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MAJOR ARTICLE

The Association Between Empirical Antibiotic Treatment and Mortality in Severe Infections Caused by Carbapenem-resistant Gram-negative Bacteria: A Prospective Study

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Background. Empirical colistin should be avoided. We aimed to evaluate the association between covering empirical antibiotics (EAT) and mortality for infections caused by carbapenem-resistant gram-negative bacteria (CRGNB).

Methods. This was a secondary analysis of a randomized controlled trial, including adults with bloodstream infections, pneumonia, or urosepsis caused by CRGNB. All patients received EAT followed by covering targeted therapy. The exposure variable was covering EAT in the first 48 hours. The outcome was 28-day mortality. We adjusted the analyses by multivariable regression analysis and propensity score matching.

Results. The study included 406 inpatients with severe CRGNB infections, mostly *Acinetobacter baumannii* (312/406 [77%]). Covering EAT was given to 209 (51.5%) patients, mostly colistin (n = 200). Patients receiving noncovering EAT were older, more frequently unconscious and dependent, carrying catheters, and mechanically ventilated with pneumonia. Mortality was 84 of 197 (42.6%) with noncovering vs 96 of 209 (45.9%) with covering EAT ($P = .504$). Covering EAT was not associated with survival in the adjusted analysis; rather, there was a weak association with mortality (odds ratio [OR], 1.37; 95% confidence interval [CI], 1.02–1.84). Results were similar for colistin monotherapy and colistin-carbapenem combination EAT. In the propensity score–matched cohort (n = 338) covering antibiotics were not significantly associated with mortality (OR, 1.42; 95% CI, .91–2.22). Similar results were obtained in an analysis of 14-day mortality.

Conclusions. Empirical use of colistin before pathogen identification, with or without a carbapenem, was not associated with survival following severe infections caused by CRGNBs, mainly *A. baumannii*.

Keywords. appropriate empirical antibiotics; multidrug-resistant bacteria; carbapenemase-producing; colistin; gram-negative bacteria.

The importance of covering empirical antibiotic treatment in decreasing mortality [1–4] and shortening hospital stay [5] in severe infections has been well established. The increasing prevalence of multidrug-resistant (MDR) bacteria poses a challenge to covering empirical antibiotic prescription [6]. Predicting pathogens' susceptibilities becomes very difficult in healthcare-associated infections, but also in community-acquired infections with the trickle of MDR bacteria to the community. Coupled with the difficulty in deciding for whom coverage targeting carbapenem-resistant is needed is the paucity and doubtful effectiveness of antibiotics available for the treatment of these infections. These mostly include colistin or polymyxin B and aminoglycosides, whose efficacy is considered inferior to that of β-lactams and which are nephrotoxic [7, 8]. New US Food and Drug Administration–approved antibiotics, such as ceftazidime-avibactam, meropenem-vaborbactam, or ceftolozane-tazobactam, lack a spectrum of coverage inclusive of all the different carbapenem-resistant gram-negative bacteria (CRGNBs) needed for empirical treatment.

The physician, who strives primarily to achieve covering empirical treatment, opts usually toward broad-spectrum antibiotics, usually combination therapy [9]. This induces selective pressure, creating a vicious cycle of MDR selection and further antibiotic use. Defining whether empirical treatment

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with currently available antibiotics against CRGNBs, primarily colistin, is beneficial to patients is important to direct the use of these drugs before documentation of a CRGNB infection. Our study aims to assess the association between covering empirical treatment, primarily with colistin, and survival in CRGNB infections.

METHODS

Study Design

This is a secondary analysis of a randomized controlled trial (RCT) [10], enrolling patients from October 2013 to January 2017 at the following centers: Monaldi Hospital in Naples, Italy; Laikon and Attikon Hospitals in Athens, Greece; Sourasky Medical Center in Tel Aviv, Rabin Medical Center, Beilinson Hospital in Petah-Tikva, and Rambam Health Care Campus in Haifa, Israel. Data collection was planned to allow this analysis, including prospective documentation of the in vitro coverage of empirical antibiotic treatment using uniform definitions. The study was approved by the ethics committees of all participating hospitals.

