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A Multicenter Observational Study Evaluating Outcomes Associated With Antibiotic Combination Versus Monotherapy in Patients With Septic Shock

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OBJECTIVES: To explore the association between antibiotic combination therapy and in-hospital mortality in patients with septic shock in two tertiary ICUs in different countries.

DESIGN: Retrospective observational study.

SETTING: ICUs of two tertiary hospitals, Royal Brisbane and Women's Hospital, Brisbane, QLD, Australia, and Rigshospitalet, Copenhagen, Denmark.

PATIENTS: Adult patients with antibiotic treatment greater than or equal to 72 hours and vasopressor therapy greater than or equal to 24 hours.

INTERVENTION: Combination versus mono antibiotic therapy.

MEASUREMENTS AND MAIN RESULTS: Combination antibiotic therapy was defined as receiving two or more antibiotics from different classes, started within 12 hours of each other and with an overlapping duration of greater than or equal to 12 hours. Bivariate and multiple logistic regression analysis were performed comparing combination antibiotic therapy versus antibiotic monotherapy on in-hospital mortality. The analysis was adjusted for age, gender, centre, Acute Physiology and Chronic Health Evaluation II score, and chronic health evaluation. In total, 1,667 patients were included with 953 (57%) receiving combination therapy. Patients given combination therapy were older (60 ± 16 vs 56 ± 18), more likely admitted to Rigshospitalet (58% vs 16%), and had a higher Acute Physiology and Chronic Health Evaluation II score (26 ± 8 vs 23 ± 8). Combination therapy was associated with an increased mortality in univariate analysis (odds ratio = 1.33; 95% CI, 1.07–1.66); however, there was no significant association in the adjusted analysis (odds ratio = 0.88; 95% CI, 0.68–1.15).

CONCLUSIONS: In this retrospective study, no association was found between use of combination therapy and in-hospital mortality. The large differences between centers probably reflect local traditions and lack of definitive evidence.

KEY WORDS: antibiotic; combination therapy; critical care; intensive care; sepsis; septic shock

Sepsis is the dysregulated host response to an infection (1). Timely and adequate antibiotic therapy is necessary to treat the infection and stop progression of the inflammatory response and associated organ dysfunction. Combination antibiotic therapy is sometimes recommended as part of

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the antibiotic regime for the following reasons: it can broaden the spectrum, antibiotics acting on the same bacteria can have synergistic effects, and more rapid bacterial killing may reduce the risk of emergence of resistance. Even though preclinical data support these assumptions (2, 3), clinical data on the benefits of combination therapy are still conflicting (4–6).

The current iteration of the Surviving Sepsis Campaign guidelines recommends combination therapy for initial empiric management of septic shock. This is, however, a weak recommendation based on low quality of evidence (7). For targeted therapy, the evidence for using combination therapy is also conflicting (8–10). Arguments against combination therapy include increased exposure to antibiotics which can drive the development of antimicrobial resistance, an increased risk of toxicity, increased collateral damage to commensal flora, and increased cost.

Combination therapy is widely used as shown in a recent study where combination therapy was prescribed in 50% of patients with a large variation between different ICUs. These differences can not only indicate both a variation in local ecology but also a variation in therapy traditions (11). The aim of the present study was to evaluate if combination antibiotic therapy, as treatment for patients with septic shock, is associated with improved in-hospital mortality compared with antibiotic monotherapy.

METHODS

Study Design and Setting

This was a retrospective observational study of all patients admitted to the ICU with septic shock at two large tertiary referral public teaching and university hospitals, Royal Brisbane and Women's Hospital (RBWH), Australia, and Rigshospitalet, Denmark, during a 5-year period. RBWH has a general ICU treating trauma patients, as well as those with medical and surgical diagnoses, including neurotrauma and surgery. The Rigshospitalet is a tertiary hospital with both general and specialized ICUs, that is, a neurosurgical ICU and thoracic ICU. For the present study, patients from the general ICU were included.

