific hazard ratio. SHR=subdistribution hazard ratio. APACHE=acute physiology and chronic health evaluation. SAPS 2=simplified acute physiology score.

Table 4: **Results of competing risks analysis**

older studies may no longer be comparable with current practices, which would reduce the generalisability of our findings. Second, not all investigators could provide individual patient data, and, therefore, data from 21 studies were not included. However, if we analyse the aggregated data of the 24 studies included in a classic meta-analysis approach, results are in agreement with those reported in our previous published meta-analysis, in which all studies of prevention of ventilator-associated pneumonia were included (58 comparisons with 12 830 patients).[5] We, therefore, conclude that the included studies are reliable representatives of all studies of ventilator-associated-pneumonia prevention studies. Third, there was no information on the adequacy of antimicrobial treatment and antibiotic susceptibilities of causative pathogens. Therefore, we can not answer the question of how much the attributable mortality is influenced by the adequacy of treatment and susceptibility of the causative pathogens. Yet, as patients were randomised within ICUs, it is rather unlikely that those randomised to a certain preventive measure would be treated differently in case of ventilator-associated pneumonia.

Fourth, misattribution of decreased mortality to prevention of ventilator-associated pneumonia rather than to other mechanisms of mortality reduction might have led to overestimation of ventilator-associated pneumonia attributable mortality. Based on our previous study[5] in which we did subgroup analyses for specific intervention, we feel that these other mechanisms have, at best, a minor effect on the noted estimates of attributable mortality of ventilator-associated pneumonia.

Fifth, since there is no gold standard for the diagnosis of ventilator-associated pneumonia and different diagnostic methods were used, misclassification of patients with this disorder might underestimate the observed attributable mortality. However, we noted no evidence that diagnostic methods applied were associated with differences in attributable mortality.

In conclusion, based on the individual patient data from 24 trials of ventilator-associated pneumonia prevention, the attributable mortality of the disorder was estimated to be 13%. A higher attributable mortality rate was seen in surgical patients and patients with mid-range severity of illness on admission. These findings are of crucial importance for the future design and analyses of intervention studies. It has been stated that, considering the difficulties in diagnosing ventilator-associated pneumonia, prevention studies should focus on showing favourable effects on more solid endpoints, such as ICU survival.[31,32] Consequently, prevention studies should include thousands of patients to be adequately powered to show beneficial effects on mortality. Furthermore, considering the large differences in attributable mortality between subgroups, investigators could consider primarily focusing on those subgroups of patients with the highest risk.

Contributors

WGM designed and planned the study, and gathered, analysed, and interpreted the data. MMR and MJMB contributed to the initial idea and design of the study, interpreted the data, and supervised the study. RHHG contributed to the analyses and interpretation of the data. DCJJB, CC, TTB, EWH, BK, MK, WAK, JCL, LL, ZAM, LEM, GN, CAvN, GEO'K, GN, FAS, PS, TS, AT, and MIF provided the data from the original trials, contributed to the protocol, and interpreted the data. The manuscript was prepared by WGM, and all authors have seen and approved the final version.

Conflicts of interest

We declare that we have no conflicts of interest.

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of sepsis than is one procalcitonin measurement on the day of fever.[5]

This finding suggests the need to investigate an approach that uses procalcitonin kinetics (eg, two measurements within 8–12 h for newly admitted patients) and differential cutoffs to distinguish SIRS from sepsis. Stored blood samples from day 1 are frequently available for procalcitonin testing in inpatients and ICU patients with new onset fever. Once patients have started on antibiotics, intensivists are frequently reluctant to stop antibiotics unless cultures are negative at 48 h. Serial procalcitonin testing within 24 h could reduce unnecessary use of antibiotics and selective pressure for multiresistant pathogens. We have suggested an approach to the use of procalcitonin in ICU patients with suspected sepsis (appendix).

See Online for appendix

Procalcitonin might truly be a very useful marker if used as one test in the right context for ruling out sepsis, or by use of its short half-life to rationalise antibiotics. However, a one-size-fits-all approach (as tested in a recent study[4]) will only generate substantial costs with no benefits for patients.

We declare that we have no conflicts of interest.