Participants

We included adult inpatients ≥18 years with bacteremia, hospital-acquired pneumonia, or ventilator-associated pneumonia and urosepsis caused by carbapenem-nonsusceptible gram-negative bacteria: *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, or any Enterobacteriaceae. We included each patient only once in the study. Only patients who survived until targeted therapy were included in this analysis, since all received at least 1 dose of covering targeted therapy as part of the RCT. Complete inclusion and exclusion criteria were previously published [11].

Variables

The exposure variable was covering empirical antibiotic treatment, defined as that given in the first 48 hours after culture taking and before reporting of final culture results and found a posteriori to be susceptible in vitro to the antibiotics used. In sensitivity analyses we assessed covering empirical antibiotics in the first day (24 hours) after culture taking and covering empirical therapy using colistin-carbapenem combination therapy. The outcome assessed was all-cause mortality at 28 days. In a secondary analysis, we assessed 14-day mortality. Data were ascertained bedside and from patients' written and electronic records and microbiology laboratory records prospectively. We considered additional variables potentially associated with 28-day mortality, including the clinical site, patient demographics, background conditions including the revised Charlson comorbidity index, sepsis severity, including the Sequential Organ Failure Assessment (SOFA) score, laboratory tests including renal function, blood count, and albumin levels, devices present at infection onset, and all antibiotics used from onset of treatment until day 28.

Microbiology Methods

Pathogen identification and antibiotic susceptibilities were performed locally in each hospital using VITEK-2 or PHOENIX systems. Carbapenem nonsusceptibility was defined as minimal inhibitory concentration (MIC) >2 mg/L for imipenem and meropenem. Colistin susceptibility was assessed using Etests in all study centers alone or for confirmation of the semiautomated system results. In one center in Greece, microbroth dilution was used to confirm results for MIC ≥1 mg/L. Colistin susceptibility was defined as MIC ≤2 mg/L for *Acinetobacter* species and Enterobacteriaceae and ≤4 mg/L for *Pseudomonas* species.

Sample Size

Assuming a death rate of 45% with covering empirical antibiotics, our sample of 406 patients had a power of >80% with significance of $\alpha = .05$ to detect a difference of at least 17% in mortality between patients who received covering empirical treatment and those who did not.

Statistical Analysis

We compared patients prescribed covering vs noncovering empirical antibiotics and survivors vs deceased. Categorical variables were compared with a χ^2 test and continuous variables using *t* test or Mann-Whitney *U* test according to their distribution. Confounders and other risk factors for mortality found significant on univariate analysis and noncorrelated were entered into a multivariable logistic regression. Predictive performance of the model was assessed using the area under the receiver operating characteristic curve (AUC). Odds ratios (ORs) with 95% confidence intervals (CIs) are reported. In addition, we conducted a propensity score (PS)–matched analysis. A PS was generated for each patient from a regression analysis predicting prescription of covering or noncovering empirical antibiotic treatment. We matched patients given covering with those given noncovering treatment by their PS, comparing mortality between groups in the PS-matched cohort. The PS was generated without replacement and with a caliper of 0.1. Analyses were conducted using SPSS version 23 software.

RESULTS

All 406 patients included in the study received antibiotics empirically and noncovering empirical treatment was prescribed to 197 (48.5%). Colistin was the empirical treatment in 200 of 209 patients classified as having received covering therapy and was the only in vitro covering antibiotic in all cases. Carbapenems were combined with colistin empirically in 99 of 200 (49.5%) patients receiving covering empirical treatment (Figure 1). Nine patients received sulfamethoxazole-trimethoprim, tigecycline, ampicillin-sulbactam, minocycline, or an aminoglycoside (5 patients) as covering empirical treatment.