Ethics Approval

At RBWH, institutional human research ethics committee (HREC) approval was obtained (HREC 14/QRBW/11). At Rigshospitalet, the Danish Health and Medicines Authority gave permission to extract data from clinical information systems (3-3013-544/1). Due to the retrospective nature of the study, a waiver of informed consent was obtained at both sites.

Study Participants

Study eligibility was defined according to three criteria: 1) admitted to the ICU between 1 January 2009 and 31 December 2013; 2) shock, defined as inotropic use for greater than 24 hours with noradrenaline, adrenaline, dobutamine, dopamine, vasopressin, or metaraminol; and 3) bacterial infection, defined as treatment with any antibiotic for greater than 72 hours. Patients less than 18 years old were excluded from analysis.

Data Collection

For patients fulfilling these criteria, data were retrieved retrospectively. As different electronical medical records systems were used at RBWH and Rigshospitalet, only equivalent data were included. The following covariates were retrieved: age, gender, infectious focus, Acute Physiology and Chronic Health Evaluation (APACHE) II score, and APACHE II chronic health evaluation (respiratory, cardiac, liver, renal, and immunosuppression).

Many patients received several antibiotics during their ICU stay. For each antibiotic episode, the following data were retrieved: antibiotic name, prescribed daily dosage, start date/time, and cessation date/time. The primary outcome was in-hospital mortality.

Definition of Antibiotic Combination Therapy

We defined combination therapy as two antibiotics of different classes initiated within 12 hours of each other with a minimum overlap of duration of 12 hours, except for aminoglycosides that should be initiated within 12 hours of another class of antibiotic without any required duration (**Fig. 1**). This allowed us to identify antibiotics given as combination therapy, while excluding antibiotics given in series due to an early change from one antibiotic to another and short enough to avoid the effects of deescalation after microbiological findings. The exception of aminoglycosides from duration was based on the frequent administration of a single dose aminoglycoside.

