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Effect of Empirical Treatment With Moxifloxacin and Meropenem vs Meropenem on Sepsis-Related Organ Dysfunction in Patients With Severe Sepsis

A Randomized Trial

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Context Early appropriate antimicrobial therapy leads to lower mortality rates associated with severe sepsis. The role of empirical combination therapy comprising at least 2 antibiotics of different mechanisms remains controversial.

Objective To compare the effect of moxifloxacin and meropenem with the effect of meropenem alone on sepsis-related organ dysfunction.

Design, Setting, and Patients A randomized, open-label, parallel-group trial of 600 patients who fulfilled criteria for severe sepsis or septic shock (n=298 for monotherapy and n=302 for combination therapy). The trial was performed at 44 intensive care units in Germany from October 16, 2007, to March 23, 2010. The number of evaluable patients was 273 in the monotherapy group and 278 in the combination therapy group.

Interventions Intravenous meropenem (1 g every 8 hours) and moxifloxacin (400 mg every 24 hours) or meropenem alone. The intervention was recommended for 7 days and up to a maximum of 14 days after randomization or until discharge from the intensive care unit or death, whichever occurred first.

Main Outcome Measure Degree of organ failure (mean of daily total Sequential Organ Failure Assessment [SOFA] scores over 14 days; score range: 0-24 points with higher scores indicating worse organ failure); secondary outcome: 28-day and 90-day all-cause mortality. Survivors were followed up for 90 days.

Results Among 551 evaluable patients, there was no statistically significant difference in mean SOFA score between the meropenem and moxifloxacin group (8.3 points; 95% CI, 7.8-8.8 points) and the meropenem alone group (7.9 points; 95% CI, 7.5-8.4 points) (P=.36). The rates for 28-day and 90-day mortality also were not statistically significantly different. By day 28, there were 66 deaths (23.9%; 95% CI, 19.0%-29.4%) in the combination therapy group compared with 59 deaths (21.9%; 95% CI, 17.1%-27.4%) in the monotherapy group (P=.58). By day 90, there were 96 deaths (35.3%; 95% CI, 29.6%-41.3%) in the combination therapy group compared with 84 deaths (32.1%; 95% CI, 26.5%-38.1%) in the monotherapy group (P=.43).

Conclusion Among adult patients with severe sepsis, treatment with combined meropenem and moxifloxacin compared with meropenem alone did not result in less organ failure.

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INAPPROPRIATE INITIAL ANTIMICROBIAL therapy (defined as an antimicrobial regimen that lacks in vitro activity against the isolated organisms responsible for the infection) is associated with increased mortality

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and morbidity in patients with neutropenic fever and in patients with severe sepsis.[1-3] To decrease the likelihood of inappropriate antimicrobial therapy, recent international sepsis guidelines suggest empirical combination therapy targeting gram-negative bacteria, particularly for patients with suspected *Pseudomonas* infections.[4] However, the authors of this guideline[4] state that "no study or meta-analysis has convincingly demonstrated that combination therapy produces a superior clinical outcome for individual pathogens in a particular patient group."

The basis on which combination therapy provides a potential survival benefit can be related to several mechanisms. These include an increased chance that at least 1 agent with activity against the infecting organism will be susceptible to at least 1 of the components of the regimen; prevention of emergence to a resistant superinfection[5-7]; potential beneficial immunomodulatory nonantibiotic effect of the secondary agent[8,9]; and generation of an additive or even synergistic activity resulting in better bacterial clearance of the combination therapy.[10-14] In contrast to patients with febrile neutropenia, rigorous randomized trials have not been performed in the most severely ill patients with sepsis, capillary leak syndrome, and multiorgan failure in which both the volume of distribution and metabolism of the antibiotics may be altered.

The primary objective of this trial was to compare the effect of a combination therapy with the effect of a monotherapy on sepsis-related organ dysfunction using 2 broad-spectrum antibiotics for the empirical treatment of patients with severe sepsis. We hypothesized that maximizing the potential benefit and appropriateness of initial antibiotics by using 2 antibiotics would improve clinical outcomes compared with monotherapy.

METHODS

Experimental Design, Study Organization, and Patients

Severe sepsis and septic shock were defined according to published criteria.[15] Patients were eligible for study enrollment if the onset of the syndrome was not more than 24 hours prior to study inclusion. We excluded patients if they had been treated with more than 1 daily dose of a carbapenem or a quinolone within the 4 weeks prior to randomization, had received an antipseudomonal β-lactam antibiotic within the 48 hours prior to randomization, or had contraindications to the study drugs according to the manufacturer's summary of product characteristics. In addition, we excluded patients who were known to be previously infected or colonized with methicillin-resistant *Staphylococcus aureus* or vancomycin-resistant *Enterococcus* species (not susceptible to study antibiotics), had infections for which the guidelines recommend an antimicrobial therapy other than the study medication (ie, endocarditis), or were expected to die or undergo withdrawal of life support.

The trial was approved by the ethics committee of each participating institution and by Germany's Federal Institute for Drugs and Medical Devices. Written informed consent was obtained from all patients or their legal representative. For patients in whom prior consent could not be obtained because of critical illness or the use of sedative or anesthetic drugs and to enable early antibiotic therapy, the ethics committees approved a provision for delayed consent. In such cases, a surrogate decision maker was fully informed as soon as possible. Either consent was then obtained or the patient was removed from the study and all study procedures ended.

