ORIGINAL ARTICLE

Prevention of Early Ventilator-Associated Pneumonia after Cardiac Arrest

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ABSTRACT

BACKGROUND

Patients who are treated with targeted temperature management after out-of-hospital cardiac arrest with shockable rhythm are at increased risk for ventilator-associated pneumonia. The benefit of preventive short-term antibiotic therapy has not been shown.

METHODS

We conducted a multicenter, double-blind, randomized, placebo-controlled trial involving adult patients (>18 years of age) in intensive care units (ICUs) who were being mechanically ventilated after out-of-hospital cardiac arrest related to initial shockable rhythm and treated with targeted temperature management at 32 to 34°C. Patients with ongoing antibiotic therapy, chronic colonization with multidrug-resistant bacteria, or moribund status were excluded. Either intravenous amoxicillin–clavulanate (at doses of 1 g and 200 mg, respectively) or placebo was administered three times a day for 2 days, starting less than 6 hours after the cardiac arrest. The primary outcome was early ventilator-associated pneumonia (during the first 7 days of hospitalization). An independent adjudication committee determined diagnoses of ventilator-associated pneumonia.

RESULTS

A total of 198 patients underwent randomization, and 194 were included in the analysis. After adjudication, 60 cases of ventilator-associated pneumonia were confirmed, including 51 of early ventilator-associated pneumonia. The incidence of early ventilator-associated pneumonia was lower with antibiotic prophylaxis than with placebo (19 patients [19%] vs. 32 [34%]; hazard ratio, 0.53; 95% confidence interval, 0.31 to 0.92; P=0.03). No significant differences between the antibiotic group and the control group were observed with respect to the incidence of late ventilator-associated pneumonia (4% and 5%, respectively), the number of ventilator-free days (21 days and 19 days), ICU length of stay (5 days and 8 days if patients were discharged and 7 days and 7 days if patients had died), and mortality at day 28 (41% and 37%). At day 7, no increase in resistant bacteria was identified. Serious adverse events did not differ significantly between the two groups.

CONCLUSIONS

A 2-day course of antibiotic therapy with amoxicillin–clavulanate in patients receiving a 32-to-34°C targeted temperature management strategy after out-of-hospital cardiac arrest with initial shockable rhythm resulted in a lower incidence of early ventilator-associated pneumonia than placebo. No significant between-group differences were observed for other key clinical variables, such as ventilator-free days and mortality at day 28. (Funded by the French Ministry of Health; ANTHARTIC ClinicalTrials.gov number, NCT02186951.)

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Despite improved management, overall survival rates at hospital discharge among patients with out-of-hospital cardiac arrests do not exceed 20%, and neurologic outcomes remain poor.[1] Even though controversies persist, targeted temperature management at 32 to 36°C remains recommended in patients with out-of-hospital cardiac arrest with initial shockable rhythm,[2] since it has beneficial effects on morbidity and mortality.[3] However, targeted temperature management is associated with an increased risk of secondary infections[4,5] and constitutes an independent risk factor for early ventilator-associated pneumonia.[5,6]

The key early study suggesting the benefit of single-day administration of cefuroxime in patients with coma was performed more than 20 years ago.[7] Few studies have been conducted since, including one single-center, small, unblinded, prospective, randomized, controlled trial[8] and one prospective, nonrandomized cohort study.[9] Moreover, several retrospective studies showed a decreased incidence of infectious complications and decreased related morbidity when antibiotic therapy was given early to patients receiving targeted temperature management after cardiac arrest.[10-12]

Therefore, we hypothesized that systematic administration of empirical 2-day antibiotic therapy could prevent early ventilator-associated pneumonia and related complications in patients with out-of-hospital cardiac arrest treated with targeted temperature management, without clinically or biologically significant adverse effects, and could reduce intensive care unit (ICU) and hospital lengths of stay and medical costs related to ventilator-associated pneumonia. With consideration of the most frequently isolated bacteria in early ventilator-associated pneumonia after out-of-hospital cardiac arrests[5] and treatment duration in previous studies[7-9] and to avoid the development of antibiotic resistance with prolonged antibiotic therapy,[13] 2-day treatment with amoxicillin–clavulanate was chosen for the Antibiotherapy during Therapeutic Hypothermia to Prevent Infectious Complications (ANTHARTIC) trial.

METHODS

TRIAL DESIGN

This was a randomized, double-blind, placebo-controlled trial conducted in 16 ICUs in France (university and nonuniversity hospitals). The trial was approved by the Limoges Ethics Committee. Written informed consent was obtained from a relative of each patient or through an emergency consent procedure. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol, which is available with the full text of this article at NEJM.org.