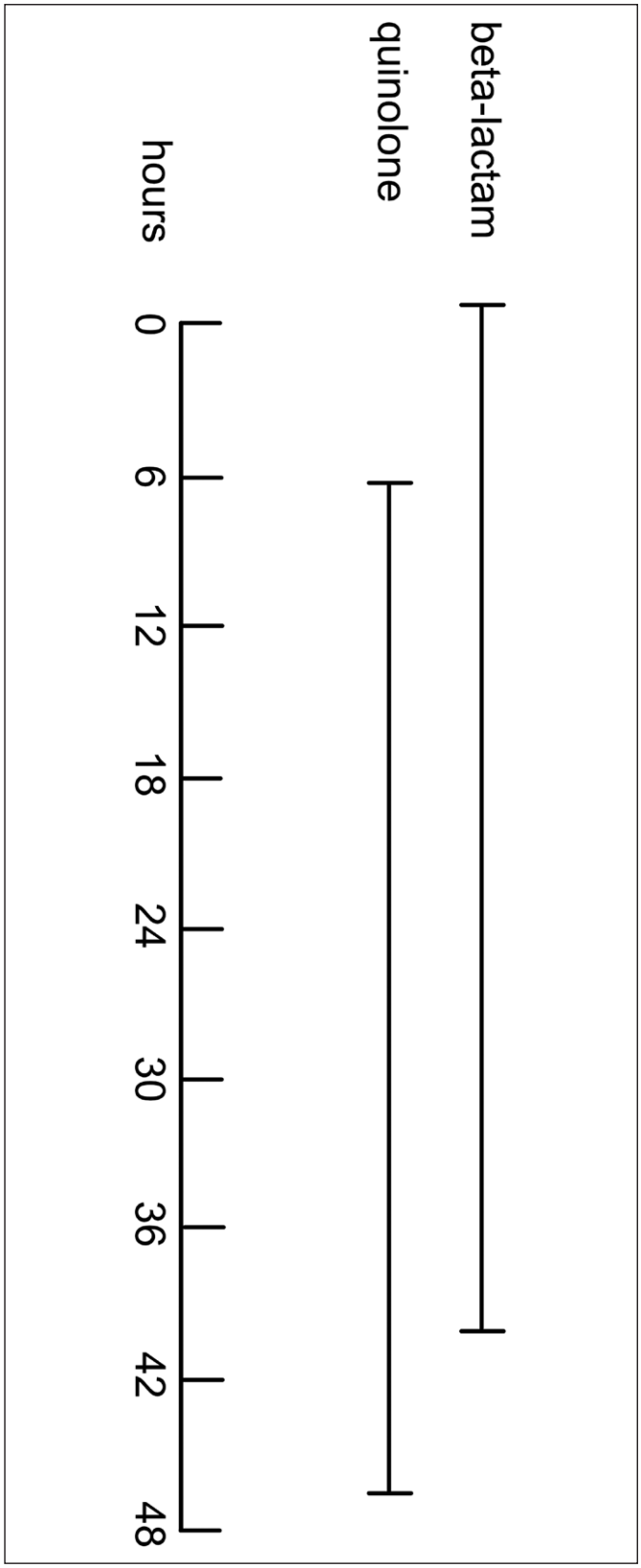

Figure 1. Example of combination therapy with two antibiotics from different classes given to the same patient. They were initiated 6 hr from each other, well within the 12 hr limit specified. The overlapping duration was 36 hr, exceeding the specified 12 hr overlap. Thus, all three criteria for a valid combination were fulfilled.

Based on the above, we defined 11 different clinically relevant antibiotic combinations: 1) beta-lactam + aminoglycoside, 2) beta-lactam + quinolone, 3) beta-lactam + macrolide, 4) beta-lactam + colistin, 5) beta-lactam + glycopeptide, 6) beta-lactam + oxazolidinone, 7) beta-lactam + lincosamide, 8) carbapenem + nitroimidazole, 9) piperacillin/tazobactam + nitroimidazole, 10) lincosamide + nitroimidazole, and 11) beta-lactam + fucidic acid.

If a patient was simultaneously treated with three or more antibiotics, for example, a carbapenem + a quinolone + metronidazole, this was counted as two separate antibiotic combinations (beta-lactam + quinolone and carbapenem + nitroimidazole).

Statistical Methods

A sample size of 1,200 was estimated to provide 80% power to detect an 8% difference in mortality between groups, assuming equal numbers in each treatment group and baseline mortality of 40%, with an alpha of 0.05 using a chi-square test.

In the Rigshospitalet data, 11% of antibiotic episodes had a missing cessation time, affecting the possibility to determine duration. Therefore, a multiple imputation by chained equation (MICE) approach was carried out to establish treatment duration. Further details of imputation and data management are described in the **Supplementary Material** (http://links.lww.com/CCX/A570).

Crude analysis was carried out against the outcome using univariate logistic regression for each covariate: odds ratios (ORs) and 95% CIs are reported. In this analysis, all variables were kept on their original scaling without transformations. The adjusted analysis was performed using a multiple regression model where the continuous variables (age and APACHE II score) were modelled as four-knot restricted cubic splines to relax the assumption of linearity. For the exposure variable, a global interaction test was performed with the intention to pursue separate interactions if positive. As the splines makes interpretation of simple main effects (i.e., ORs) nonintuitive, these were described graphically, and the relative importance of predictors was determined using an analysis of variance. The multiple regression model was internally validated through 1,000 bootstrap resamples, and its overall optimism-adjusted performance was described using the Nagelkerke R^2,

the *C*-statistic as well as Brier score. Goodness-of-fit was evaluated through Hosmer-Lemeshow test and a calibration plot.

As a sensitivity analysis, a complete case analysis, employing all the steps above on the complete case dataset without imputations was performed. A robustness analysis, using different overlapping treatment durations (12, 24, 36, 48, and 72 hr), was also conducted. All data management and calculations were performed in R (R Core Team, 2020), primarily using the MICE and Regression Modeling Strategies packages (12–14). The R script is included in the Supplementary Material (http://links.lww.com/CCX/A569).