Randomization

Patients were randomly allocated to receive either 1 g of meropenem (AstraZeneca) every 8 hours and 400 mg of moxifloxacin (Bayer HealthCare) every 24 hours (combination therapy) or 1 g of meropenem alone (monotherapy) each administered intravenously over 15 to 30 minutes for meropenem and for 60 minutes for moxifloxacin in an unblinded fashion. The randomization was stratified by the participating centers and performed by the investigators using an Internet-based randomization tool that was provided by the clinical trial center. The modified Pocock minimization algorithm (with a random component) ensures balanced randomization at any time.[16] The intervention was recommended for 7 days and up to a maximum of 14 days after randomization or until discharge from the intensive care unit (ICU) or death, whichever occurred first.

Data Collection

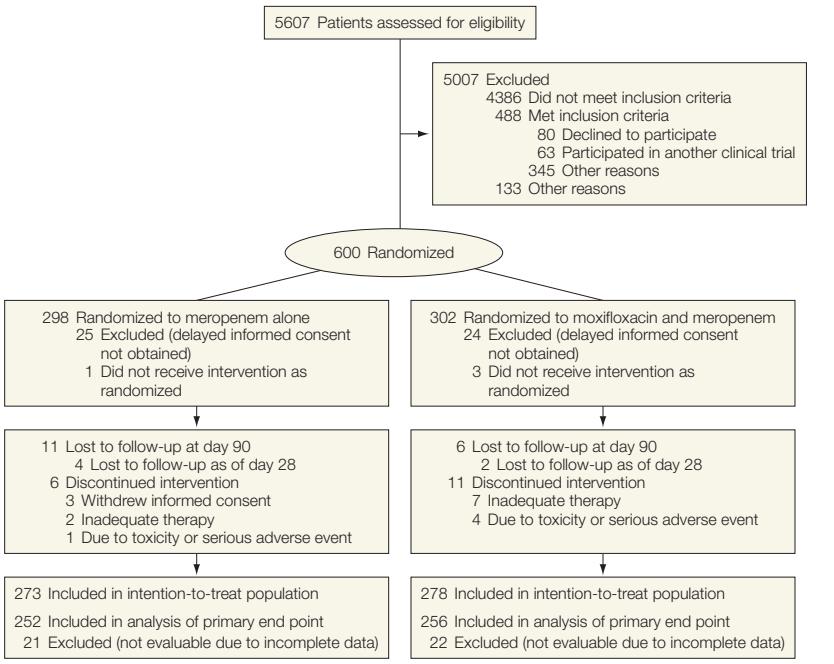
Clinical, microbiological, and laboratory examinations were performed prior to treatment, at the end of therapy (test-of-cure visit), and at day 21 or at discharge from the ICU, whichever occurred first. Site investigators used standardized definitions to determine the final clinical and microbiological outcomes (eMethods at http://www.jama.com). If *Pseudomonas* species were cultured, 2 antibiotics with activity against these species were recommended. All patients received sepsis treatment for cardiovascular, respiratory, renal, and metabolic failure according to the guidelines of the German Sepsis Society.[17]

Outcome Measures and Safety End Points

The primary end point was sepsis-related organ dysfunction as measured by the mean of daily total Sequential Organ Failure Assessment (SOFA)[18] scores over a period of 14 days or discharge from the ICU or death, whichever occurred first. The scale of the SOFA score ranges from 0 to 24, with higher scores indicating a greater severity of organ failure. Subscores of SOFA range from 0 to 4 for each of the 6 organ systems, with an aggregate score of 0 to 24. The mean SOFA score was calculated as the mean of all daily SOFA scores during the ICU stay for each patient.

Secondary end points were 28-day and 90-day all-cause mortality; mean SOFA subscores; duration of ICU and hospital stay; clinical and microbiological treatment response; intervention-free days with a ventilator, vasopressor, dialysis, or antibiotic; secondary infections; emergence of antibiotic-resistant bacteria; and adverse events. Adverse events were reported according to the ICH guideline

Figure 1. Screening and Inclusion Process for Patients in the Study



E2A and coded by the Medical Dictionary for Regulatory Activities version 13.1.

Sample Size and Statistical Analysis

The study was planned to detect a difference of 1.1 points in the mean SOFA score between the 2 interventions with a significance level of .05 and a power level of 90%. Such an effect was expected to reduce 28-day mortality from 40% to 30%.[18] Assuming an SD of 3.8 points and a dropout rate of about 15%, an enrollment of 600 patients was required. One interim analysis was planned and conducted after recruitment of half of the planned sample size. The significance level was adjusted by the α spending method,[19] which was .00288 (as specified by the O'Brien and Fleming[20] multiple testing procedure). Hence, the significance level for the final confirmatory analysis was .04712. Annual safety reports were performed and reported to the Federal Institute for Drugs and Medical Devices and the ethics committee of the Friedric-Schiller University of Jena.

The confirmatory analyses followed the intention-to-treat principle based on all patients who were randomized and provided informed consent. Per-protocol analyses excluding patients with protocol violations were performed to investigate the robustness of the results (the definition of protocol violations appear in eMethods). Safety analyses were based on the safety analysis population, which comprises all patients randomized who received at least 1 dose of study medication and who were grouped according to the treatment they actually received.

