FACTORS ASSOCIATED WITH DEATH IN INTENSIVE CARE UNIT PATIENTS WITH VENTILATOR-ASSOCIATED PNEUMONIA

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FAKTORI RIZIKA ZA SMRTNI ISHOD KOD PACIJENATA U INTENZIVNOJ NEZI NA VEŠTAČKOJ VENTILACIJI KOJI SU DOBILI PNEUMONIJU

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ABSTRACT

Background: *The incidence of ventilator-associated pneumonia (VAP) among patients on mechanical ventilation ranges from 15% to 25%, and mortality ranges from 33% to 38%.*

Aim: *The aim of our study was to analyse the importance of previously uninvestigated potential risk factors for death in intensive care unit (ICU) patients with VAP.*

Methods: *A case-control design was chosen for this study. The study population consisted of all patients who developed ventilator-associated pneumonia in the central ICU of a tertiary care hospital (n = 65) during a period of 6 months. Cases (n=45) included patients who died during their treatments in the ICU, if their primary cause of death was ventilator-VAP. Controls (n=20) included patients with VAP who survived their treatments in the ICU and who subsequently were subsequently transferred to other hospital wards.*

Results: *Significant associations were found between death and age over 65 ($OR_{adjusted}$ = 10.66; CI: 1.22, 93.12; p = 0.032), death and infection upon admission to the ICU ($OR_{adjusted}$ = 434.39; CI: 3.07, 61449.65; p = 0.016), and death and administration of ceftriaxone prior to VAP ($OR_{adjusted}$ = 69.32; CI: 1.74, 2768.92; p = 0.024). A synergistic effect on death was found only for age over 65 and infection upon admission to the ICU.*

Conclusions: *ICU patients with VAP experience have increased risk of mortality if they receive ceftriaxone prophylactically, if they have an infection upon admission to the ICU and if their age is advanced.*

Key Words: *Ventilator-associated pneumonia; risk factors; death; ceftriaxone.*

SAŽETAK

Uvod: *Učestalost pneumonije kod pacijenata na veštačkoj ventilaciji (PVV) se kreće između 15% i 25%, a smrtnost pacijenata sa takvom pneumonijom je između 33% i 38%.*

Cilj: *Cilj naše studije je bio analiza značaja prethodno nedovoljno ispitanih potencijalnih faktora rizika za smrtni ishod pacijenata u intenzivnoj nezi sa PVV-om.*

Metoda: *Studija je dizajnirana kao studija tipa slučaj-kontrola. Ispitivanu populaciju činili su svi pacijenti koji su dobili PVV u centralnoj intenzivnoj nezi Kliničkog centra (n = 65) tokom perioda od 6 meseci. Slučajevi (n=45) su pacijenti koji su umrli tokom lečenja u intenzivnoj nezi, ukoliko je njihov primarni uzrok smrti pneumonija vezana za veštačku ventilaciju. Kontrole (n=20) su pacijenti sa PVV-om koji su preživeli lečenje u intenzivnoj nezi, a zatim prebačeni na druga odeljenja.*

Rezultati: *Pronađena je značajna veza između smrtnog ishoda i starosti preko 65 godina ($OR_{adjusted}$ 10.66; CI 1.22, 93.12; p = 0.032), smrtnog ishoda i infekcije na prijemu u intenzivnu negu ($OR_{adjusted}$ 434.39; CI 3.07, 61449.65; p = 0.016), i smrtnog ishoda i primene ceftriaksona pre nastanka PVV ($OR_{adjusted}$ 69.32; 1.74, 2768.92; p = 0.024). Sinergistički efekat na smrtni ishod je bio pronađen samo za starost preko 65 godina i infekciju na prijemu u jedinicu intenzivne nege.*

Zaključak: *Pacijenti iz intenzivne nege sa pneumonijom udruženom sa veštačkom ventilacijom češće umiru ako profilaktički primaju ceftriakson, ako imaju infekciju na prijemu u intenzivnu negu i ako su stariji od 65 godina.*