RESULTS

Data were extracted for 1,667 patients with hospital mortality available for all patients. Of these, 1,006 (60%) were from RBWH, and 661 (40%) were from Rigshospitalet. Gender balance was approximately equal with 809 female (49%). The number of patients given combination therapy was 954 (57%).

At baseline, the patients receiving combination therapy were older, had higher APACHE II scores, and had a higher proportion of immunosuppression (**Table 1**). Similar differences in baseline characteristics were also seen between centers where patients at Rigshospitalet were older, patients had higher APACHE II scores, and more patients were immunosuppressed.

Antibiotics and Combinations by Center

The two centers differed substantially regarding combination therapy. At RBWH, 40% of patients (404/1,006) were given combination therapy, compared with 83% of patients (550/661) at Rigshospitalet. The number of combinations used also differed. The 404 patients at RBWH were given a total of 528 combinations for an average of 1.3 combinations per patient. At Rigshospitalet, the equivalent number was 1,054 combinations given to 550 patients for an average of 1.9 combinations per patient (**Table 2**). In addition, different combinations were used: a beta-lactam + aminoglycoside was used extensively at RBWH and not at Rigshospitalet (Table 2). The duration of combination treatments was also much shorter at RBWH with a median time of 24 hours, compared with 120 hours at Rigshospitalet. Furthermore, different beta-lactam antibiotics were used in combination treatment, where the proportion of carbapenems used at RBWH was 48% (214/447) and 93% (555/596) at Rigshospitalet.

Crude Analysis

The overall in-hospital mortality was 29% (484/1,667); 37% (243/661) at RBWH and 24% (241/1,006) at Rigshospitalet. In crude analysis, all variables except sex were associated with in-hospital mortality (**Table 3**). Antibiotic combination therapy was associated with an increase in mortality (OR = 1.33; 95% CI, 1.07–1.66).

Adjusted Analysis

In the multiple regression model, age and APACHE II score were modelled as restricted cubic splines with the main effects shown graphically in **Figure 2**. Apart from these, the other two variables, with the strongest univariate association with outcome, remained statistically significant: immunosuppression (OR = 2.44; 95% CI, 1.85–3.23) and liver disease (OR = 1.86; 95% CI, 1.19–2.92). The pooled interaction test for combination therapy was negative ($p = 0.34$), and no further interactions were tested. In the multiple regression analysis, combination therapy was no longer a significant predictor of outcome (OR = 0.88; 95% CI, 0.68–1.15).

The multiple regression model had a low Nagelkerke R^2 of 0.19, a *C*-statistic of 0.73, and a Brier score of 0.18. When internally validated through 1,000 bootstrap resamples, the optimism-corrected estimates were 0.17, 0.72, and 0.18, respectively, with a slope of 0.93, indicating a small amount of overfitting. When using 20 quantiles of risk, the Hosmer-Lemeshow test showed appropriate goodness-of-fit ($\chi^2 = 11.0$, degrees of freedom = 18, $p = 0.89$). A calibration plot is depicted in the supplementary material (**Fig. S2**, http://links.lww.com/CCX/A570).

Subgroup Analysis

We divided the various combinations into four groups by their adjudicated main intended treatment benefit and performed separate adjusted analyses. None of the combinations were associated with outcome (**Table S1**, http://links.lww.com/CCX/A570): combination therapy of Gram-negative bacteria: beta-lactam + aminoglycoside, beta-lactam + quinolone, and