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Attributable mortality of ventilator-associated pneumonia

Wilhemina Melsen and colleagues[1] estimated the attributable mortality of ventilator-associated pneumonia from individual patient data derived from randomised prevention studies. On the basis of the search terms "ventilator-associated pneumonia" and "randomisation" the investigators identified 45 trials, of which 24 were included. They state that the included studies are reliable representatives of all studies of prevention of ventilator-associated pneumonia. However, the analysis included only six decontamination studies. This point is remarkable, because a meta-analysis[2] of 36 randomised trials concluded that treatment with a combination of topical and systemic antibiotics reduces the incidence of respiratory tract infections from 40% to 19%, and overall mortality from 30% to 24%, with four patients needed-to-treat to prevent one infection, and 18 to prevent one death. From these data suggesting that a 53% reduction in respiratory tract infections leads to a 6% reduction in mortality, the attributable mortality of respiratory infections is 11%, which is similar to the 13% calculated by Melsen and colleagues.

Furthermore, Melsen and colleagues state that mortality after ventilator-associated pneumonia is mainly caused by prolonged exposure to risk of death due to increased length of stay in an intensive-care unit (ICU). However, this assumption contradicts previous findings. In a case-control study, Klompas and colleagues[3] elegantly showed that ventilator-associated pneumonia significantly prolonged both median duration of mechanical ventilation and median length of stay in an ICU by 6 days. However, hospital mortality did not differ significantly. Indeed, mortality is not proportional to length of ICU stay—severely ill patients dying early during their ICU admission have a shorter length of stay than do those recovering after prolonged mechanical ventilation.

In a retrospective analysis of 543 mechanically ventilated patients, Hayashi and colleagues[4] also reported significantly prolonged mechanical ventilation and length of stay in an ICU without an increase in mortality in patients with ventilator-associated complications; however, they did note that patients with ventilator-associated complications more often had chronic obstructive pulmonary disease and acute kidney injury than did those with no complications. In patients with ventilator-associated pneumonia, underlying illness and complicating organ failure could have a greater effect on mortality than does length of ICU stay.

I declare that I have no conflicts of interest.

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Authors' reply

We thank Anne-Cornélie de Pont for her comments. In our study[1] we selected randomised controlled trials published between 1998 and 2010, reporting rates of both ventilator-associated pneumonia and mortality (during stay in an intensive-care unit [ICU]). This selection yielded six decontamination studies, which is indeed less than the 36 randomised trials included in a different meta-analysis.[2] However, of the 36 studies, only six were published after 1998, of which no data were available for one[3] and one had no data for ventilator-associated pneumonia.[4] Therefore, we maintain our conclusion that the included studies are representative of all studies of ventilator-associated pneumonia done in this 12 year period.

Furthermore, de Pont suggests that our statement that mortality after ventilator-associated pneumonia is mainly caused by prolonged exposure to risk of death due to increased length of ICU stay, contradicts other findings, referring to two studies.[5,6] In one study, ventilator-associated pneumonia was associated with a prolonged median duration of mechanical ventilation and ICU stay, but not with hospital mortality (or ICU mortality).[6] In that study, all data, including diagnosis of ventilator-associated pneumonia, were collected retrospectively. Included patients were randomly selected and enriched with patients with longer durations of mechanical ventilation, potentially leading to selection bias. In the matched analyses, controls were matched, among other things, for duration of mechanical ventilation, which might bias the estimate of attributable mortality.[7] In the other study,[5] ventilator-associated pneumonia was associated with prolonged ICU stay with no differences in mortality. This study was also retrospective, with Cox regression analyses done with no consideration of competing risks. Moreover, the investigators assessed ventilator-associated complication rather than ventilator-associated pneumonia. For all these reasons, we believe that the results of our analysis, although contradictory to the findings of the two mentioned studies, provide strong evidence of the association between development of ventilator-associated pneumonia, and length of stay and mortality in ICU.

Finally, de Pont suggests that in patients with ventilator-associated pneumonia, underlying illness and complicating organ failure have a greater effect on mortality than does length of ICU stay. Although intuitive, our findings do not support this point: severely ill patients (ie, those scoring high with the Acute Physiology and Chronic Health Enquiry II score and the Simplified Acute Physiology Score II) had the greatest increases in ICU stay, and, in this population, development of ventilator-associated pneumonia did not contribute to additional ICU days with the attendant mortality, showing that there was no attributed effect of ventilator-associated pneumonia on mortality.

We declare that we have no conflicts of interest.

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