Ključne reči: *pneumonija kod pacijenata na veštačkoj ventilaciji; faktori rizika; smrtni ishod; ceftriakson*

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INTRODUCTION

Ventilator-associated pneumonia (VAP) is a frequent complication of mechanical ventilation in intensive care unit (ICU) patients. The incidence of VAP among patients on mechanical ventilation ranges from 15%[1] to 25%[2], and mortality ranges from 33%[3] to 38%[4]. The serious clinical and economic consequences of ventilator-associated pneumonia (e.g., patients who develop VAP are twice as likely to die, stay 6.1 days longer in intensive care units on average, and generate more than $10,019 of additional hospital costs[5] as compared compared with similar patients without VAP) make efficacious treatment of VAP an extremely important health issue.

A number of risk factors for death in patients with VAP have been identified in previous studies, the following factors show ing high strong associations: inadequate initial treatment with antibiotics[6], concomitant bacteraemia[6], advanced age[7,9], female sex[7], disease severity at VAP onset[7], nonfermenting Gram-negative bacilli or methicillin-resistant *S. aureus* as VAP-causative pathogens[7], prolonged mechanical ventilation dependency[7,9], persistent fever[7], severity of lung injury[7], septic shock[8], severe sepsis[8], previous carbapenem usage within 72 hours[8], presence of neurologic disease at admission[9], and failure of the Pao2/Fio2 ratio to improve by day three[9]. However, there are numerous factors that play significant roles in the treatment of patients with VAP whose relationships to death have not been investigated, or were were investigated in inadequately powered studies, such as individual antibiotic agents, prophylactic use of antibiotics, duration of antibiotic use, dosage of antibiotics, and concomitant medication. The aim of our study was to analyse the importance of previously uninvestigated potential risk factors for death in ICU patients with VAP.

MATERIALS AND METHODS

Setting

Our study was conducted in a tertiary care university hospital (Clinical Center) in Kragujevac, Republic of Serbia, which covers a population of approximately 1.5 million inhabitants. The study population consisted of all patients who developed ventilator-associated pneumonia in the central ICU of the Kragujevac hospital (n = 65) during the 6-month period lasting from May 1st, 2010, to October 31st ,, 2010. Demographic, drug prescription and (co) morbidity data were obtained from the medical records. All data were obtained anonymously, with previous written consent of the patients or their relatives, and the study protocol was approved by the Ethics Committee of the Kragujevac Clinical Center. Ventilator-associated pneumonia was diagnosed using any one of the following criteria: rapid cavitation of a pulmonary infiltrate in the absence of cancer or tuberculosis, a positive pleural fluid culture, a species with the same antibiogram isolated from blood and respiratory secretions without another identifiable source of bacteraemia , histopathologic examination of lung tissue at autopsy or non-bronchoscopic bronchoalveolar lavage through a distally wedged catheter with $\geq 10^5$ CFU/mL or $\leq$1% squamous epithelial cells in the retrieved fluid[10,11,12,13].

Study design

The design of our study was of a case-control type, with an aim to assess the association between various risk factors and the occurrence of death in patients with ventilator-associated pneumonia. Cases and controls (comprising the study population) were selected from the list of patients with VAP in the central ICU of Kragujevac Clinical Center, with "cases" being defined as patients who died in the ICU and "controls" as patients who survived treatment of VAP and were transferred to non-intensive care wards of the hospital. Patients younger than 18 and pregnant females were not included in the study population.

Cases

Cases (n=45) were chosen from the study population if they died during their treatment in the central ICU of Kragujevac Clinical Center and if their primary cause of death was ventilator-associated pneumonia, as judged by their physicians.

Controls

Controls (n=20) were chosen from the study population (patients with VAP) if they survived their treatment in the central ICU of Kragujevac Clinical Center and were transferred to non-intensive care wards of the clinical centre.