TABLE 1.
Baseline Characteristics by Therapy and Center

Variables	No Combination (*n* = 713)	Combination Therapy (*n* = 954)	Royal Brisbane and Women's Hospital (*n* = 1006)	Rigshospitalet (*n* = 661)
Age, mean (SD)	56 (18)	60 (15)	55 (17)	63 (14)
Sex, male, *n* (%)	420 (59)	438 (46)	607 (60)	251 (38)
Rigshospitalet hospital	111 (16)	550 (58)		
Acute Physiology and Chronic Health Evaluation II score, mean (SD)	23 (8)	26 (8)	23 (8)	27 (8)
Respiratory disease, *n* (%)	32 (4)	55 (6)	44 (4)	43 (7)
Cardiac disease, *n* (%)	33 (5)	58 (6)	35 (3)	56 (8)
Liver disease, *n* (%)	31 (4)	70 (7)	34 (3)	67 (10)
Renal disease, *n* (%)	30 (4)	60 (6)	38 (4)	52 (8)
Immunosuppression, *n* (%)	93 (13)	233 (24)	149 (17)	177 (27)
ICU stay, d, median (interquartile range)	10 (6–16)	12 (7–21)	12 (7–18)	9 (5–18)
Combination therapy, *n* (%)	0	953 (100)	404 (40)	550 (83)

beta-lactam + colistin (OR = 0.86; 95% CI, 0.62–1.21); combination therapy of anaerobes: carbapenem + metronidazole, piperacillin/tazobactam + metronidazole, and lincosamide + metronidazole (OR = 0.78; 95% CI, 0.44–1.37); Gram-positive double coverage and extended spectrum: beta-lactam + lincosamide, beta-lactam + glycopeptide, beta-lactam + oxazolidinone, and beta-lactam + fucidic acid (OR = 0.85; 95% CI, 0.62–1.16); extended spectrum for atypical pathogens: beta-lactam + quinolone and beta-lactam + macrolide (OR = 0.75; 95% CI, 0.52–1.09).

Sensitivity Analysis

As a sensitivity test, all results were analyzed with only complete cases and no imputation of missing duration. These analyses showed only minor differences when compared with the full dataset and did not alter any of the conclusions (see **Tables S2–S4**, http://links.lww.com/CCX/A570 and **Fig. S3**, http://links.lww.com/CCX/A570). An adjusted analysis for different durations of combination therapy was also performed. There was no difference in outcome when compared between different durations of therapy from 12 hours to 72 hours (**Table S5**, http://links.lww.com/CCX/A570).

DISCUSSION

This large retrospective multicenter international study of patients admitted to the ICU, with infection and need of vasopressor support, did not demonstrate any difference between antibiotic combination therapy compared with monotherapy in terms of in-hospital mortality in multivariable analysis. There was also no indication of benefit in the various subgroups of combinations, such as combinations for Gram-negative or atypical coverage. The strengths of this study include a large study population of severely ill patients from two different centers with different antibiotic treatment policies. Only prespecified variables were included in the multiple regression model, and on univariate analysis, they were all significantly associated with the outcome in the expected way. Upon internal validation, the multivariate model proved quite robust with only a small amount of overfitting.

Combination therapy was associated with increased hospital mortality in univariate analysis. This was not surprising as these patients were older, had more comorbidities, and had higher acute disease severity. The baseline difference might reflect conscious treatment decisions, with the clinician more prone to start

TABLE 2.
Antibiotics and Combinations by Center

	Royal Brisbane and Women's Hospital		Rigshospitalet Hospital	
Antibiotic Combinations	***n***	**Duration (hr), Median (IQR)**	***n***	**Duration (hr), Median (IQR)**
Beta-lactam + quinolone	15	24 (14–36)	479	120 (64–216)
Beta-lactam + glycopeptide	238	33 (19–52)	122	122 (63–216)
Carbapenem + nitroimidazole	4	42 (30–52)	234	144 (72–233)
Beta-lactam + aminoglycoside	156	0 (0–0)	0	
Beta-lactam + lincosamide	31	48 (22–84)	110	96 (58–168)
Beta-lactam + macrolide	72	44 (24–72)	8	110 (72–120)
Beta-lactam + oxazolidinone	9	24 (16–44)	23	72 (37–168)
Beta-lactam + colistin	0		30	168 (72–312)
Lincosamide + nitroimidazole	0		28	144 (55–192)
Beta-lactam + fucidic acid	1	84 (84–84)	19	96 (26–168)
Piperacillin/tazobactam + nitroimidazole	2	68 (64–72)	1	65 (65–65)
All combinations	528	24 (0–48)	1,054	120 (59–216)

