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Clinical epidemiology, treatment and prognostic factors of extensively drug-resistant *Acinetobacter baumannii* ventilator-associated pneumonia in critically ill patients

Constantinos Tsioutis, MD, PhD,[1*] Evangelos I. Kritsotakis, MSc, PhD, [2]
Spyridon A. Karageorgos, MD,[1] Soultana Stratakou, MD,[1] Charalambos Psarologakis, MD,[3]
Sofia Kokkini, MD,[3] Prof. Achilleas Gikas, MD, PhD[1]

[1] Department of Internal Medicine / Infectious Diseases, University Hospital of Heraklion, Crete, Greece
[2] School of Health and Related Research, University of Sheffield, Sheffield, UK
[3] Intensive Care Medicine Department, University Hospital of Heraklion, Crete, Greece

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***Corresponding author**
Constantinos Tsioutis,
Department of Internal Medicine / Infectious Diseases,
University Hospital of Heraklion, 71110, Crete, Greece
Tel.: +302810392359, Fax: +302810392359
Email: kostsioutis@gmail.com

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Abstract

Limited data exist regarding prognostic factors and optimal antimicrobial treatment of infections from extensively drug-resistant (XDR) *Acinetobacter baumannii* (AB). This retrospective cohort study included 93 adult patients who developed ventilator-associated pneumonia (VAP) due to XDR-AB in the intensive-care unit of the University Hospital of Heraklion, Greece, from October 2012 to April 2015. XDR-AB isolates were mainly susceptible to colistin (93.5%) and tigecycline (25.8%), whereas 6 (6.5%) strains were pandrug-resistant. Prior to infection, patients had long durations of mechanical ventilation and hospital stay and multiple exposures to antibiotics. Median Charlson comorbidity and APACHE II scores were 2 and 17, respectively. Mortality at 28 days of infection onset was high (34.4%), despite the high rates of active-in-vitro empirical (81.7%) and definitive (90.3%) treatment. Active colistin-based combination therapy (n=55) and monotherapy (n=29) groups had similar 28-day mortality (27.6% vs 30.9%, respectively) and Kaplan-Meier survival estimates over time. In multivariable Cox regression, advanced age (adjusted hazard ratio [aHR] 1.05 per year increase; 95% confidence interval [CI] 1.02 – 1.09), rapidly fatal underlying disease (aHR 2.64; 95% CI 0.98–9.17) and APACHE II score (aHR 1.06 per unit increase; 95% CI 0.99-1.14) were identified as independent predictors of 28-day mortality, but no difference in mortality hazards between the active colistin-based combination therapy and monotherapy groups was produced (aHR 0.88; 95% CI 0.35–2.38). These results support the use of colistin as a first-line agent against VAP in settings where XDR-AB is endemic, but oppose the introduction of colistin-based combination therapy as standard treatment.

Keywords: Acinetobacter; extensively drug-resistant; ventilator-associated pneumonia; antimicrobial resistance; colistin; treatment.

1. Introduction

Ventilator-associated pneumonia (VAP) is a common lethal infection in critical care settings which is also associated with increased morbidity and health care costs [1]. *Acinetobacter baumannii* (AB), a pathogen with an alarming ability to rapidly develop antimicrobial resistance, is a major cause of VAP worldwide [1,2]. The emergence of extensively-drug resistant (XDR) strains that are resistant to all but one or two antibiotic classes and often cause hospital outbreaks has become a serious public health threat [2–6]. However, clinical studies in affected patients are scarce and factors predictive of poor outcome have rarely been investigated [7]. Importantly, limited in vivo data exist on the efficiency of the few therapeutic options available to treat infections from XDR Gram-negative bacteria. Currently, there are suggestions in the literature that combination therapy should be used, which may even include antibiotics to which the causative pathogen demonstrates in vitro resistance [5,8]; but these have been severely criticized [9].

The purpose of this study is to describe the clinical and therapeutic profile of XDR-AB VAP in a cohort of critically ill patients and assess prognostic factors of 28-mortality, with a focus on elucidating the effect of active definitive treatment regimens.