The *t* test for independent groups was used to investigate the primary end point of mean SOFA score. The χ^2 test, Fisher exact test, and the Mann-Whitney test were applied to analyze the secondary end points of efficacy and safety, as appropriate. Overall survival was estimated using the Kaplan-Meier method. Proportional hazard models and generalized linear models were used to identify factors influencing overall mortality and mean SOFA score. All reported *P* values are 2-sided. Statistical analyses were performed using SAS version 9.1.3 (SAS Institute Inc).

RESULTS

Between October 16, 2007, and March 23, 2010, 5607 patients were screened in 44 ICUs from different academic tertiary hospitals in Germany; 1088 were eligible and 600 patients were randomized (FIGURE 1). Delayed informed consent could not be obtained in 49 patients from the patient or the patient's legal representative. These patients were excluded from the intention-to-treat analysis, but were included in the safety analysis.

Among the remaining 551 evaluable patients, demographic and baseline characteristics (TABLE 1), site and source of infection (TABLE 2), pathogens present at the time of enrollment (TABLE 3), indicators of severity of disease, and antibiotics used 1 week prior to randomization (eTable 1 at http://www.jama.com) were well balanced comparing the combination therapy (meropenem and moxifloxacin) group with the monotherapy (meropenem alone) group. The median time from enrollment to initiation of study antibiotics was 0.7 (interquartile range [IQR], 0.4-1.0) hours in the combination therapy group compared with 0.8 (IQR, 0.5-1.4) hours in the monotherapy group ($P=.08$).

The most common pathogens cultured from enrollment specimens appear in Table 3. Blood cultures were positive in 183 patients (33%) with *Escherichia coli* and methicillin-sensitive *S aureus* as the most common pathogens. Blood cultures were positive for *Pseudomonas* species in only 9 patients (5 in the combination therapy and 4 in the monotherapy group). The susceptibility profiles and numbers of study drugs resistant to gram-negative bacteria grown in enrollment specimens appear in eTable 2. Of all patients whose specimens were tested for susceptibility to meropenem, 58 of 58 (100%; 95% CI, 93.8%-100%) were susceptible in the combination therapy group compared with 65 of 69 (94.2%; 95% CI, 85.8%-98.4%) in the monotherapy group ($P=.13$).

Primary and Secondary Outcomes

The mean SOFA score was 8.3 points (95% CI, 7.8-8.8 points) in the combi-

nation therapy group compared with 7.9 points (95% CI, 7.5-8.4 points) in the monotherapy group ($P = .36$; TABLE 4 and FIGURE 2A). In the per-protocol analysis, the mean SOFA score was 7.9 points (95% CI, 7.4-8.5 points) in the combination therapy group compared with 7.6 points (95% CI, 7.0-8.1 points) in the monotherapy group ($P = .37$; Figure 2B). The respiratory SOFA subscore was statistically significantly different between the 2 study groups; the median score was 2.5 points (IQR, 2.0-2.9 points) in the combination therapy group compared with 2.4 points (IQR, 2.0-2.8 points) in the monotherapy group ($P = .02$; Table 4).

There were no significant differences comparing combination therapy with monotherapy for the secondary end points of duration of ICU and hospital stay; intervention-free days with a ventilator, vasopressor, dialysis, or antibiotic; the rates of secondary infections (Table 4); or clinical and microbiological treatment response (eTable 4). Antibiotic resistance to meropenem was detected more often in the monotherapy group (8/88; 9.1% [95% CI, 4.0%-17.1%) compared with the combination therapy group (1/78; 1.3% [95% CI, 0.03%-6.9%]; $P = .04$). However, the number of specimens tested for susceptibility was low (Table 4).

The rates for 28-day and 90-day mortality were not statistically significantly different between the 2 treatment groups (Table 4 and FIGURE 3A). By day 28, there were 66 deaths (23.9%; 95% CI, 19.0%-29.4%) in the combination therapy group compared with 59 deaths (21.9%; 95% CI, 17.1%-27.4%) in the monotherapy group ($P = .58$). By day 90, there were 96 deaths (35.3%; 95% CI, 29.6%-41.3%) in the combination therapy group compared with 84 deaths (32.1%; 95% CI, 26.5%-38.1%) in the monotherapy group ($P = .43$).

The results of the per-protocol analysis of the 28-day and 90-day mortality rates also did not significantly differ between the 2 study groups (Figure 3B). By day 28, there were 48 deaths (n = 214; 22.4% [95% CI, 17.0%-28.6%]) in the combination therapy group compared with 39 deaths (n = 195; 20.0% [95% CI, 14.6%-26.3%]) in the monotherapy group ($P = .55$). By day 90, there were 70 deaths (n = 213; 32.9% [95% CI, 26.6%-39.6%]) in the combination therapy