Potential risk factors

To identify potential risk factors, the following data were collected for each patient: age, sex, emergency hospitalisation, diagnosis upon admission to the ICU, infection upon admission to the hospital, concomitant chronic diseases, causative agent of VAP, resistance of the causative agent to antibiotics, type of surgery, duration of hospitalisation after operation, sepsis, use of a peripheral intravenous catheter, duration of peripheral intravenous (IV) catheterisation, duration of peripheral IV catheterisation prior to VAP, use of a central intravenous catheter, duration of central IV catheterisation, duration of central IV catheterisation prior to infection, infection of the urinary tract, use of a urinary catheter, duration of urinary tract catheterisation, duration of urinary tract catheterisation prior to infection, use of endotracheal intubation, duration of intubation, duration of intubation prior to infection, use of artificial ventilation, duration of artificial ventilation, time from the beginning of artificial ventilation until infection, duration of hospitalisation in the ICU, previous hospitalisation, duration of hospitalisation prior to admission to the ICU , total duration of hospitalisation, indication for antibiotics, antibiotic administration prior to hospital infection , use of cefuroxime, metronidazole, ciprofloxacin, ceftriaxone, azythromycin, ampicillin-sulbactam, meropenem, imipenem, ertapenem,

vancomycin, ampicillin, gentamycin, cefotaxime or piperacillin-tazobactam prior to VAP, daily dose of cefuroxime, metronidazole, ciprofloxacin, ceftriaxone, azythromycin, ampicillin-sulbactam, meropenem, imipenem, ertapenem, vancomycin, ampicillin, gentamycin, cefotaxime or piperacillin-tazobactam prior to VAP, use of cefuroxime, metronidazole, ciprofloxacin, ceftriaxone, azythromycin, ampicillin-sulbactam, meropenem, imipenem, ertapenem, vancomycin, ampicillin, gentamycin, cefotaxime or piperacillin-tazobactam after the occurrence of VAP, daily dose of cefuroxime, metronidazole, ciprofloxacin, ceftriaxone, azythromycin, ampicillin-sulbactam, meropenem, imipenem, ertapenem, vancomycin, ampicillin, gentamycin, cefotaxime or piperacillin-tazobactam after the occurrence of VAP, use of tigecycline after the occurrence of VAP and its daily dose, and transfusion of blood or its derivatives.

Data analysis

The prevalence of each risk factor was determined for both cases and controls. The differences between cases and controls in the observed characteristics were assessed by a Student t-test for continuous variables and a chi-squared test for frequencies. The differences were considered significant if the probability of falsely rejecting a null hypothesis was less than 0.05 . To estimate the association between potential risk factors and death from VAP, crude and adjusted odds ratios (OR) with 95% confidence intervals (95% CI) were calculated using logistic regression[14,15].

RESULTS

Sixty-five patients were enrolled in the study. The baseline characteristics of cases and controls and the differences between them are shown in Table 1. Cases and controls did not significantly differ in terms of age, sex, emergency hospitalisation, diagnosis upon admission to the ICU, infection upon admission to the hospital, concomitant chronic diseases, causative agent of VAP, resistance of the causative agent to antibiotics, type of surgery, duration of hospitalisation after the operation, sepsis, use of a peripheral intravenous catheter, duration of peripheral IV catheterisation, duration of peripheral IV catheterisation prior to VAP, use of a central intravenous catheter, duration of central IV catheterisation, duration of central IV catheterisation prior to infection, infection of the urinary tract, use of a urinary catheter, duration of urinary tract catheterisation, duration of urinary tract catheterisation prior to infection, use of endotracheal intubation, duration of intubation, duration of intubation prior to infection, use of artificial ventilation, duration of artificial ventilation, time from the beginning of artificial ventilation until infection, duration of hospitalisation in the ICU, previous hospitalisation, duration of hospitalisation prior to admission to the ICU, total duration of hospitalisation, indication for antibiotics, antibiotic administration prior to hospital infection, use of cefuroxime, metronidazole, ciprofloxacin, ceftriaxone, azythromycin, ampicillin-sulbactam, meropenem, imipenem, ertapenem, vancomycin, ampicillin, gentamycin, cefotaxime or piperacillin-tazobactam prior to VAP, daily dose of cefuroxime, metronidazole, ciprofloxacin, ceftriaxone, azythromycin, ampicillin-sulbactam, meropenem, imipenem, ertapenem, vancomycin, ampicillin, gentamycin, cefotaxime or piperacillin-tazobactam prior to VAP, use of cefuroxime, metronidazole, ciprofloxacin, ceftriaxone, azythromycin, ampicillin-sulbactam, meropenem, imipenem, ertapenem, vancomycin, ampicillin, gentamycin, cefotaxime or piperacillin-tazobactam after occurrence VAP, daily dose of cefuroxime, metronidazole, ciprofloxacine, ceftriaxone, azythromycin, ampicillin-sulbactam, meropenem, imipenem, ertapenem, ampicillin, gentamycin, cefotaxime or piperacillin-tazobactam after occurrence of VAP, use of tigecycline after the occurrence of VAP and its daily dose, and transfusion of blood or its derivatives.