PATIENTS

Adult patients (>18 years of age) hospitalized in the ICU after an out-of-hospital cardiac arrest with shockable rhythm and treated with 32-to-34°C targeted temperature management were eligible; eligibility criteria were based on previous randomized, controlled trials.[14,15] Exclusion criteria were out-of-hospital cardiac arrest with nonshockable rhythm, in-hospital cardiac arrest, ongoing pneumonia or gross aspiration identified during direct laryngoscopy for tracheal intubation and confirmed by the presence of lung infiltrates on chest radiographs at admission, pregnancy, previous lung disease precluding accurate interpretation of chest radiographs, the use of extracorporeal life support, ongoing antibiotic therapy or during the week before admission, known chronic colonization with multidrug-resistant bacteria, known allergy to beta-lactam antibiotics, contraindications to amoxicillin or clavulanate, predictable decision of early care limitation (within 7 days), moribund status, and participation in another trial within the previous 30 days. Patients had to undergo randomization within 6 hours after the return of spontaneous circulation to uniformly start antibiotics early enough to prevent early ventilator-associated pneumonia.

INTERVENTIONS

Patients in the antibiotic group received a 2-day antibiotic therapy (amoxicillin–clavulanate at a dose of 1 g and 200 mg, respectively, with three injections per day), whereas patients in the control group received saline at the same frequency (three injections per day for 2 days). Targeted temperature management was maintained at 32 to 34°C for 24 to 36 hours, and body temperature was monitored hourly. Although the sedation protocol, the use of neuromuscular blockade agents, and the method of targeted temperature management were left to the inves-

tigators' discretion, rapid initiation of targeted temperature management was required (e.g., infusion of iced saline). When indicated and after careful documentation, all patients who had a secondary infection received curative antibiotic therapy according to local guidelines.

RANDOMIZATION AND BLINDING

Patients were randomly assigned by means of a secure, computer-generated, Web-response system in a 1:1 ratio. Randomization was stratified according to center, and the sequence was computer generated by a statistician not involved in recruitment using a fixed block size of four units. Patients, care providers, and members of the adjudication committee were unaware of the trial-group assignments. (For details on the procedure for adjudicating ventilator-associated pneumonia, see the Supplementary Appendix, available at NEJM.org.)

OUTCOMES

Daily during the ICU stay, patients were evaluated for nosocomial infections, especially ventilator-associated pneumonia. Patients' vital status and scores on the Cerebral Performance Category scale were followed during 12 months (months 3, 6, and 12). The primary outcome was the onset of early ventilator-associated pneumonia (during the first 7 days of hospitalization). Because there is no universally accepted cutoff value to differentiate early from late ventilator-associated pneumonia,[16] we purposely used 7 rather than 5 days of hospitalization to better assess the potential benefit of a 2-day antibiotic treatment and to best document microbiologically the cases of ventilator-associated pneumonia. The main secondary outcomes were late ventilator-associated pneumonia (after day 7 of hospitalization through ICU discharge or death), other nosocomial infections (bloodstream and urinary tract infections), mortality at day 28, intestinal acquisition of multidrug-resistant bacteria on day 7 according to solid selective media for the detection of such bacteria in stool samples (enterobacteria resistant to third-generation cephalosporins, carbapenemase-producing enterobacteria, methicillin-resistant *Staphylococcus aureus*, and vancomycin-resistant enterococcus on the Drigalski–MacConkey BLSE, the chromID CARBA SMART, the chromID MRSA, and the chromID VRE agar plates, respectively [bioMérieux]), percentage of days with antibiotic use (outside the trial intervention) during the ICU stay, length of stay in the ICU, number of ventilator-free days until day 28, and costs consequence analysis.

DIAGNOSIS OF VENTILATOR-ASSOCIATED PNEUMONIA AND ADJUDICATION PROCESS

Routine use of a bundle of measures for the prevention of ventilator-associated pneumonia (elevation of the head of the bed, daily "sedation vacations" and assessment of readiness to extubate, and deep-vein thrombosis prophylaxis) and daily oral care were highly recommended, and specific attention was given to standardize patient care.[17] In cases of suspected ventilator-associated pneumonia, the Clinical Pulmonary Infection Score and Sequential Organ Failure Assessment score were assessed, and bedside anteroposterior chest radiography, arterial blood gas analysis, blood cultures, and quantitative sampling of the lower respiratory tract[18] (by either bronchoalveolar lavage or endotracheal aspiration, at the discretion of the attending physician) were performed before any antibiotics were administered. An adjudication committee, composed of three senior intensivists who had experience in trials of ventilator-associated pneumonia and who were unaware of the trial-group assignments, reviewed all patients' medical charts and adjudicated all respiratory tract infections. Such infections were defined as early if they occurred within 7 days after randomization and as late if they occurred after 7 days, according to an adjudication charter (see the Supplementary Appendix) and the definition of ventilator-associated pneumonia.