2. Materials and methods

2.1 Setting and study design

A retrospective cohort study was conducted in the adult intensive care unit (ICU) of the University Hospital of Heraklion, from October 2012 to April 2015. This is a 750-bed tertiary-care institution that receives approximately 55,000 admissions per year and serves as a referral hospital for the island of Crete in Greece. The ICU has 12 beds and covers for all

medical and surgical cases. The study was approved by the hospital's Ethics Committee and is reported according to the STROBE recommendations [10].

The study cohort included all adult patients who were mechanically ventilated for more than 48 hours and developed VAP because of XDR-AB. Patients were eligible for inclusion if the infection developed during the ICU stay or were admitted to the ICU for this infection. Only the first episode of XDR-AB VAP was recorded for each patient. Patients with polymicrobial VAP and patients with other previous or concurrent infections were included in the study. Eligible patients were identified by review of clinical culture results as part of the hospital's surveillance programme to identify multidrug-resistant isolates.

2.2 Data collection and definitions

VAP was defined as pneumonia that occurred in a patient at least 48 hours following mechanical ventilation. Pneumonia was defined according to the Centers for Disease Control and Prevention criteria [11]. Patients with no clinical symptoms or radiological evidence of an infiltrate were considered to have colonization and were excluded from the study. Onset of VAP was defined as the date of collection of the first clinical culture that yielded the study organism. The diagnosis of VAP was confirmed by positive quantitative microbial cultures of aspirate: (1) non-protected bronchoscopic specimen cultures $>10^6$ colony forming units (cfu)/mL, (2) specimen cultures obtained by transbronchial aspirate $>10^5$ cfu/mL, or (3) protected bronchoscopic lavage cultures $>10^4$ cfu/mL.

XDR-AB was resistant to all except for two or less classes of antibiotics [4]. Species identification and antibiotic susceptibility testing were performed by the Vitek 2 system (bioMérieux SA, Marcy L'Etoile, France) in accordance with the Clinical and Laboratory Standards Institute standards for all antibiotics except tigecycline [12]. Susceptibility to

tigecycline was performed by the Etest (AB Biodisk, Solna, Sweden). According to the susceptibility breakpoints of Enterobacteriaceae used by the U.S. Food and Drug Administration, an AB organism with an MIC≤2 μg/mL to tigecycline was considered susceptible [13].

Clinical, biological and treatment data were obtained retrospectively from the patients' medical charts and electronic records. Co-morbid conditions were recorded in accordance with the Charlson weighted co-morbidity index [14]. The underlying illnesses at the time of admission in the ICU were classified as rapidly fatal, ultimately fatal, and nonfatal according to the McCabe and Jackson classification [15]. Acute Physiology and Chronic Health Evaluation (APACHE) II scores were measured at the time of ICU admission and at VAP onset [16].

Data on antimicrobial therapy, as selected at the discretion of the attending physicians, were recorded. Treatment given before obtaining susceptibility results was defined as "empirical". Therapy given after the susceptibility data became available was defined as "definitive". An "active" drug was an antibiotic to which XDR-AB was in vitro susceptible. Definitive treatment regimens were classified as monotherapy (treatment with only one in vitro active agent) or combination therapy (treatment with two or more in vitro active agents). According to our institutional guidelines for the administration of last line antibiotics and in the absence of impaired renal function, antibiotic regimens were standardized and administered as follows: colistin as a 9 million IU loading dose followed after 24 hours by 3 million IU every 8 hours; tigecycline 100 mg every 12 hours; high dose prolonged infusion of carbapenems, ie. meropenem 2g over 4 hours every 8 hours or imipenem 1g over 3 hours every 8 hours. Dosages were adjusted to renal function as indicated [17]. Inhaled antibiotics were not regularly administered. The duration of all definitive treatment regimens ranged from 7 to 10 days.