IQR = interquartile range.
Individual patients can have more than one combination.

combination therapy in sicker patients. However, it may also represent differences between the two centers, with regard to both case-mix and treatment protocols. As expected, we found substantial differences between centers: at Rigshospitalet, a larger proportion of patients received combination therapy, multiple combinations were given more frequently and for a substantially longer time, as this is part of the department's protocol for empirical (and some targeted) treatment of patients with septic shock. Furthermore, the two centers used different types of antibiotic combinations, where a combination of beta-lactam and aminoglycoside where the most prevalent combination at RBWH, whereas aminoglycosides, as per department protocol, are not used at Rigshospitalet. In addition, carbapenems were used in 93% of combinations at Rigshospitalet. These differences reflect the lack of definitive evidence of optimal antibiotic treatment in the literature and the development of local treatment protocols based on tradition and expert opinion.

In multiple regression analysis, only four variables remained significantly associated with in-hospital mortality: age, APACHE II score, chronic liver disease, and immunosuppression. These were also the variables with the strongest univariate associations. Neither center nor combination therapy was significant predictors, suggesting that the difference in the other covariates explained the association seen for combination therapy in univariate analysis.

Some of the selected combinations also extend the spectrum of activity and could thus potentially have a beneficial effect by increasing the rate of appropriate initial treatment in the case of empirical treatment. We do not have any detailed data on the causative pathogens or on the relation between empirical and targeted treatment. However, both centers are in settings with low prevalence of multidrug resistant pathogens, such as methicillin-resistant *Staphylococcus aureus* (MRSA) (approximately 14% at RBWH and 2% at Rigshospitalet, of all positive *S. aureus* cultures) or extended spectrum beta-lactamase *Enterobacteriaceae* (approximately 2% at both RBWH and Rigshospitalet, of all positive *Enterobacteriaceae* cultures). The most used combination was beta-lactam + quinolone, which

TABLE 3.
Crude Analysis of Mortality

Variables	Regression Coefficient (β)	SE	Wald Z	OR (95% CI)	*p*
Acute Physiology and Chronic Health Evaluation II score (points)	0.09	0.007	11.6	1.09 (1.07–1.10)	< 0.001
Immunosuppression	1.11	0.13	8.7	3.03 (2.35–3.89)	< 0.001
Age (yr)	0.03	0.004	7.7	1.03 (1.02–1.04)	< 0.001
Rigshospitalet hospital	0.61	0.11	5.6	1.85 (1.49–2.29)	< 0.001
Liver disease	0.85	0.21	4.1	2.35 (1.56–3.52)	< 0.001
Renal disease	0.86	0.22	3.9	2.36 (1.54–3.62)	< 0.001
Cardiac disease	0.74	0.22	3.4	2.10 (1.37–3.22)	< 0.001
Respiratory disease	0.58	0.22	2.6	1.78 (1.15–2.77)	0.01
Combination therapy	0.29	0.11	2.6	1.33 (1.07–1.66)	0.01
Sex, male	−0.15	0.11	−1.4	0.86 (0.69–1.05)	0.16

OR = odds ratio.

will provide a dual coverage of most Gram-negative bacteria, but will also extend spectrum to cover atypical pathogens. The need for cover of atypical pathogens in pneumonia is still controversial, where the most recent clinical trial did not find any beneficial effect of a beta-lactam + macrolide combination (15). Further, with low MRSA prevalence, any beneficial effect for extended spectrum by glycopeptide or oxazolidinone would be small compared with settings with higher MRSA prevalence. Thus, the combinations chosen would primarily act by dual activity on the same pathogen. Also, the performed subgroup analysis did not show any association with outcome in any of the more specific combinations.