Factors Associated With Noncovering Empirical Treatment

Prescription of noncovering empirical treatment was associated with older age, being female, and with dependent functional

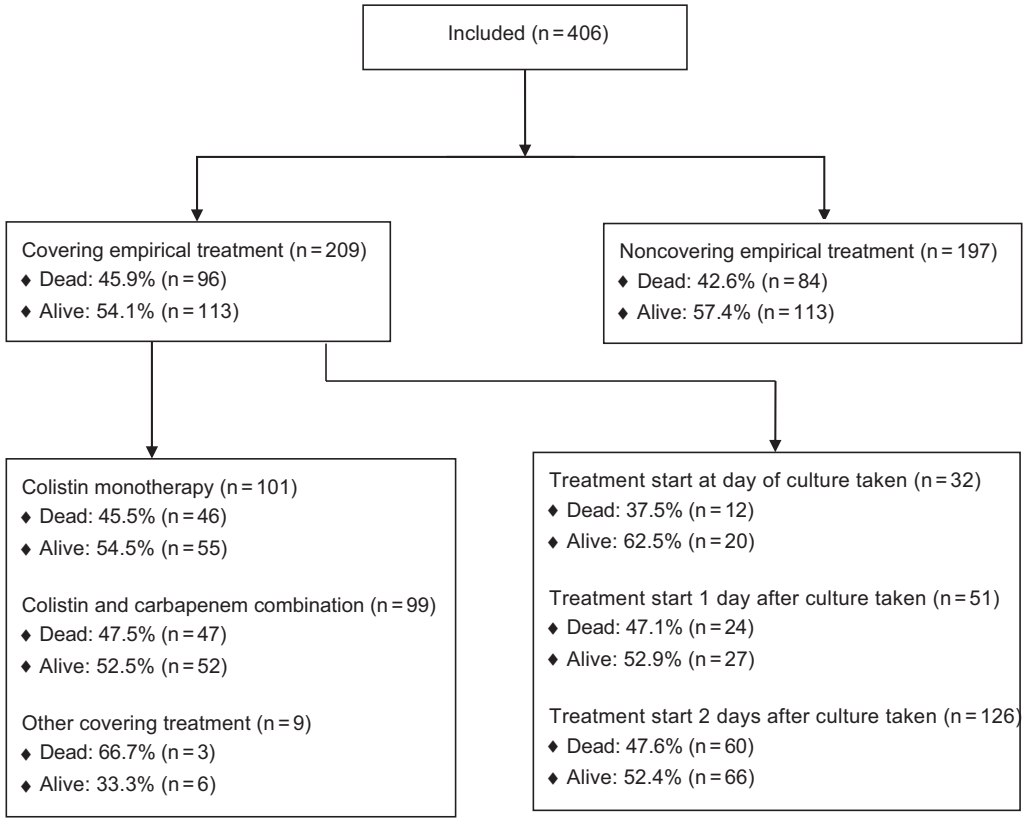

Figure 1. Patient flow and mortality by time to covering treatment and colistin alone or combined with carbapenem.

capacity before infection onset (Table 1). A set of variables reflecting that mechanically ventilated patients were at higher risk for noncovering empirical treatment included invasive ventilation, presence of urinary catheters and nasogastric tube, and pneumonia as the type of infection. Known colonization with CRGNB before infection onset and bloodstream infections (BSIs) were associated with covering empirical treatment. In the study centers, patients were mechanically ventilated also outside the intensive care unit (ICU) and acquisition of the infection in the ICU was not associated with empirical treatment appropriateness. Covering empirical treatment was given to 48.9% (132/270) of patients in Israel, 64.5% (49/76) of patients in Greece, and 46.7% (28/60) of patients in Italy (Table 1). None of the variables we collected reflecting sepsis severity were associated with the prescription of covering empirical treatment. Significant variables were used to construct the propensity score for noncovering empirical antibiotic treatment. The score had acceptable prediction (AUC, 0.71; 95% CI, .66–.76).