Table 1. Demographics and Baseline Characteristics

	All Patients (N = 551)	Meropenem Alone (n = 273)	Moxifloxacin and Meropenem (n = 278)
Age, mean (SD), y	64.6 (14.5)	63.7 (14.4)	65.5 (14.5)
Male sex, No. (%)	354 (64)	176 (64)	178 (64)
Body mass index, mean (SD)[a]	27.0 (6.0)	26.5 (5.8)	27.5 (6.1)
APACHE II score, mean (SD)[b]	21.6 (7.2)	21.9 (7.1)	21.3 (7.4)
SOFA score, mean (SD)[c]	9.52 (3.16)	9.68 (3.17)	9.36 (3.15)
Laboratory values, median (IQR)			
White blood cell count, cells/μL	14 150 (8700-20 300)	15 560 (10 000-20 400)	13 100 (7500-20 200)
Plasma procalcitonin, ng/mL	7.25 (1.74-26.32)	7.10 (1.70-28.10)	7.56 (1.80-24.00)
Plasma C-reactive protein, mg/L	200.6 (108.1-289.0)	200.0 (110.0-269.1)	202.0 (102.9-303.0)
Plasma lactate, mg/dL	23.4 (13.5-43.2)	23.2 (13.0-47.7)	24.0 (14.0-40.0)
Plasma creatinine, mg/dL	1.5 (1.0-2.3)	1.5 (0.9-2.3)	1.5 (1.0-2.4)
Creatinine clearance, mL/min	49 (29-83)	50 (28-86)	49 (29-83)
Plasma albumin, g/dL	2.3 (1.7-2.7)	2.2 (1.7-2.7)	2.3 (1.8-2.7)
Preexisting conditions, No. (%)[d]			
History of diabetes	144 (26)	75 (27)	69 (25)
Heart failure	97 (17.60)	46 (16.85)	51 (18.35)
Cerebrovascular disease	41 (7.44)	25 (9.16)	16 (5.76)
Renal dysfunction	97 (17.60)	51 (18.68)	46 (16.55)
Chronic obstructive pulmonary disease	35 (6.35)	19 (6.96)	16 (5.76)
Liver cirrhosis	16 (2.90)	8 (2.93)	8 (2.88)
History of cancer	131 (23.77)	58 (21.25)	73 (26.26)
Immunosuppression	38 (6.90)	21 (7.69)	17 (6.12)
Required mechanical ventilation, No. (%)	420 (76)	204 (75)	216 (78)
Recent surgical history, No. (%)			
Elective	67 (12.16)	26 (9.52)	41 (14.75)
Emergency	242 (43.92)	120 (43.96)	122 (43.88)
No history	241 (43.74)	127 (46.52)	114 (41.01)
Not known	1 (0.18)	0	1 (0.36)

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; IQR, interquartile range; SOFA, Sequential Organ Failure Assessment.
SI conversion factors: To convert plasma albumin from g/dL to g/L, multiply by 1.0; plasma C-reactive protein from mg/dL to mg/L, multiply by 10; plasma creatinine from mg/dL to μmol/L, multiply by 88.4; creatinine clearance from mL/min to mL/s, multiply by 0.0167; plasma lactate from mg/dL to mmol/L, multiply by 0.111.
[a] Calculated as weight in kilograms divided by height in meters squared.
[b] Missing subscores were counted as 0. The scale score range is from 0 to 71, with higher scores indicating a greater severity of illness.
[c] The scale score range is from 0 to 24, with higher scores indicating a greater severity of organ failure.
[d] Multiple responses per patient possible.

Table 2. Site and Source of Infection

	No. (%) of Patients		
	All (N=551)	Meropenem Alone (n = 273)	Moxifloxacin and Meropenem (n = 278)
Site of infection			
Pneumonia	224 (40.65)	105 (38.46)	119 (42.81)
Other respiratory tract	36 (6.53)	18 (6.59)	18 (6.47)
Intra-abdominal	210 (38.11)	99 (36.26)	111 (39.93)
Bones or soft tissue	36 (6.53)	20 (7.33)	16 (5.76)
Surgical wound infection	20 (3.63)	15 (5.49)	5 (1.80)
Urogenital	64 (11.62)	39 (14.29)	25 (8.99)
Primary bacteremia	16 (2.90)	5 (1.83)	11 (3.96)
Other[a]	24 (4.36)	13 (4.76)	11 (3.96)
Source of infection			
Community-acquired	277 (50.27)	136 (49.82)	141 (50.72)
Nosocomial	273 (49.55)	137 (50.18)	136 (48.92)
Missing	1 (0.18)	0	1 (0.36)
Infection at study enrollment			
Microbiologically confirmed	196 (35.57)	97 (35.53)	99 (35.61)
Clinical evidence	355 (64.43)	176 (64.47)	179 (64.39)

[a]Other includes surgical site infection, meningitis, and central line–associated bloodstream infection.

group compared with 58 deaths (n=189; 30.7% [95% CI, 24.2%-37.8%]) in the monotherapy group (P=.64).

Study Treatment

Meropenem was administered initially for a median of 8 days (IQR, 5-10 days) in the combination therapy group and 8 days (IQR, 4-10 days) in the monotherapy group. In the combination therapy group, moxifloxacin was administered for a median of 7 days (IQR, 4-10 days). The total dose of meropenem administered was 18 g (IQR, 8-24 g) in the combination therapy group and 19 g (IQR, 8-25 g) in the monotherapy group. The total dose of moxifloxacin administered was 2.8 g (IQR, 1.6-4.0 g).