The eligibility criteria of our cohort consisted of patients with infection requiring vasopressor support, which was a proxy for patients with septic shock. The severity of disease was also reflected in the high APACHE II scores (23 and 26 in patients receiving monotherapy and combination antibiotic therapy, respectively). In two other retrospective analyses of patients with sepsis, a beneficial effect on outcome was only found in the most severely sick patients (i.e., APACHE II scores > 20). However, when stratifying for primary antibiotic and outcome, it was clear that the benefit was present when the primary antibiotic was penicillin or first- or second-class cephalosporins and nonpseudomonas covering third-generation cephalosporins. In our study, a majority of patients were treated with a broad-spectrum antibiotic as the primary agent. As also shown in other studies, it is therefore reasonable to draw the conclusion that the benefit of combination lies more in the extension of the spectrum than in the synergistic effect on the causative pathogen (4, 16, 17). The largest prospective clinical study to date, investigating combination versus monotherapy with a broad-spectrum antibiotic (meropenem) and a fluoroquinolone (moxifloxacin), did not improve outcome, such as decreased organ failure. For combination therapy with aminoglycosides, systematic reviews and a recent two center-study corroborate our finding that combination therapy does not improve outcome (6, 18–20).

There are a number of limitations of our study that deserve mentioning. The study was retrospective, and the monotherapy and combination antibiotic therapy groups were not comparable at baseline. Even though a set of prespecified potentially confounding covariates were included, the explanatory value of the model was low. This is not surprising given the adequate, but relatively few, covariates included in the model and the complexity of prognostication in modern intensive