2.3 Statistical analysis

Data were processed and analysed using the SPSS 22 software package (IBM, New York, USA). The main outcome measured was the all-cause mortality within 28 days after the onset of VAP. Patients discharged before day 28 were considered survivors. Mortality was analysed both as a binary outcome (yes/no) and as survival time data with patients discharged before day 28 or hospitalized and alive at day 28 considered censored observations. Survivors and nonsurvivors were compared to identify independent prognostic factors among a set of variables which were chosen a priori based upon clinical judgment and previous studies in different settings. Emphasis was given on elucidating the effect of active definitive treatment (i.e. monotherapy versus combination therapy).

Bivariate associations between categorical variables were assessed using the χ^2 test or Fisher's exact test, whereas the Mann-Whitney U test was used for continuous predictor variables. In the survival analysis, Kaplan-Meier estimates of the probability of survival were obtained and survival curves were compared between groups using the log rank test. A multivariable Cox proportional hazards model was used to identify prognostic factors independently associated with 28-day mortality. To avoid excluding potentially useful prognostic factors, the purposeful approach for selecting variables was used [18]. Variables that were identified from univariate analysis as statistically significant at a conservative alpha level of 0.25 were initially assessed using backward stepwise selection (exclusion/inclusion: $P \leq 0.05/P > 0.10$, respectively) with the likelihood-ratio test. Variables that did not retain statistical significance at the usual significance level of 0.05 were tested for confounding by adding them one at a time to the model and examining their impact on the effect estimate for the treatment variable. Those causing substantial confounding (change in the hazard ratio greater than 10%) were retained in the final model. Empirical and definitive treatment, being

predictor variables of primary clinical interest, were forced into the model. Confidence intervals were calculated by the profile likelihood method. Collinearity was assessed by examining pairwise correlations and variance inflation factors. Tests of time-covariate interactions were used to verify the PH assumption and bootstrap was employed to assess the validity of standard errors in the final cox regression model.

Patients who died within 48h after the onset of infection and those who received definitive treatment with no active drug were excluded from the analysis of prognostic factors. Patients with polymicrobial infection were included in the analysis only if they had received antibiotics active in vitro against the other co-infecting organism(s).

3. Results

Of the 1333 adult patients who were admitted to the ICU during the 31-month study period, 124 (9.3%) patients had XDR-AB isolated in the aspirate. A total of 93 (75%) of those patients fulfilled the diagnostic criteria for VAP and were included in the study. The hospital-wide incidence rate of XDR-AB VAP was 2.6/10,000 patient-days and 90.3/10,000 ICU-days.

3.1 Baseline characteristics on ICU admission

The mean age of the patients was 59.7 ± 18.3 years (median, 62 years; range, 17 to 92 years) and 71 (76.3%) patients were male. Admission diagnoses to the ICU were acute respiratory failure in 29 patients (31.2%), multiple trauma (21 patients, 22.6%), septic shock - multiorgan failure (14 patients; 15.1%), cerebral haemorrhage (11 patients; 11.8%) postoperative observation (7 patients; 7.5%), acute neurological complications (6 patients; 6.5%) and post-resuscitation syndrome (5 patients; 5.4%). The most frequent underlying diseases were

diabetes mellitus in 24 (25.8%) patients, malignancy in 19 (20.4%) patients, and chronic pulmonary disease in 14 (15.1%) patients. The mean Charlson comorbidity index was 2.7 ± 2.7 (median, 2; interquartile range, 0-5), mean APACHE II score was 19.0 ± 7.5 (median, 17; interquartile range, 14-23), and 84.9% of the patients were classified as having a rapidly fatal or ultimately fatal underlying disease.

3.2 Clinical characteristics of infections and empirical treatment

Prior to the onset of XDR-AB VAP, the mean duration of mechanical ventilation was 13.6 ± 14.2 days (median, 10; interquartile range 6-15.5) and the mean length of stay in the ICU was 13.5 ± 14.3 days (median, 11; interquartile range 5.5-15.5). Eighty-four patients (90.3%) had a history of antibiotic use in the 30 days preceding the onset of VAP, which most frequently included b-lactam/b-lactamase inhibitor combinations (45 patients), carbapenems (43 patients), glycopeptides (25 patients), colistin (23 patients) and cephalosporins (22 patients). During the XDR-AB VAP, ten patients (10.8%) experienced septic shock, 14 (15.1%) developed severe sepsis and 8 (8.6%) developed multi-organ failure.