Table 3. Gram-Positive, Gram-Negative, and Fungi Pathogens at Enrollment

	Absolute Frequency (%)[a]					
	All Patients (N=551)		Meropenem Alone (n = 273)		Moxifloxacin and Meropenem (n = 278)	
	Proven by Any Material	Proven by Blood Culture	Proven by Any Material	Proven by Blood Culture	Proven by Any Material	Proven by Blood Culture
Gram-positive pathogen	296 (53.72)	107 (19.42)	140 (51.28)	49 (17.95)	156 (56.12)	58 (20.86)
Staphylococcus aureus	91 (16.52)	27 (4.90)	41 (15.02)	13 (4.76)	50 (17.99)	14 (5.04)
Methicillin-resistant *S aureus*	18 (3.27)	9 (1.63)	7 (2.56)	3 (1.10)	11 (3.96)	6 (2.16)
Coagulase-negative staphylococci	112 (20.33)	48 (8.71)	59 (21.61)	23 (8.42)	53 (19.06)	25 (8.99)
Methicillin-resistant coagulase-negative staphylococci	36 (6.53)	12 (2.18)	18 (6.59)	5 (1.83)	18 (6.47)	7 (2.52)
Streptococcus pneumoniae	25 (4.54)	12 (2.18)	9 (3.30)	3 (1.10)	16 (5.76)	9 (3.24)
Enterococcus species	90 (16.33)	11 (2.00)	50 (18.32)	9 (3.30)	40 (14.39)	2 (0.72)
Vancomycin-resistant *Enterococcus* species	43 (7.80)	6 (1.09)	26 (9.52)	4 (1.47)	17 (6.12)	2 (0.72)
Other *Streptococcus* species	82 (14.88)	13 (2.36)	38 (13.92)	5 (1.83)	44 (15.83)	8 (2.88)
Other[b]	38 (6.90)	8 (1.45)	15 (5.49)	1 (0.37)	23 (8.27)	7 (2.52)
Gram-negative pathogen	271 (49.18)	74 (13.43)	149 (54.58)	41 (15.02)	122 (43.88)	33 (11.87)
Escherichia coli	159 (28.86)	45 (8.17)	83 (30.40)	27 (9.89)	76 (27.34)	18 (6.47)
Klebsiella species	60 (10.89)	7 (1.27)	33 (12.09)	2 (0.73)	27 (9.71)	5 (1.80)
Proteus species	35 (6.35)	4 (0.73)	22 (8.06)	3 (1.10)	13 (4.68)	1 (0.36)
Enterobacter	38 (6.90)	8 (1.45)	18 (6.59)	5 (1.83)	20 (7.19)	3 (1.08)
Pseudomonas aeruginosa	38 (6.90)	8 (1.45)	19 (6.96)	3 (1.10)	19 (6.83)	5 (1.80)
Other *Pseudomonas* species	7 (1.27)	1 (0.18)	4 (1.47)	1 (0.37)	3 (1.08)	0
Serratia	12 (2.18)	1 (0.18)	6 (2.20)	1 (0.37)	6 (2.16)	0
Citrobacter	16 (2.90)	1 (0.18)	10 (3.66)	1 (0.37)	6 (2.16)	0
Acinetobacter	7 (1.27)	1 (0.18)	6 (2.20)	1 (0.37)	1 (0.36)	0
Haemophilus	12 (2.18)	2 (0.36)	9 (3.30)	1 (0.37)	3 (1.08)	1 (0.36)
Bacteroides species	18 (3.27)	1 (0.18)	11 (4.03)	1 (0.37)	7 (2.52)	0
Other[c]	28 (5.08)	4 (0.73)	17 (6.23)	2 (0.73)	11 (3.96)	2 (0.72)
Fungi	159 (28.86)	13 (2.36)	79 (28.94)	9 (3.30)	80 (28.78)	4 (1.44)
Candida albicans	109 (19.78)	7 (1.27)	53 (19.41)	5 (1.83)	56 (20.14)	2 (0.72)
Other *Candida* species	74 (13.43)	7 (1.27)	36 (13.19)	5 (1.83)	38 (13.67)	2 (0.72)
Aspergillus species	2 (0.36)	0	0	0	2 (0.72)	0
Other[d]	16 (2.90)	0	9 (3.30)	0	7 (2.52)	0

[a]Multiple responses per patient possible. Pathogens were detected during last 7 days before or 4 days after study enrollment.
[b]Other includes other gram-positive cocci and other aerobic gram-positive bacteria (eg, *Bacillus* species, *Corynebacterium* species, *Lactobacillus*).
[c]Other includes *Legionella*, *Moraxella*, *Neisseria*, *Bacteroides* species, and *Salmonella*.
[d]Other includes *Phycomyces* species, *Coccidioides*, *Zygomyces*, *Rhizopus*, *Mucor*, and *Microsporum* species.

Concomitant Treatment

Activated protein C was administered to 8 patients (3%) in the combination therapy group and to 9 patients (3%) in the monotherapy group (*P*=.78). Low-dose hydrocortisone for septic shock was administered to 111 patients (39.9%) in the combination therapy group and to 91 patients (33.3%) in the monotherapy group (*P*=.11) at comparable doses (median of mean daily dose: 136 mg [IQR, 99-175 mg] vs 134 mg [IQR, 100-169 mg], respectively; *P*=.67). Selenium as an adjunctive sepsis treatment was administered to 92 patients (33.1%) in the combination therapy group and to 87 patients (31.9%) in the monotherapy group (*P*=.76). Immunosuppressive treatment with a prednisolone equivalent was administered at a daily dose of greater than 5 mg to 13 patients (4.7%) in the combination therapy group and to 13 patients (4.8%) in the monotherapy group (*P*=.96).