Significant differences between cases and controls were found only with regard to the administration of vancomycin for treatment of VAP.

The results of the logistic regression analysis (Cox & Snell R-square = 0.386, Nagelkerke R-square = 0.545, Hosmer and Lemeshow chi-square = 2.516, df = 8, p = 0.961), with adjustment for potential confounders, are shown in Table 2. The only significant associations were between the variables death and age over 65 ($OR_{adjusted}$ = 10.66; CI: 1.22, 93.12; p = 0.032), death and infection upon admission to ICU ($OR_{adjusted}$ = 434.39; CI: 3.07, 61449.65; p = 0.016), and death and administration of ceftriaxone prior to VAP ($OR_{adjusted}$ = 69.32; CI: 1.74, 2768.92; p = 0.024). Although the crude odds ratios for administration of tigecycline for treatment of VAP and multi-drug resistance of the causative agent were significantly different from one (see Tables 1 and 2), confidence limits of these odds ratios after adjustment included thethe value of one.

The interactions between factors likely to introduce greater risk for death after VAP were investigated (Table 3). The analyses showed clear synergistic effects only for the interaction of age over 65 and infection upon admission to the ICU. Although crude and adjusted odds ratios increased when age over 65 interacted with administration of ceftriaxone prior to VAP and when infection upon admission to the ICU interacted with administration of ceftriaxone prior to VAP, synergistic effects could not be confirmed by either crude or adjusted odds ratios because their confidence limits also widened substantially to include the value of one.

DISCUSSION

Although several previous studies[16,17,18] found the deaths of patients with VAP to be associated with the severity of the primary disease precipitating ICU admission and surgery, this association was not confirmed in our study. One of the reasons for our findingthis difference could be the very high mortality rate suffered by our patients (69%), which