Susceptibility testing showed that all XDR-AB strains were non-susceptible to carbapenems and aminoglycosides, 69 strains (74.2%) were non-susceptible to tigecycline, and 6 strains (6.5%) were non-susceptible to colistin; all of the latter were pandrug-resistant, i.e. resistant to all antibiotics tested.

For empirical treatment of XDR-AB VAP, 76 (81.7%) patients received at least one active drug, while 17 (18.3%) patients received no active empirical drug. Empirical regimens were largely colistin-based (77 patients; 83.7%), including colistin alone (22 patients; 23.7%), or colistin combined with carbapenem (29 patients; 31.2%), with tigecycline (22 patients; 23.7%), or with carbapenem and tigecycline (4 patients; 4.3%).

3.3 Definitive antimicrobial treatment and treatment outcomes

Definitive antimicrobial treatment was administered 48 to 72 hours after the onset of VAP. Five patients (5.4%) were infected with pandrug-resistant AB and received therapy with no active drug. Four patients (4.3%) died within 48h after the onset of VAP, before the susceptibility results were available, including one patient infected with pandrug-resistant AB. In total, 84 (90.3%) subjects received at least one XDR-AB-active drug: 29 patients (34.5%) received combination therapy comprising two active antibiotics which were colistin plus tigecycline. The remaining 55 patients (65.6%) received monotherapy with active colistin. All patients with polymicrobial VAP received at least one antibiotic which was active against the other co-infecting organism(s).

The monotherapy and combination therapy groups were comparable in terms of ICU admission diagnosis, comorbidity index, severity of underlying disease, APACHE II score, length of stay before infection, and duration of mechanical ventilation before infection (Table 1). However, younger patients and those infected by a strain susceptible to tigecycline were more likely to have received combination therapy. There were 32 deaths (34.4%) within 28 days of the onset of XDR-AB VAP. Combination therapy and monotherapy groups had similar 28-day mortality rates (27.6% vs 30.9%, respectively; p=0.751) and Kaplan-Meier survival estimates over time (p=0.582), as seen in Fig. 1. There was no significant variation in 28-day mortality rates (Table 2) or survival times for the different regimens used for definitive treatment (Fig. 2).

3.4 Prognostic factors of 28-day mortality

The effects of patient-, infection-, and treatment-related factors on 28-day mortality were assessed in a univariate Cox regression analysis (Table 3). Adverse outcome appeared to be more likely among females and patients with advanced age, higher Charlson comorbidity index, higher APACHE II score at onset of infection, and infection complications. Empirical treatment with at least one active antibiotic and use of combination therapy as opposed to monotherapy for definitive treatment did not appear to have any apparent association with poor outcome. In multivariable analysis, advanced age (adjusted HR = 1.05 per year increase, 95%CI 1.02 – 1.09; p=0.001) and rapidly fatal disease (adjusted HR = 2.64. 95%CI 0.98 – 9.17; p=0.054) were identified as independent predictors of adverse outcome, while length of hospital stay before infection onset was independently predictive of survival (adjusted HR = 0.96 per day increase, 95%CI 0.92 – 1.00; p=0.035). Apache II score at the onset of infection was retained in the model as an important confounder. Neither the empirical nor the definitive treatment variables showed a significant association with 28-day mortality.

4. Discussion

In line with previous research [19–21], the risk profile of patients who developed XDR-AB VAP in this study comprised of high disease severity, long hospital and ICU stay, long duration of mechanical ventilation, and prior exposure to several antibiotics. Reported mortality rates have been high, ranging between 38% and 46% despite appropriate treatment [7,22–25]. Similarly in this study, mortality reached 34% at 28 days following the onset of VAP despite the high rates of appropriate empirical and definitive treatment. In vitro inactive therapy presented even higher mortality: four of the six patients (67%) in this study who were infected with a pandrug resistant strain died, while in another study all patients with pneumonia due to XDR-AB who received a non-active antibiotic died within 28-days of infection onset [7]. The median APACHE II score of our patients at the time of infection

corresponds to an expected mortality rate of 12-24% [16]. Therefore the true attributable mortality of XDR-AB infections remains high, even when empirical and definitive treatment regimens are in vitro active.