Safety End Points

At least 1 adverse event occurred in 85 patients (n=303; 28.1% [95% CI, 23.1%-33.5%]) in the combination therapy group and in 71 patients (n=293; 24.2% [95% CI, 19.4%-29.6%]) in the monotherapy group (*P*=.31). There were significantly more study-related adverse events reported in the combination therapy group (n=26; 8.6% [95% CI, 5.7%-12.3%]) compared with the monotherapy group (n=11; 3.8% [95% CI, 1.2%-6.6%]; *P*=.02). However, there were no differences in the rates of adverse events classified as serious, serious and study-related, resulting in death, or study-related and resulting in death (eTable 3 at http://www.jama.com). Adverse events assigned to the system organ class of cardiac disorders were reported in 37 patients (12.2%; 95% CI, 8.8%-16.4%) in the combination therapy group and in 31 patients (10.6%; 95% CI, 7.3%-14.7%) in the monotherapy group (*P*=.61). Of these patients, 10 patients (3.3%; 95% CI, 1.6%-6.0%) in the combination therapy group and 7 patients (2.4%; 95% CI, 1.0%-4.9%) in the monotherapy group were classified as serious (*P*=.63). Ad-

Table 4. Study Outcomes

Outcome	All Patients (N = 551)	Meropenem Alone (n = 273)	Moxifloxacin and Meropenem (n = 278)	*P* Value[a]
SOFA score, mean (95% CI)	8.1 (7.8-8.5)	7.9 (7.5-8.4)	8.3 (7.8-8.8)	.36
Mortality, No. (%) [95% CI]				
At 28 d	(n = 545) 125 (22.9) [19.5-26.7]	(n = 269) 59 (21.9) [17.1-27.4]	(n = 276) 66 (23.9) [19.0-29.4]	.58
At 90 d	(n = 534) 180 (33.7) [29.7-37.9]	(n = 262) 84 (32.1) [26.5-38.1]	(n = 272) 96 (35.3) [29.6-41.3]	.43
SOFA subscores, median (IQR)				
Cardiovascular	2.0 (1.1-3.2)	2.0 (1.1-3.1)	2.0 (1.1-3.3)	.54
Respiratory	2.4 (2.0-2.9)	2.4 (2.0-2.8)	2.5 (2.0-2.9)	.02
Coagulation	0.3 (0-1.0)	0.2 (0-1.0)	0.3 (0-1.1)	.48
Renal	0.4 (0-1.7)	0.3 (0-1.6)	0.4 (0-1.8)	.28
Hepatic	0 (0-0.5)	0 (0-0.5)	0 (0-0.5)	.86
Central nervous system	0.9 (0-2.1)	0.9 (0-2.3)	0.9 (0-2.0)	.65
Length of stay, median (IQR), d				
In ICU	12 (6-22)	11 (5-24)	12 (6-21)	.90
In hospital	27 (14-44)	29 (14-45)	26 (15-42)	.64
Intervention-free days, median (IQR)				
Ventilator[b]	2 (0-6)	2 (0-6)	2 (0-6)	.59
Renal replacement therapy[b]	8 (3-16)	8 (3-19)	8 (3-14)	.43
Antibiotic[b]	0 (0-4)	0 (0-4)	0 (0-4)	.95
Vasopressor[c]	4 (1-7)	3 (1-8)	4 (0-7)	.73
Secondary infection, No. (%) [95% CI][c]	(n = 549) 176 (32.1) [28.2-36.1]	(n = 272) 89 (32.7) [27.2-38.7]	(n = 277) 87 (31.4) [26.0-37.2]	.95
Resistance to antibiotic, No. (%) [95% CI][d]				
Meropenem	(n = 166) 9 (5.4) [2.5-10.0]	(n = 88) 8 (9.1) [4.0-17.1]	(n = 78) 1 (1.3) [0.03-6.9]	.04
Moxifloxacin	(n = 101) 27 (26.7) [18.4-36.5]	(n = 55) 16 (29.1) [17.6-42.9]	(n = 46) 11 (23.9) [12.6-38.8]	.65
Tobramycin or gentamicin	(n = 171) 16 (9.4) [5.4-14.8]	(n = 90) 12 (13.3) [7.1-22.1]	(n = 81) 4 (4.9) [1.4-12.2]	.07

Abbreviations: ICU, intensive care unit; IQR, interquartile range; SOFA, Sequential Organ Failure Assessment.
[a] Calculated using the *t* test, Mann-Whitney test, χ^2 test, or Fisher exact test as appropriate.
[b] Until ICU discharge or day 28 (maximum).
[c] Until ICU discharge or day 14 (maximum).
[d] Restricted to patients whose specimens were tested for susceptibility until ICU discharge or day 21 (maximum). The denominator is the subset of patients tested for susceptibility against the named antibiotic.

verse events assigned to the system organ class of hepatobiliary disorders were reported in 8 patients (2.6%; 95% CI, 1.2%-5.1%) in the combination therapy group and in 3 patients (1.0%; 95% CI, 0.2%-3.0%) in the monotherapy group ($P=.22$), of whom 1 event was classified as serious in the monotherapy group. The QT interval corrected for heart rate at end of therapy was not different between groups (median, 423 milliseconds; IQR, 400-443 milliseconds in the combination therapy group; median, 417 milliseconds; IQR, 394-447 milliseconds in the monotherapy group; $P=.85$).