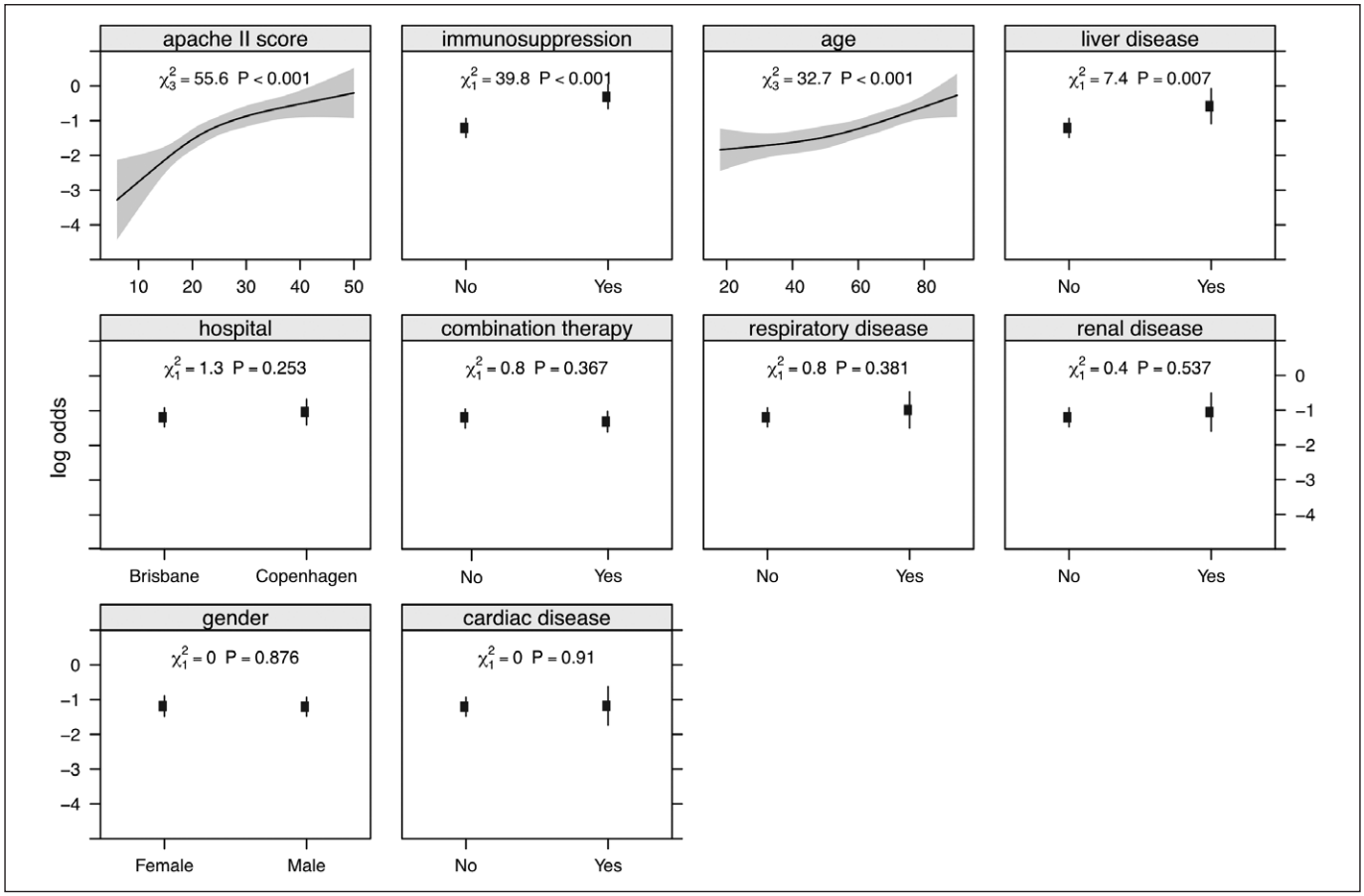

Figure 2. Main effects of a multivariable model displaying log odds for the predictors, including nonlinear effects, sorted horizontally by decreasing association with the outcome in-hospital mortality. The numbers for χ^2, degrees of freedom, and *p* values are from analysis of variance of the model. Note: the nonlinear shape of Acute Physiology and Chronic Health Evaluation (APACHE) II score, motivating the need for a nonlinear fit.

care. However, our aim was not to construct a valid prediction model, but to explore the association of combination therapy and mortality.

In addition, we have no microbiology data to evaluate the appropriateness of the various empirical treatment strategies and can thus not draw any conclusion regarding the impact on outcome if the causative pathogens were covered by the antibiotic regime or not. The study was performed in a setting of low levels of antibiotic resistance, and the conclusions may not be valid in settings with higher prevalence of resistant bacteria.

There were also no data as to whether antibiotic concentrations reached adequate levels with the prescribed dosing as therapeutic drug monitoring was rarely used during the study period.

There were some data quality issues with missing values on length of therapy. This was addressed through a multiple imputation approach, and the results from the imputed dataset did not differ significantly from the sensitivity analysis of complete cases, suggesting that the conclusions drawn are valid.

CONCLUSIONS

In this hypothesis-generating retrospective study, we found no association between the use of combination therapy and mortality when adjusting for severity of illness. We observed that the use of combination therapy seems to be largely dependent on site-specific treatment traditions. Although randomized trials on this question are needed, based on current observational evidence, it is likely that clinical trials will need to be large to reach adequate power. Therefore, cluster randomized trials or adaptive trial designs may have merit. Areas of focus should be trials separating combinations that exert dual action on a certain group of bacteria versus combinations that are aimed

at extending antibacterial spectrum and settings with low compared with high prevalence of drug resistant bacteria. In addition, future studies should include measures of target attainment as the use of combination therapy should not be an excuse for poor dosing regimens.

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Drs. Perner, Lipman, and Sjövall conceived the study. Drs. Dulhunty and Sjövall wrote the study protocol. Drs. Schmidt Davidsen, Dulhunty, and Sjövall collected and assembled the data. Drs. Torisson, Bruun Madsen, and Dulhunty performed data management and analysis. Drs. Torisson and Sjövall drafted the article. All authors reviewed and gave input to the article and approved of the final draft.

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All deidentified data underlying the study results can be requested from: fredrik.sjovall@med.lu.se. The R code used is supplied in the **Supplementary Material** *(http://links.lww.com/CCX/A569).*

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