Colistin is widely used for the treatment of multidrug-resistant AB VAP [26] and is a recommended treatment option for pneumonia caused by multidrug-resistant AB [27]. XDR-AB isolates remain largely susceptible to colistin in most settings [25], but excessive or inadequate use of colistin may be associated with the emergence of colistin-resistant strains [28]. On the other hand, high resistance rates are increasingly reported for other last-line antibiotics, such as tigecycline, not only in AB, but also in Enterobacteriaceae [28,29]. In our study, a notable percentage of patients had already received colistin in the month prior to VAP but only a small, though alarming, proportion of XDR-AB isolates (6.5%) exhibited resistance to colistin. In contrast, three quarters of XDR-AB isolates were non-susceptible to tigecycline and more than a third exhibited an MIC>8 μg/mL. Similarly high rates of non-susceptibility to tigecycline have been previously reported in other studies of XDR-AB infections [30,31], while the development of resistance during treatment has also been documented [30]. Although few, new antibiotics that are active against gram-negative bacteria have been recently introduced into clinical practice, but clinical experience with infections from XDR pathogens is still limited [28].

The present study supports the use of intravenous colistin as an effective treatment of XDR-AB VAP, but our analysis showed that colistin combinations (with carbapenems and/or tigecycline) did not differ from colistin monotherapy in terms of mortality risk. Studies comparing the effectiveness of colistin combinations to colistin monotherapy in XDR-AB infections are scarce and conflicting. In a multicenter randomized controlled trial comparing colistin-rifampicin combinations to colistin monotherapy in XDR-AB infections (the majority of which were VAP), no difference was found in 30-day mortality, infection-related deaths,

or length of stay between the two treatment arms [24]. On the other hand, an observational multicentre study of XDR-AB bloodstream infections suggested that colistin combinations had significantly lower in-hospital mortality and higher microbiological eradication rates than colistin monotherapy [22]. Even more perplexing is the fact that other studies report conflicting results regarding the impact of different colistin combinations on patient survival. In one study, combinations of colistin with sulbactam, tigecycline or high-dose carbapenems had comparable 28-day survival rates which were significantly higher than those in the patient group that received non-active antibiotics [7]. Another study involving different types of infection due to XDR-AB (most of which were VAP) in solid organ transplant patients, reported that colistin-carbapenem combinations had significantly higher 28-day survival rate compared to other colistin combinations and other antibiotics [23]. Discrepancies between different studies may have resulted from heterogeneity in microbiological properties, infection types and antibiotic dosing schemes [5,23], but may also have arisen because of small sample sizes and a high potential for confounding and selection bias [9].

Important implications from promoting combination therapy as a standard of care should also be emphasized. We have previously demonstrated the role of treatment and duration of treatment with combinations of fluoroquinolones and carbapenems (used coincidently or sequentially) in increasing the risk of subsequent infection with carbapenem-resistant *Klebsiella pneumoniae* [32]. Unnecessary use of combination therapy may also result in increased healthcare costs, selection pressure in hospitals where multidrug-resistant or XDR pathogens are already established, persistence of colonization, and increased risk of side effects or other adverse events such as *Clostridium difficile* infection [9,24].

There are limitations and strengths in this study that should be acknowledged. First of all, the fact that this was a single-centre study may limit the generalizability of our results. Secondly, despite the fact that the electronic records in our ICU were complete and missing

values were not an issue, the retrospective nature of the study did not allow us to safely document antibiotic toxicity. Another issue is the subjectivity in the diagnosis of VAP: the nearly complete randomness of the level of agreement between observers has been previously demonstrated [33], while in another study, interobserver agreement was low for diagnosis of VAP compared to other infection types in the ICU [34]. Requiring a combination of clinical, microbiological and radiological parameters to confirm diagnosis increases the likelihood of variability, but confidence in the diagnosis of VAP is higher when specific clinical signs are present [34,35]. In our ICU, in an effort to limit variability in the diagnostic procedure, all infections are discussed between clinical staff and infectious diseases physicians.