Risk Factors for 28-day Mortality

Of 209 patients prescribed covering empirical antibiotics, 96 (45.9%) died, compared with 84 of 197 (42.6%) of patients prescribed noncovering therapy (P = .504). Stratifying covering therapy by time, similar results were observed when covering therapy was prescribed within 24 hours of culture taking. When separating empirical monotherapy (49/110 deaths [44.5%]) and colistin-carbapenem combination therapy (47/99 deaths [47.5%]), results were similarly nonsignificant (Table 2). Among patients with bacteremia, 55 of 112 (49.1%) of patients receiving covering antibiotics died compared with 24 of 61 (39.3%) of patients receiving noncovering empirical treatment (P = .218).

The confounders identified, associated both with noncovering empirical antibiotic treatment and mortality, included age, dependent functional capacity, invasive ventilator support at the day of culture taking, nasogastric tube, albumin levels, and known colonization with CRGNB. The direction of all these factors explained a baseline survival advantage to the patients receiving covering empirical treatment who were younger, more independent, etc. An opposite direction of factors associated with survival that were more prevalent among patients prescribed noncovering empirical treatment included being cared for in Greece and receiving a hemodynamic support at onset of infection. Other risk factors are shown in Table 2.

Empirical treatment and significant risk factors for mortality were included in the multivariate analysis, except for the presence of a nasogastric tube, which was correlated with mechanical ventilation (Table 3). Adjusted to other risk factors for mortality and country, covering empirical antibiotic treatment was not associated with survival; rather, there was a weak association with mortality (OR, 1.372; 95% CI, 1.022–1.843).

Table 1. Factors Associated With Receiving Covering Empirical Treatment

Factor	Covering Empirical Treatment (n = 209)	Noncovering Empirical Treatment (n = 197)	*P* Value for Covering vs Noncovering
Age, mean ± SD	63.47 ± 17.32	68.33 ± 15.85	.003
Female sex	64 (30.6)	87 (44.2)	.005
BMI, kg/m^2, mean ± SD	27.370 ± 6.34 (n = 204)	27.385 ± 5.22 (n = 190)	.979
Arrived from home	144 (68.9)	132 (67)	.683
Country			.04
Israel	132 (63.2)	138 (70.1)	
Greece	49 (23.4)	27 (13.7)	
Italy	28 (13.4)	32 (16.2)	
Dependent functional capacity before infection onset	166 (79.4)	180 (91.4)	.001
Congestive heart failure	45 (21.5)	47 (23.9)	.576
Dementia	18 (8.6)	22 (11.2)	.388
Pulmonary disease	53 (25.4)	38 (19.3)	.143
Active malignancy			.118
None	169 (80.9)	165 (83.8)	
Solid	29 (13.9)	29 (14.7)	
Hematological	11 (5.3)	3 (1.5)	
Liver disease			.721
None	200 (95.7)	186 (94.4)	
Mild	3 (1.4)	5 (2.5)	
Severe	6 (2.9)	6 (3.0)	
Diabetes mellitus with end organ damage	40 (19.1)	50 (25.4)	.130
Renal disease	36 (17.2)	43 (21.8)	.242
Total Charlson score, median (IQR)	2 (0–3)	2 (1–3)	.327
SOFA score on day of onset, median (IQR)	5 (3–8)	6 (4–8)	.202
Creatinine (mg/dL) at culture taken day, median (IQR)	1.03 (0.69–1.50)	0.86 (0.60–1.75)	.293
Albumin (g/dL) at day of culture taking, median (IQR)	2.47 (2.00–2.80)	2.20 (1.90–2.80)	.069
WBC (×10^9/L) at day of culture taking, median (IQR)	13.01 (9.28–17.84) (n = 208)	12.2 (8.81–16.23) (n = 196)	.160
Systolic blood pressure (mm Hg) at culture taken day, mean ± SD	107.82 ± 21.11 (n = 209)	110.65 ± 20.62 (n = 196)	.249
Immunosuppression	35 (16.7)	26 (13.2)	.317
Hemodynamic support at culture taken day	46 (22.0)	29 (14.7)	.059
Invasive ventilator support at culture taken day	124 (59.3)	140 (71.1)	.013
Normal consciousness	92 (44.0)	68 (34.5)	.050
Arterial line	84 (40.2)	67 (34.0)	.198
Urine catheter	174 (83.3)	180 (91.4)	.014
Central line	114 (54.5)	111 (56.3)	.715
Nasogastric tube	136 (65.1)	149 (75.6)	.020
Acquisition in ICU	78 (37.3)	70 (35.5)	.708
Known colonization	59 (28.2)	37 (18.8)	.025
Recent surgery	54 (25.8)	60 (30.5)	.301
Type of bacteria			.522
Acinetobacter	159 (76.1)	153 (77.7)	
Enterobacteriaceae (*Klebsiella*)	41 (19.6)	32 (16.2)	
Pseudomonas/other	9 (4.3)	12 (6.1)	
Type of clinical infection			<.001
BSI	112 (53.6)	61 (31.0)	
VAP/HAP	77 (36.8)	105 (53.3)	
Probable VAP	8 (3.8)	17 (8.6)	
UTI	12 (5.7)	14 (7.1)	