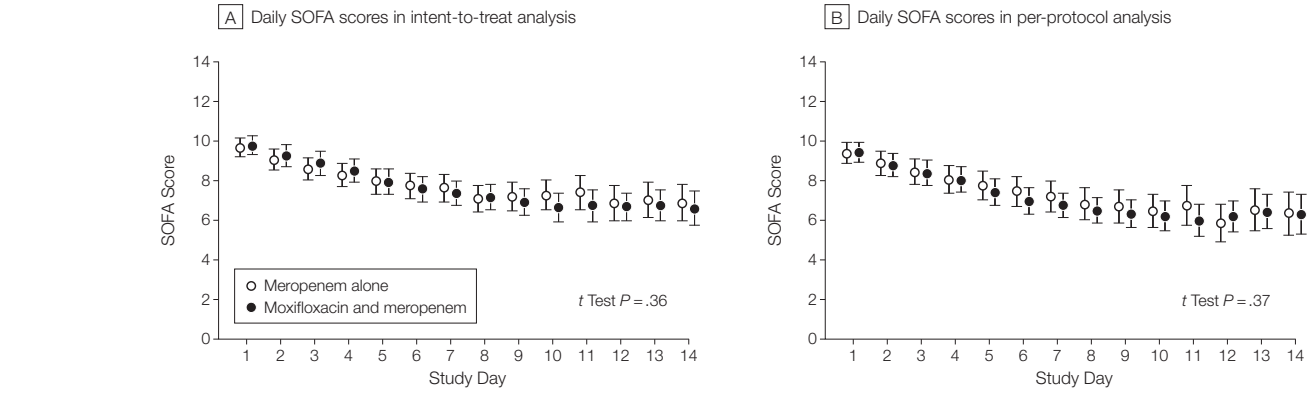
Multivariable Analyses

The risk factors for higher mean SOFA score at 14 days identified by general linear model risk factors were SOFA score at enrollment (regression coefficient per point, 0.6 [95% CI, 0.5-0.7]; $P<.001$), renal failure at enrollment (regression coefficient, 3.9 [95% CI, 3.1-4.8]; $P<.001$), and age (regression coefficient per year, 0.02 [95% CI, 0.002-0.04]; $P=.03$). In Cox regression analysis, independent risk factors for time to death were SOFA score at baseline (hazard ratio [HR] per point, 1.08 [95% CI, 1.03-1.14]; $P=.003$), renal failure at enrollment (HR, 3.56 [95% CI, 2.51-5.06]; $P<.001$), and age (HR per year, 1.04 [95% CI, 1.03-1.06]; $P<.001$). In contrast, study therapy, prior antibiotic treatment, bacterial resistance, and gram-negative enrollment pathogens were not associated with the mean SOFA score or time to death.

Subgroup Analyses

Unplanned subgroup analyses stratified by prerandomization SOFA score or with patients categorized by site and origin of infection or by enrollment organisms did not show significant differences in survival or mean

Figure 2. Daily Sequential Organ Failure Assessment (SOFA) Scores



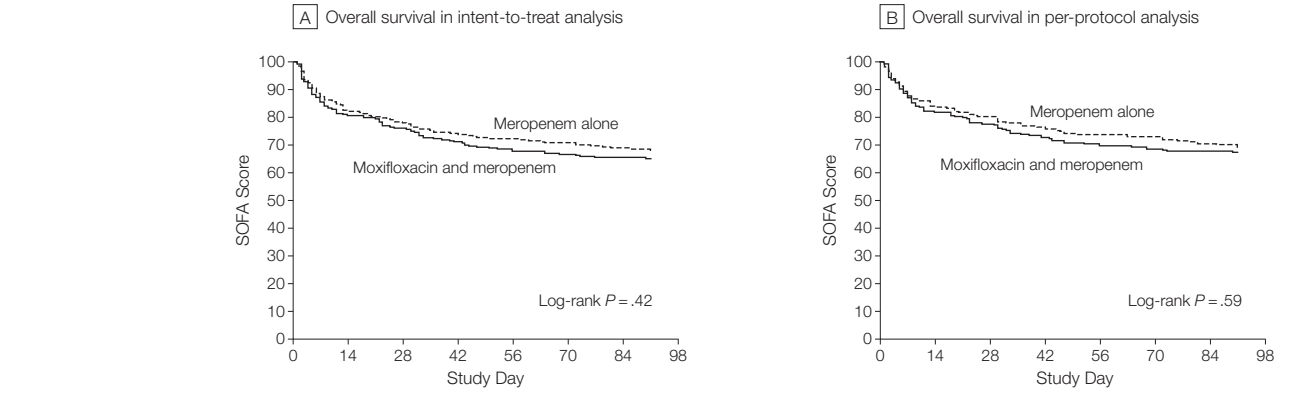
No. of evaluable patients

Meropenem alone	249	212	167	137	124	103	89
Moxifloxacin and meropenem	255	209	179	153	125	95	81

Meropenem alone	181	156	122	96	88	71	63
Moxifloxacin and meropenem	198	165	141	119	96	71	57

The data markers indicate means and the error bars indicate 95% CIs.