On the other hand, this study is one of the largest series of XDR-AB infections reported to date. The fact that we focused exclusively on XDR-AB VAP is a strong point in this study, as AB is among the most frequent causes of VAP worldwide. Further strengths in this study include the high percentage of active empirical treatment which limits the potential for a confounding effect on definitive therapy, and the use of optimal intravenous antibiotic dosing. Indeed, our patients received high dose and prolonged infusion of carbapenems; a loading dose of colistin; and high daily dose of tigecycline. Compared to conventional doses, these dosing schemes have been confirmed to be more efficacious in achieving the desired pharmacokinetic targets and result in higher rates of clinical response [28,29]. Moreover the main treatment groups compared in this study had similar baseline characteristics and were well balanced in important confounders, including disease severity and comorbidity indices upon admission in the ICU, length of stay and duration of mechanical ventilation before the onset of infection and prognosis at the onset of the infection as measured by the APACHE II score.

5. Conclusion

The risk profile for XDR-AB VAP is characterized by high disease severity and comorbidity indexes, long hospital and ICU stay, long duration of mechanical ventilation and prior exposure to several antibiotics. Mortality following XDR-AB VAP remains high even when empirical and definitive treatment regimens are active in vitro. Intravenous colistin is an effective first-line antimicrobial against VAP in settings where XDR-AB is endemic. However, colistin-based combination therapy does not appear to offer improved survival compared to colistin monotherapy, opposing the introduction of combination therapy as standard treatment against XDR-AB VAP.

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Table 1

Characteristics of patients with extensively drug-resistant *A. baumannii* ventilator-associated pneumonia according to definitive active treatment regimen.

Variable	Monotherapy (n=55)[d,e]	Combination therapy (n=29)[d,f]	p-value
Age (years), median (IQR)	66.0 (55.0 – 77.0)	57.0 (38.0 – 68.0)	0.018
Female sex, no. (%)	14 (25.5)	5 (17.2)	0.392
ICU admission diagnosis, no. (%)			0.518
Septic shock - Multiorgan failure	8 (14.5)	3 (10.3)	
Acute respiratory failure	20 (36.4)	7 (24.1)	
Acute trauma	11 (20.0)	9 (31.0)	
Neurosurgery	11 (20.0)	5 (17.2)	
Other	5 (9.1)	5 (17.2)	
Charlson comorbidity index, median (IQR)	3.0 (0.0- 5.0)	1.0 (0.0 – 4.0)	0.159
Rapidly fatal underlying disease, no. (%)[a]	36 (65.5)	24 (82.8)	0.095
Length of hospital stay (days), median (IQR)[b]	14.0 (8.0 – 25.0)	13.0 (9.0 – 18.0)	0.696
Length of ICU stay (days), median (IQR)[b]	11.0 (6.0 – 16.0)	12.0 (7.0 – 14.0)	0.578
Duration of mechanical ventilation (days), median (IQR)[b]	11.0 (6.0 – 15.0)	10.0 (7.0 – 16.0)	0.966
APACHE II score, median (IQR)[c]	20.0 (12.0 – 22.0)	19.0 (15.0 – 21.0)	0.607
Polymicrobial infection, no. (%)	26 (47.3)	16 (55.2)	0.491
Secondary bacteraemia, no. (%)	12 (21.8)	3 (10.3)	0.192
Concurrent infection, no. (%)	5 (9.3)	3 (10.3)	0.852
In vitro susceptibility to antibiotics, no. (%)			
Imipenem-susceptible isolate	55 (100)	29 (100)	
Tigecycline-susceptible isolate	10 (18.2)	12 (41.4)	0.024
Colistin-susceptible isolate	55 (100)	29 (100)	

IQR, interquartile range; ICU, intensive care unit; APACHE, Acute Physiology and Chronic Health Evaluation.

a. Measured at time of admission in the ICU according to the McCabe-Jackson classification.

b. Measured before the onset of infection.

c. Measured at the onset of infection.

d. Excluding patients infected with a pandrug-resistant strain and those who died within 48 h of infection onset.

e. Treatment with one in vitro active agent.

f. Treatment with two or more in vitro active agents.