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: BMI, body mass index; BSI, bloodstream infection; HAP, hospital-acquired pneumonia; ICU, intensive care unit; IQR, interquartile range; SD, standard deviation; SOFA, Sequential Organ Failure Assessment; UTI, urinary tract infection; VAP, ventilator-associated pneumonia; WBC, white blood cell.

Table 2. Factors Associated With 28-day Mortality

Factor	Dead (n = 180)	Alive (n = 226)	*P* Value for Dead vs Alive
Age, mean ± SD	70.27 ± 14.30	62.29 ± 17.78	<.001
Female sex	71 (39.4)	80 (35.4)	.402
BMI, kg/m^2, mean ± SD	27.55 ± 6.03 (n = 175)	27.24 ± 5.66 (n = 219)	.600
Arrived from home	114 (63.3)	162 (71.7)	.073
Country			.051
Israel	121 (67.2)	149 (65.9)	
Greece	26 (14.4)	50 (22.1)	
Italy	33 (18.3)	27 (11.9)	
Dependent functional capacity	166 (92.2)	180 (79.6)	<.001
Congestive heart failure	56 (31.1)	36 (15.9)	<.001
Dementia	21 (11.7)	19 (8.4)	.274
Pulmonary disease	44 (24.4)	47 (20.8)	.381
Active malignancy			.276
None	144 (80.0)	190 (84.1)	
Solid	27 (15.0)	31 (13.7)	
Hematological	9 (5.0)	5 (2.2)	
Liver disease			.857
None	171 (95.0)	215 (95.1)	
Mild	3 (1.7)	5 (2.2)	
Severe	6 (3.3)	6 (2.7)	
Diabetes mellitus with end-organ damage	49 (27.2)	41 (18.1)	.029
Renal disease	42 (23.3)	37 (16.4)	.078
Total Charlson score, median (IQR)	2 (0–4)	2 (0–3)	<.001
SOFA score on day of onset, median (IQR)	6 (4–9)	4 (3–7)	<.001
Creatinine (mg/dL) at culture taken day, median (IQR)	1.10 (0.72–1.80)	0.83 (0.60–1.41)	.001
Albumin (g/dL) at culture taken day, median (IQR)	2.20 (1.80–2.70)	2.48 (2.00–2.90)	.001
WBC (×10^9/L) at culture taken day, median (IQR)	13.02 (9.70–17.12) (n = 178)	12.19 (8.80–16.63) (n = 226)	.081
Systolic blood pressure (mm Hg) at culture taken day, mean ± SD	107.82 ± 21.11 (n = 209)	110.65 ± 20.62 (n = 196)	.085
Immunosuppression	30 (16.7)	31 (13.7)	.409
Hemodynamic support at culture taken day	47 (26.1)	28 (12.4)	<.001
Invasive ventilator support at culture taken day	127 (70.6)	137 (60.6)	.037
Normal consciousness	62 (34.4)	98 (43.4)	.068
Arterial line	68 (37.8)	83 (36.7)	.828
Urine catheter	163 (90.6)	191 (84.5)	.070
Central line	111 (61.7)	114 (50.4)	.024
Nasogastric tube	143 (79.4)	142 (62.8)	<.001
Acquisition in ICU	61 (33.9)	87 (38.5)	.338
Known colonization	34 (18.9)	62 (27.4)	.044
Recent surgery	42 (23.3)	72 (31.9)	.058
Type of bacteria			.001
Acinetobacter	154 (85.6)	158 (69.9)	
Enterobacteriaceae (*Klebsiella*)	20 (11.1)	53 (23.5)	
Pseudomonas/other	6 (3.3)	15 (6.6)	
Type of clinical infection			.876
BSI	79 (43.9)	94 (41.6)	
VAP/HAP	79 (43.9)	103 (45.6)	
Probable VAP	12 (6.7)	13 (5.8)	
UTI	10 (5.6)	16 (7.1)	
Covering empirical treatment	96 (53.3)	113 (50.0)	.504
Covering empirical treatment by type			.771
Noncovering	84 (46.7)	113 (50)	
Colistin monotherapy	46 (25.6)	55 (24.3)	
Colistin-carbapenem combination therapy[a]	47 (26.1)	52 (23)	