Variable	Cases (n=45)	Controls (n=20)	Test value and significance of the null hypothesis	Crude odds ratios with confidence intervals (1.96*SE)
Sex (M/F)	30/15 (67%/33%)	15/5 (75%/25%)	$\chi^2 = 0.451$, p = 0.502	1.44 (0.78, 2.67)
Age (years, mean ± SD)	62.4 ± 16.2	51.6 ± 19.3	T = 1.725, p = 0.194	1.03 (1.01, 1.05)
Emergency hospitalisation (yes/no)	42/3 (93%/7%)	17/3 (85%/15%)	$\chi^2 = 1.148$, p = 0.284	3.35 (1.51, 7.43)
Principal diagnosis (internal disease/trauma/surgical disease/infectious disease)	8/4/26/7 (18%/9%/58%/15%)	3/3/14/0 (15%/15%/70%/0%)	$\chi^2 = 3.991$, p = 0.262	0.96 (0.66, 1.41)
Infection upon admission to ICU (yes/no)	8/37 (18%/82%)	1/19 (5%/95%)	$\chi^2 = 1.895$, p = 0.169	1.68 (0.72, 3.97)
Having a chronic disease (yes/no)	18/27 (40%/60%)	5/15 (25%/75%)	$\chi^2 = 1.363$, p = 0.243	1.28 (0.69, 2.37)
Age over 65 (yes/no)	25/20 (56%/44%)	6/14 (30%/70%)	$\chi^2 = 3.625$, p = 0.057	2.41 (1.33, 4.37)
Causative agent (*Stenotrophomonas/Acinetobacter/Proteus/S.aureus/Pseudomonas/Klebsiella/E.coli/Providencia*)	3/14/1/2/11/13/0/1 (7%/31%/2%/4%/24%/29%/0%/3%)	1/7/1/2/3/5/1/0 (5%/35//5%/10%/15%/25%/5%/0%)	$\chi^2 = 6.077$, p = 0.639	1.36 (1.19, 1.54)
Multiresistance of the causative agent (yes/no)	41/4 (91%/9%)	19/1 (95%/5%)	$\chi^2 = 0.295$, p = 0.587	5.15 (2.74, 9.65)
Surgery (yes/no)	35/10 (78%/22%)	19/1 (95%/5%)	$\chi^2 = 2.921$, p = 0.087	0.50 (0.24, 1.05)
Having a central intravenous catheter (yes/no)	33/12 (73%/27%)	13/7 (65%/35%)	$\chi^2 = 0.465$, p = 0.495	1.67 (0.92, 3.01)
Hospitalisation at another hospital ward prior to admission to the ICU (yes/no)	28/17 (62%/38%)	14/6 (70%/30%)	$\chi^2 = 0.366$, p = 0.545	0.63 (0.34, 1.16)
Reason for the administration of antibiotics prior to pneumonia (prophylaxis/treatment of a hospital infection/treatment of an infection upon admission/unknown)	31/2/9/3 (69%/4%/20%/7%)	18/0/1/1 (90%/0%/5%/5%)	$\chi^2 = 3.795$, p = 0.284	1.38 (1.04, 1.83)
Administration of cefuroxime prior to VAP (yes/no)	16/29 (36%/64%)	8/12 (40%/60%)	$\chi^2 = 0.662$, p = 0.718	1.06 (0.61, 1.84)
Administration of ciprofloxacin prior to VAP (yes/no)	5/40 (11%/89%)	1/19 (5%/95%)	$\chi^2 = 0.616$, p = 0.432	0.66 (0.27, 1.61)
Administration of ceftriaxone prior to VAP (yes/no)	9/36 (20%/80%)	2/18 (10%/90%)	$\chi^2 = 0.985$, p = 0.321	3.55 (1.49, 8.46)
Administration of ampicillin+ sulbactam prior to VAP (yes/no)	3/42 (7%/93%)	2/18 (10%/90%)	$\chi^2 = 0.217$, p = 0.642	2.04 (0.53, 7.84)
Administration of meropenem prior to VAP (yes/no)	7/38 (16%/84%)	3/17 (15%/85%)	$\chi^2 = 0.003$, p = 0.954	1.67 (0.69, 4.08)
Administration of vancomycin prior to VAP (yes/no)	1/44 (2%/98%)	2/18 (10%/90%)	$\chi^2 = 1.903$, p = 0.168	0.94 (0.22, 4.06)
Administration of meropenem for the treatment of VAP (yes/no)	11/34 (24%/76%)	4/16 (20%/80%)	$\chi^2 = 0.154$, p = 0.695	4.30 (1.45, 12.77)
Administration of imipenem for the treatment of VAP (yes/no)	8/37 (18%/82%)	2/18 (10%/90%)	$\chi^2 = 0.643$, p = 0.422	5.89 (1.57, 22.20)
Administration of tigecycline for the treatment of VAP (yes/no)	14/31(31%/69%)	4/16 (20%/80%)	$\chi^2 = 0.854$, p = 0.356	5.18 (1.78, 15.09)
Administration of ciprofloxacin for the treatment of VAP (yes/no)	6/39 (13%/87%)	1/19 (5%/95%)	$\chi^2 = 1.001$, p = 0.317	3.40 (0.99, 11.73)
Administration of ampicillin+sulbactam for the treatment of VAP (yes/no)	4/41 (9%/91%)	1/19 (5%/95%)	$\chi^2 = 0.295$, p = 0.587	4.14 (0.78, 21.91)
Administration of piperacillin+tazobactam for the treatment of VAP (yes/no)	8/37 (18%/82%)	5/15 (25%/75%)	$\chi^2 = 0.451$, p = 0.502	1.89 (0.66, 5.46)
Administration of vancomycin for the treatment of VAP (yes/no)	2/43 (4%/96%)	4/16 (20%/80%)	$\chi^2 = 3.999$, p = 0.046**	0.51 (0.10, 2.61)
Duration of endotracheal intubation prior to VAP (days)	10.6 ± 10.4	9.2 ± 7.1	T = -0.602, p = 0.549	1.16 (1.08, 1.24)
Time elapsed from the beginning of artificial ventilation to VAP (days)	10.6 ± 10.6	8.8 ± 6.1	T = -0.723, p = 0.472	1.17 (1.09, 1.25)
Duration of hospitalisation prior to admission to the ICU (days)	5 ± 6.9	4.5 ± 4.4	T = -0.298, p = 0.766	0.99 (0.94, 1.04)