Figure 3. Overall Survival



No. of patients at risk

Meropenem alone	273	222	211	193	188	184	179
Moxifloxacin and meropenem	276	224	210	193	186	180	177

Meropenem alone	199	164	156	143	138	137	132
Moxifloxacin and meropenem	214	176	166	155	150	146	144

SOFA score (eFigure at http://www.jama.com). In addition, a predefined analysis excluding all patients treated for less than 4 days with study medication did not reveal significant differences (eFigure).

COMMENT

In this clinical trial of 551 patients with severe sepsis or septic shock, we found no beneficial effect of combination therapy including meropenem and moxifloxacin with regard to the 14-day mean SOFA score, or with regard to any secondary end point. There were no statistical differences in serious adverse events or major adverse event profiles between the 2 study groups.

To our knowledge, this is the first randomized trial of the empirical use of combination therapy compared with monotherapy in patients with severe sepsis or septic shock. However, several randomized trials of combination therapy vs monotherapy in serious infections, including endocarditis, gram-negative bacteremia, and neutropenic sepsis,[5,10,21] and animal models,[11,22,23] have supported the possibility of clinically relevant antimicrobial synergism with appropriate combinations of antibiotics. Two separate meta-analyses have failed to demonstrate any consistent benefit with combination therapy of β-lactams and aminoglycosides in immunocompetent patients with sepsis, gram-negative bacteremia, or both.[24,25]

In contrast, a meta-regression study by Kumar et al[26] suggested that the beneficial effect of combination therapy may be restricted to critically ill patients with septic shock. Another retrospective, propensity-matched, multicenter cohort study of 4662 patients with culture-positive, bacterial septic shock, also by Kumar et al,[27] demonstrated that combination therapy may decrease 28-day mortality (36.3% vs 29.0%; HR, 0.77 [95% CI, 0.67-0.88]; $P<.001$) and hospital mortality (47.8% vs 37.4%; odds ratio, 0.69 [95% CI, 0.59-0.81]; $P<.001$). The use of combination therapy also was associated with increased ventilator-free and pressor/inotrope-free days and significant reductions in stay in the ICU. The beneficial effects of combination therapy in the study by Kumar et al[27] applied to both gram-positive and gram-negative infections but these findings were restricted to patients treated with β-lactams in combination with aminoglycosides, fluoroquinolones, or macrolides/clindamycin. Carbapenems, extended-spectrum β-lactam or β-lactamase inhibitor combinations, and antipseudomonal cephalosporins, which tend to demonstrate optimal pharmacokinetic indices (with presumably maximal kill rates) for most septic shock pathogens, yielded the weakest evidence of benefit with combination therapy.

The findings from our clinical trial must be interpreted carefully. The specific antibiotic combination used in this trial failed to be superior to monotherapy. The rationale to select moxifloxacin was 3-fold. First, it was thought to increase the antimicrobial coverage to community-acquired infections, particularly gram-positive pathogens such as streptococci and staphylococci as well as atypical pathogens. Second, dual coverage of pathogens typically involved in intra-abdominal infections might be of value. Third, rapid antibacterial killing and anti-inflammatory effects described for moxifloxacin might exert additional beneficial effects. In fact, community-acquired infections comprised about 50% of cases. However, occurrence of *Streptococcus pneumoniae* was uncommon in our trial (4.5% of pathogens), and we cannot exclude the possibility that a trial including mainly patients with severe sepsis and septic shock due to community-acquired pneumonia would show a benefit from receiving combination treatment including moxifloxacin and meropenem.[28] Dual coverage of gram-negative Enterobacteriaceae would not result in superior outcomes due to the low number of such pathogens resistant to meropenem, although combination therapy may still be efficacious in the presence of a high rate of multidrug-resistant pathogens.

The outcome of septic shock (and probably severe sepsis) not only depends on adequate antimicrobial coverage but also on the timing of treatment initiation.[29] In our study, the rate of adequate initial antimicrobial treatment with meropenem was 96.8% (94.2% in the monotherapy group and 100% in the combination therapy group) among patients tested. Initiation of antimicrobial treatment occurred predominantly within the first 1½ hours after enrollment. In observational studies, both factors might be less controlled and account for differences in outcomes. Therefore, our results must be interpreted on the background of optimal management of patients within the predefined study setting.

We found a higher rate of carbapenem-resistant pathogens in the monotherapy compared with the combination therapy group after treatment (until ICU discharge or day 21). However, the numbers were small (8 patients vs 1 patient; Table 4). Development of carbapenem resistance during treatment has been described and initial combination with fluoroquinolones may prevent the risk for selection of carbapenem-resistant pathogens during treatment.[30]

Our data provide evidence for shorter treatment duration for patients with severe sepsis and septic shock. Using a procalcitonin-guided treatment protocol on study days 7 and 10, the median treatment duration was 8 days for monotherapy and 7 days for combination therapy, and the upper IQR for both groups was 10 days. This finding is consistent with recent data using procalcitonin as a guide to limit treatment duration in a similar patient population.[31]

In conclusion, in this randomized multicenter trial of adult patients with severe sepsis or septic shock, empirical treatment with the combination of meropenem and moxifloxacin compared with meropenem alone did not result in less organ failure.

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Online-Only Material: The eMethods, eTables 1-4, and the eFigure are available at http://www.jama.com.

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