Table 2. Continued

Factor	Dead (n = 180)	Alive (n = 226)	*P* Value for Dead vs Alive
Covering empirical therapy by time			.673
Noncovering	84 (46.7)	113 (50)	
Same day as culture	12 (6.7)	20 (8.8)	
Day +1	24 (13.3)	27 (11.9)	
Day +2	60 (33.3)	66 (29.2)	

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: BMI, body mass index; BSI, bloodstream infection; HAP, hospital-acquired pneumonia; ICU, intensive care unit; IQR, interquartile range; SD, standard deviation; SOFA, Sequential Organ Failure Assessment; UTI, urinary tract infection; VAP, ventilator-associated pneumonia; WBC, white blood cell.

[a]Other covering therapy given to 3 patients who died and 6 who survived.

Significant risk factors for mortality included age, acquisition of infection in medical wards, the SOFA score, low albumin levels at onset of infection, presence of a central venous catheter, and infection caused by *A. baumannii*. The model was predictive with an AUC of 0.78 (95% CI, .74–.82). Classifying empirical treatment by time to covering therapy and type of covering therapy showed similar results for covering antibiotics administered within 1 day of culture taking (OR for mortality compared to noncovering empirical antibiotics, 1.86; 95% CI, .97–3.56) and for empirical colistin-carbapenem combination therapy (OR, 1.77; 95% CI, .97–3.24).

Table 3. Risk Factors for 28-day Mortality, Multivariate Analysis[a]

Factor	OR	95% CI Lower	95% CI Upper	*P* Value
Age	1.034	1.017	1.051	.000
Dependent functional capacity	1.551	.638	3.770	.332
Congestive heart failure	1.178	.865	1.606	.299
Diabetes mellitus	1.149	.647	2.039	.636
Charlson score	1.066	.945	1.203	.297
Country				
Israel	Reference			
Greece	0.638	.269	1.515	.309
Italy	1.116	.480	2.593	.799
Acquisition place				
ICU	Reference			
Medical/long-term care facility	3.060	1.511	6.198	.002
Surgical	1.513	.615	3.720	.367
SOFA[b]	1.233	1.112	1.368	.000
Albumin blood level[b]	0.620	.418	.921	.018
Creatinine blood level[b]	0.848	.697	1.032	.100
Invasive ventilator support[b]	0.561	.294	1.069	.079
Hemodynamic support[b]	0.979	.486	1.973	.953
Central IV	2.496	1.339	4.652	.004
Known colonization	0.760	.422	1.369	.361
Acinetobacter baumannii infection	1.997	1.048	3.808	.036
Covering empirical antibiotic treatment	1.372	1.022	1.843	.036