Table 2

All cause 28-day mortality of patients with extensively drug-resistant *A. baumannii* ventilator-associated pneumonia according to definitive treatment regimen.

Antibiotic regimen	No. of patients[a]			Mortality
	Total	Survived	Died	%
Active combination therapy				
Colistin + tigecycline	29	21	8	27.6
Active monotherapy	55	38	17	30.9
Colistin		15	8	30.9
Colistin + carbapenem		15	5	34.8
Colistin + tigecycline		5	3	25.0
Colistin + tigecycline + carbapenem		3	1	37.5
No active agent	6[b]	2	4	66.7

a. Three patients died within 48 h after infection onset before antibiotic susceptibility results were available and were excluded from analysis.

b. All six patients were infected with panresistant *Acinetobacter baumannii*.

Table 3

Analysis of factors associated with all-cause 28-day mortality in 84 patients with extensively drug-resistant *A. baumannii* ventilator-associated pneumonia.

Variable	Survived (n=59)[e]	Died (n=25)[e]	Unadjusted effect[f]		Adjusted effect[g]	
			Hazard Ratio (95% CI)	p-value	Hazard Ratio (95% CI)	p-value
Age (years), median (IQR)	57.0 (41.0 – 72.0)	74.0 (68.0 – 78.0)	1.05 (1.02 - 1.08)	<0.001	1.05 (1.02 – 1.09)[h]	0.001
Female sex, no. (%)	10 (16.9)	12 (36.0)	2.75 (1.21 - 6.26)	0.023		
ICU admission diagnosis, no. (%)				0.338		
Septic shock - Multiorgan failure	8 (13.6)	3 (12.0)	1.57 (0.26 – 9.40)			
Acute respiratory failure	17 (28.8)	10 (40.0)	2.28 (0.50 – 10.40)			
Acute trauma	17 (28.8)	3 (12.0)	0.84 (0.14 – 5.04)			
Neurosurgery	9 (15.3)	7 (28.0)	2.64 (0.55 – 12.69)			
Other	8 (13.6)	2 (8.0)	Ref.			
Charlson comorbidity index, median (IQR)	16.0 (13.0 – 20.0)	21.0 (16.0 – 28.0)	1.25 (1.08 - 1.44)	0.002		
Rapidly fatal underlying disease, no. (%)[a]	39 (66.1)	21 (84.0)	2.19 (0.75 – 6.39)	0.117	2.64 (0.98 – 9.17)	0.054
Length of hospital stay (days), median (IQR)[b]	14.0 (8.0 – 24.0)	12.0 (10.0 – 18.0)	0.98 (0.94 - 1.01)	0.137	0.96 (0.92 – 1.00)[h]	0.035
Length of ICU stay (days), median (IQR)[b]	11.0 (6.0 – 16.0)	11.0 (5.0 – 13.0)	0.98 (0.94 - 1.02)	0.168		
Duration of mechanical ventilation (days), median (IQR)[b]	11.0 (6.0 – 16.0)	10.0 (7.0 – 13.0)	0.98 (0.94 - 1.02)	0.188		