*For the sake of clarity, variables occurring with less than 2% frequency were omitted from the table, as were several less important variables having insignificant differences between cases and controls.
**significant difference

Table 1. Baseline characteristics of cases and controls*.

was two- to three-times higher than in other studies[1,2,3]. In such circumstances, treatment-related factors become more important predictors of the outcome of VAP (at least statistically speaking) than the severity of the disease itself. Causative agents of VAP werewere also not associated with death in our patients. This is not surprising, considering that for both cases and controls, the dominant causative agents, *Stenotrophomonas maltophilia* and *Acinetobacter*, were bacterial species characteristic of an environment subject to overutilisation of wide-spectrum antibiotics. In both groups, more than 75% of patients were receiving intravenous, wide-spectrum antibiotics prophylactically (see Table 1), although controversy still exists regarding whether and at what dosage systemic antibiotic prophylaxis regimens against VAP reduce the incidence and the mortality of infection[19,20]. There is solid body of evidence that short systemic adminis-

Risk factors	Crude OR (95% CI)	Adjusted* OR (95% CI)
Infection upon admission to the ICU	**1.68 (0.72, 3.97)**	**434.39 (3.07, 61449.65)**
Hospitalisation at another hospital ward prior to admission to the ICU	0.63 (0.34, 1.16)	1.25 (1.03, 1.52)
Administration of ceftriaxone prior to VAP	**3.55 (1.49, 8.46)**	**69.32 (1.74, 2768.92)**
Administration of vancomycin prior to VAP	0.94 (0.22, 4.06)	0.01 (0.00, 1.43)
Administration of vancomycin for treatment of VAP	0.51 (0.10, 2.61)	0.03 (0.00, 2.18)
Administration of tigecycline for treatment of VAP	5.18 (1.78, 15.09)	1.34 (0.14, 13.16)
Age over 65	**2.41 (1.33, 4.37)**	**10.66 (1.22, 93.12)**
Multi-drug resistance of the causative agent	5.15 (2.74, 9.65)	1.95 (0.04, 97.93)

* Adjusted for age†, sex†, infection on admission to ICU, hospitalisation at another hospital ward prior to ICU, age over 65, multi-drug resistance of the causative agent, administration of antibiotics prior to VAP†, time elapsed from onset of artificial ventilation to VAP†, time elapsed from endotracheal intubation to VAP†, use of a central intravenous catheter†, causative agent†, chronic diseases†, emergency admission to the ICU†, administration of ceftriaxone prior to VAP, administration of vancomycin prior to VAP, administration of vancomycin for treatment of VAP, administration of ciprofloxacin prior to VAP, administration of meropenem prior to VAP†, administration of tigecycline for treatment of VAP, administration of ciprofloxacin for treatment of VAP†, administration of piperacillin+tazobactam for treatment of VAP†, administration of ampicillin+sulbactam for treatment of VAP†, administration of imipenem for treatment of VAP†, and administration of amikacin for treatment of VAP†.
†Crude and Adjusted odds ratios are not shown in the table for the sake of clarity.
OR = odds ratio

Table 2. Crude and adjusted odds ratios of the risk factors for death in patients with VAP.