Abbreviations: CI, confidence interval; ICU, intensive care unit; IV, intravenous; OR, odds ratio; SOFA, Sequential Organ Failure Assessment.

[a]Model fit, Hosmer-Lemeshow $P = .313$; Cox-Snell R^2 0.234.

[b]At infection onset.

The PS-matched cohort included all 209 patients prescribed covering and 131 prescribed noncovering empirical antibiotic treatment. Among them, all differences noted in the full cohort were of smaller magnitude and statistically nonsignificant (Supplementary Table 1). In the PS-matched cohort, there was no significant association between covering empirical treatment and mortality (PS-score adjusted OR, 1.42; 95% CI, .91–2.22).

Risk Factors for 14-day Mortality

At 14 days, 72 of 209 (34.4%) patients receiving covering empirical antibiotics vs 62 of 197 (31.5%) of patients receiving noncovering empirical antibiotic died ($P = .524$). Similar results were observed among patients with bacteremia (39/112 [34.8%] vs 17/61 [27.19%], respectively; $P = .350$). The risk factors for 14-day mortality were similar to the 28-day analysis, except for dementia, nonsurgical patients, and hemodialysis at infection onset, which were associated with 14-day mortality only, while diabetes mellitus with end-organ damage and ventilator support at infection onset were associated only with 28-day mortality. Adjusted to other significant risk factors for mortality, covering empirical antibiotics were not significantly associated with 14-day mortality (OR, 1.47; 95% CI, .93–2.35). Results were similar when covering therapy was assessed at 24 hours (OR, 1.42; 95% CI, .73–2.76). When specifically assessing colistin-carbapenem empirical covering therapy, there was a significant association of covering combination therapy with death (OR, 1.9; 95% CI, 1.06–3.4). No significant difference was observed in the PS-matched cohort (Supplementary Table 1), with a PS-adjusted OR of 1.56 (95% CI, .96–2.54) for 14-day mortality with covering empirical antibiotics.

DISCUSSION

In a relatively large cohort of patients with invasive infections caused by CRGNB, we found no association between covering empirical treatment and 28-day or 14-day mortality. Neither on univariate nor on adjusted analysis was there a signal showing advantage of covering empirical treatment, and the 95% CIs excluded an association favoring covering empirical treatment. The covering antibiotic was nearly always colistin. Results were

robust to sensitivity analyses examining different time points for start of covering treatment until 48 hours and whether colistin was administered alone or in combination with a carbapenem empirically. The cohort included patients with BSI or pneumonia in 94% (380/406) and different CRGNBs, dominated by *A. baumannii* (77% [312/406]). Among significant risk factors for 28-day mortality, patients with infections caused by *A. baumannii* were at higher risk for mortality than *K. pneumoniae* or *P. aeruginosa* (OR, 2.1; 95% CI, 1.11–4) and the SOFA score at onset of infection was an important predictor for death (OR for a 1-point increase in SOFA, 1.23; 95% CI, 1.11–1.37). The predictive performance of our model (AUC, 0.78; 95% CI, .74–.82) was similar to that described in a recent large multicenter study of patients with bloodstream infections caused by extended-spectrum β-lactamase–producing Enterobacteriaceae, reporting an AUC of 0.78 (95% CI, .73–.83) for 30-day mortality in the derivation cohort[12].