APACHE II score, median (IQR)[c]	19.0 (11.0 – 22.0)	21.0 (19.0 – 25.0)	1.07 (1.01 - 1.13)	0.020	1.06 (0.99 – 1.14)[h]	0.072
Polymicrobial infection, no. (%)	30 (50.8)	12 (48.0)	0.86 (0.39 - 1.89)	0.706		
Secondary bacteraemia, no. (%)	12 (20.3)	3 (12.0)	0.54 (0.16 - 1.81)	0.284		
Concurrent infection, no. (%)	4 (6.8)	4 (16.0)	1.58 (0.54 - 4.61)	0.426		
Infection complication, no. (%)	15 (25.4)	13 (52.0)	2.48 (1.13 - 5.45)	0.025		
Active empirical treatment, no. (%)	53 (89.8)	22 (88.0)	0.83 (0.25 – 2.78)	0.770	1.03 (0.32 – 4.57)	0.967
Active definitive treatment, no. (%)[d]				0.581		0.791
Monotherapy	38 (64.4)	17 (68.0)	Ref.		Ref.	
Combination therapy	21 (35.6)	8 (32.0)	0.79 (0.34 - 1.84)		0.88 (0.35 – 2.38)	

IQR, interquartile range; ICU, intensive care unit; APACHE, Acute Physiology and Chronic Health Evaluation; HR, hazard ratio; CI, confidence interval; Ref., reference category.

a. Measured at time of admission in the ICU according to the McCabe-Jackson classification.

b. Measured before the onset of infection.

c. Measured at the onset of infection.

d. Patients who received at least one active antibiotic.

e. Excludes patients infected with a pandrug-resistant strain and those who died within 48 h of infection onset.

f. Univariate Cox proportional hazards regression

g. Multivariable Cox proportional hazards regression. Likelihood ratio test = 25.205, df = 6 $p<0.001$.

h. Hazard ratio corresponds to a unit increase in the continuous scale of the variable.

Fig. 1. Kaplan-Meier survival estimates for death at 28 days after the onset of extensively drug-resistant *Acinetobacter baumannii* ventilator-associated pneumonia according to type of treatment: combination therapy (solid line) versus monotherapy (dashed line). P = 0.582 (log-rank test).

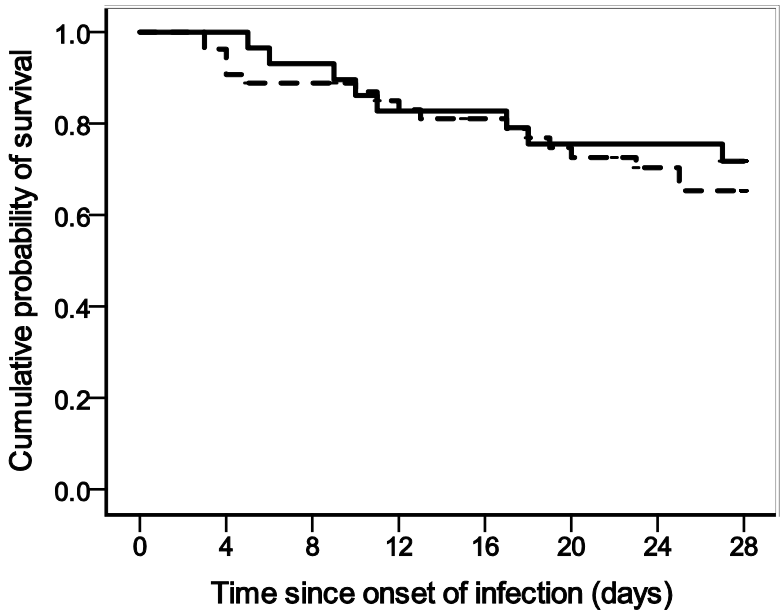

Fig. 2. Kaplan-Meier survival estimates for death at 28 days after the onset of extensively drug-resistant *Acinetobacter baumannii* ventilator-associated pneumonia according to treatment regimen by log-rank test: (i) Active colistin vs active colistin + inactive carbapenem, P=0.580; (ii) Active colistin vs active colistin + inactive tigecycline, P=0.852; (iii) Active colistin vs active colistin + active tigecycline, P=0.455; (iv) Active colistin + inactive carbapenem vs active colistin + inactive tigecycline, P=0.740; (v) Active colistin + inactive carbapenem vs active colistin + active tigecycline, P=0.976; (vi) Active colistin + inactive tigecycline vs active colistin + active tigecycline, P=0.701.