	Crude odds ratio (95% CI)	Adjusted* odds ratio (95% CI)
Age not over 65	1.0 (reference)	1.0 (reference)
Only age over 65	2.41 (1.33, 4.37)	10.66 (1.22, 93.12)
Only infection upon admission to the ICU	1.68 (0.72, 3.97)	434.39 (3.07, 61449.65)
Both age over 65 and infection upon admission to the ICU	**6.59 (0.72, 60.15)**	**28.20 (1.70, 469.94)**
Only administration of ceftriaxone prior to VAP	3.55 (1.49, 8.46)	69.32 (1.74, 2768.92)
Both age over 65 and administration of ceftriaxone prior to VAP	6626.01 (0.00, >10000)	9466,89 (0.00, >10000)
No infection upon admission to the ICU	1.0 (reference)	1.0 (reference)
Both infection upon admission to the ICU and administration of ceftriaxone prior to VAP	796.25 (0.00, >10000)	1205.96 (0.00, >10000)

* Adjusted for age, sex, infection on admission to ICU, hospitalisation in another hospital ward prior to admission to the ICU, age over 65, multi-drug resistance of the causative agent, administration of antibiotics prior to VAP, time elapsed from onset of artificial ventilation to VAP, time elapsed from endotracheal intubation to VAP, use of a central intravenous catheter, causative agent, chronic diseases, emergency admission to the ICU, administration of ceftriaxone prior to VAP, administration of vancomycin prior to VAP, administration of vancomycin for treatment of VAP, administration of ciprofloxacin prior to VAP, administration of meropenem prior to VAP, administration of tigecycline for treatment of VAP, administration of ciprofloxacin for treatment of VAP, administration of piperacillin+tazobactam for treatment of VAP, administration of ampicillin+sulbactam for treatment of VAP†, administration of imipenem for treatment of VAP, administration of amikacin for treatment of VAP, and for combinations of variables shown in the table.

Table 3. Interactions between age over 65 and infection upon admission to the ICU, age over 65 and administration of ceftriaxone prior to VAP, and infection upon admission to the ICU and administration of ceftriaxone prior to VAP.

tration of antibiotics as a part of selective decontamination of the digestive tract (SDD) reduces[21] VAP incidence by over 50% and mortality by approximately 25%, but this effect no longer holds true if antibiotics are administered for a prolonged period of time and in empiric dose regimens, as was the practice at our study site. Therefore, the high mortality observed in our study could be the consequence of an inappropriate use of antibiotics for the prophylaxis of VAP.

To further explore this presumption, we analysed the associations of individual antibiotics administered both for prophylaxis and for treatment of VAP with death. Out of a set of more than 10 different antibiotics, prophylactic administration of only one antibiotic, the third-generation cephalosporin ceftriaxone, was strongly linked to death in the patients with VAP (see Tables 2 and 3). The patients who prophylactically received ceftriaxone had more than

3-times greater risk of death than those who did not receive such prophylaxis ; the risk increased to more than 6 times in patients older than 65 years. This adverse effect of third-generation cephalosporins on mortality was previously shown among other types of patients in ICUs[22,23] and has been explained by the selection of multidrug-resistant bacteria producing extended-spectrum beta-lactamases[24,25]. Although in our study, multi-drug resistance of isolated causative agents was not statistically associatedstatistically with death, more than 90% of our patients in both groups were suffering from VAP caused by multi-drug resistant bacteria. In such a situation, other disabling factors that compromise defence against infection, such as advanced age and additional infection upon admission to the ICU, can add to the negative effects of ceftriaxone and increase the likelihood of death, as was observed in our study.

Assessment of the individual risk of death for each patient who may develop VAP must take into account prophylactic ceftriaxone administration, the presence of infection upon admission to the ICU, and the advanced age of the patient . If one of these factors applies to a given patient's case, he or she deserves special attention and careful selection of antibiotics, both for prophylaxis and for treatment of VAP.

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