Previous studies assessed the association between early covering empirical antibiotic treatment and mortality among patients with infections caused by MDR bacteria [4]. Overall, in 12 studies focusing on CRGNB [13–25], 5 studies reported a significant adjusted association of noncovering empirical antibiotic treatment and mortality, with a median of 55% of patients prescribed noncovering empirical antibiotic treatment (Supplementary Table 2). Of 10 studies we identified assessing the association among patients with bacteremia caused by extended-spectrum β-lactamase–producing Enterobacteriaceae, only 2 found a significant adjusted association [26–35]. The median rate of noncovering empirical antibiotic treatment in these studies was 49%. Thus, looking at our study and previous data, covering empirical antibiotic treatment is not necessarily associated with survival among patients with different types of infections caused by CRGNBs. These findings may reflect the doubtful efficacy of the available agents against CRGNBs. Moreover, all studies demonstrate the difficulty in targeting covering empirical antibiotic treatment, which was achieved in <40% of patients with CRGNB in most studies, and the high mortality rates of these infections.

Our study has several limitations. The cohort included patients participating in an RCT comparing colistin monotherapy to colistin-meropenem combination therapy. Thus, all included patients survived to pathogen identification and all received covering targeted therapy. It is unknown whether empirical therapy can affect the very early mortality; however, this exclusion could bias results in favor of no effect if covering empirical therapy can prevent early deaths. We do not have full data on early deaths and their empirical treatment. In the hospital contributing the most patients to the analysis (Rambam), we identified 18 of 167 patients who died before recruitment to the RCT (and thus were excluded from the current analysis), of whom 7 received covering empirical treatment (colistin). With them included, the Rambam cohort consists of 41 of 86 (47.7%) patients who died while receiving noncovering empirical treatment, and 40 of 81 (49.4%) who died while receiving covering empirical treatment (OR, 1.07; 95% CI, .58–1.96). All patients received empirical antibiotics and there were no patients in whom treatment was considered futile. Contrary to the biological hypothesis of an advantage to early covering treatment in sepsis, we observed a small but significant association between covering empirical antibiotic treatment and mortality. Because empirical treatment consisted of colistin, a nephrotoxic antibiotic, this finding might be true among 48-hour survivors. However, this is more likely a spurious association related to unattended confounding. Overall, the dominance of confounding in favor of survival benefit with covering empirical treatment strengthens the finding that there is no such association or the opposite. We analyzed all gram-negative bacteria and sources of infection together; results might be different in specific patient subgroups. However, the pathogen causing the infection is unknown at the time of empirical antibiotic prescription, and although our study was not powered for analysis of separate sources of infection, results for the subgroup of patients with bloodstream infections were similar to the overall results. Only 2 patients in our cohort were neutropenic (<500 neutrophils) at infection onset; thus, our results might not be applicable to patients with neutropenia. Colistin susceptibility was not tested routinely with microbroth dilution, as currently recommended [36]; underestimation of colistin resistance might explain the lack of association observed. However, In Israel and the participating Italian center, colistin resistance has not been observed and the association we describe is so far from benefit that even if a few of the isolates were actually resistant to colistin, it is doubtful that we could show a benefit for colistin empirical therapy.

In summary, in a prospective cohort of patients with severe infections caused by CRGNB receiving covering targeted therapy, we found no association between start of colistin before final culture results and survival at 14 and 28 days. Within 95% confidence, our results excluded a possible association. The RCT from which the current cohort was derived showed no advantage to colistin-meropenem combination therapy over colistin monotherapy following pathogen identification [10]. Both results are applicable to our cohort where *A. baumannii* infections dominated and are relevant to similar settings. Restricting empirical use of colistin and avoiding carbapenems for CRGNB infection are important strategies for antibiotic stewardship in hospitals. To improve the dismal prognosis of patients with severe infections caused by CRGNB, we probably need antibiotics more effective than colistin that will cover all CRGNB for the empirical treatment phase and rapid tests that will identify the pathogen and carbapenem resistance to allow start of better-directed therapy.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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