To confirm reported clinical ventilator-associated pneumonia, the events were defined in a standardized approach with the use of criteria from 2010 Food and Drug Administration guidance for diagnosis and confirmation of ventilator-associated pneumonia,[19] which relies on clinical, radiologic, and microbiologic criteria (patients had to meet all three types of criteria). Clinical criteria were documented fever or hypothermia (with fever defined as an oral or tympanic temperature ≥38°C and hypothermia defined as a core body temperature <35°C), an abnormal total peripheral white-cell count (>10,000 per cubic millimeter or >15% immature neutrophils [bands], regardless of white-cell count, or leukopenia with a white-cell count <4500 per cubic milli-

meter), new-onset purulent sputum or change in the character of sputum, and a Clinical Pulmonary Infection Score of more than 6 (scores range from 0 to 10, with higher scores associated with a greater probability of pneumonia) plus at least one of the following two features: auscultatory findings on pulmonary examination of rales or evidence of pulmonary consolidation, or acute changes made in the ventilator support system to enhance oxygenation, as determined by arterial blood gas analysis, or a worsening ratio of partial pressure of arterial oxygen to the fraction of inspired oxygen. Radiographic criteria were the presence of new or progressive and persistent infiltrate characteristic of bacterial pneumonia or new consolidation. Microbiologic criteria were a respiratory culture that was positive and at the specified thresholds to be considered clinically significant amounts, as determined by standard culture (endotracheal aspirate, 10^6 colony-forming units [CFU] per milliliter; bronchoalveolar-lavage specimen, 10^4 CFU per milliliter).

The intensivists had access to all monitored data, chest radiographs obtained during the ICU stay, and microbiologic documentation. Two of them analyzed data from every patient independently, and in case of disagreement, the third one arbitrated the diagnosis of ventilator-associated pneumonia. All secondary infections that occurred during the ICU stay were also recorded. To document the potential emergence of multidrug-resistant bacteria, a rectal swab was obtained on day 0 and day 7 for central laboratory analysis.

STATISTICAL ANALYSIS

In the control group, we assumed that the incidence of ventilator-associated pneumonia on day 7 would reach 68%, since other trials showed an incidence of 63%[20] and 65%.[5] Hypothesizing a 25% lower incidence of early ventilator-associated pneumonia in the antibiotic group than in the control group on the basis of previous randomized, controlled trials[7-9] and considering a two-sided, 5% type I error rate and 90% power, we calculated that the required number of events to be observed was 91 and the required number of patients to be included was 163. Because death was a competing event relative to ventilator-associated pneumonia, the sample size was adjusted with the use of Schulgen's approach.[21] Considering a mortality of 15% (without previous occurrence of ventilator-associated pneumonia), we calculated that 192 patients ($163 \div 0.85$) were needed.

Patients who did not receive any dose of amoxicillin–clavulanate or placebo were excluded from the analysis.[22] Cumulative incidence curves of the primary outcome were estimated and compared with the use of the Fine–Gray approach.[23] No adjustment for multiple testing on secondary outcomes was performed. The between-group difference in mortality at day 28 was estimated on the basis of the two-sided 95% confidence interval. For the percentage of days with antibiotic use during the ICU stay and the number of ventilator-free days until day 28, two-sided 95% confidence intervals of median differences were estimated on the basis of the Hodges–Lehmann estimator.[24] Safety data were assessed with the use of chi-square tests. Statistical analyses were performed with the use of SAS software, version 9.4 (SAS Institute), and R software, version 3.3.1. Additional information is provided in the Supplementary Appendix.

RESULTS

DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

From August 18, 2014 to September 14, 2017, a total of 1116 patients were screened in the emergency departments of the trial centers, and 198 were included and underwent randomization (median age, 61 years [interquartile range, 50 to 73]; 80% men). The main reasons for screening failure were out-of-hospital cardiac arrest with nonshockable rhythm, in-hospital cardiac arrest, an interval of 6 hours or longer between the return of spontaneous circulation and randomization, aspiration pneumonia, and moribund status. Four patients (all assigned to receive placebo) were excluded after randomization because they did not receive any injection or they withdrew their consent. Finally, 194 patients were included in the analysis (99 in the antibiotic group and 95 in the control group) (Fig. 1). Targeted temperature management was initiated a median of 5.4 hours (interquartile range, 4.3 to 6.1) after out-of-hospital cardiac arrest. External cooling was used in 87% of the patients in each group. Patients' characteristics are presented in Table 1.

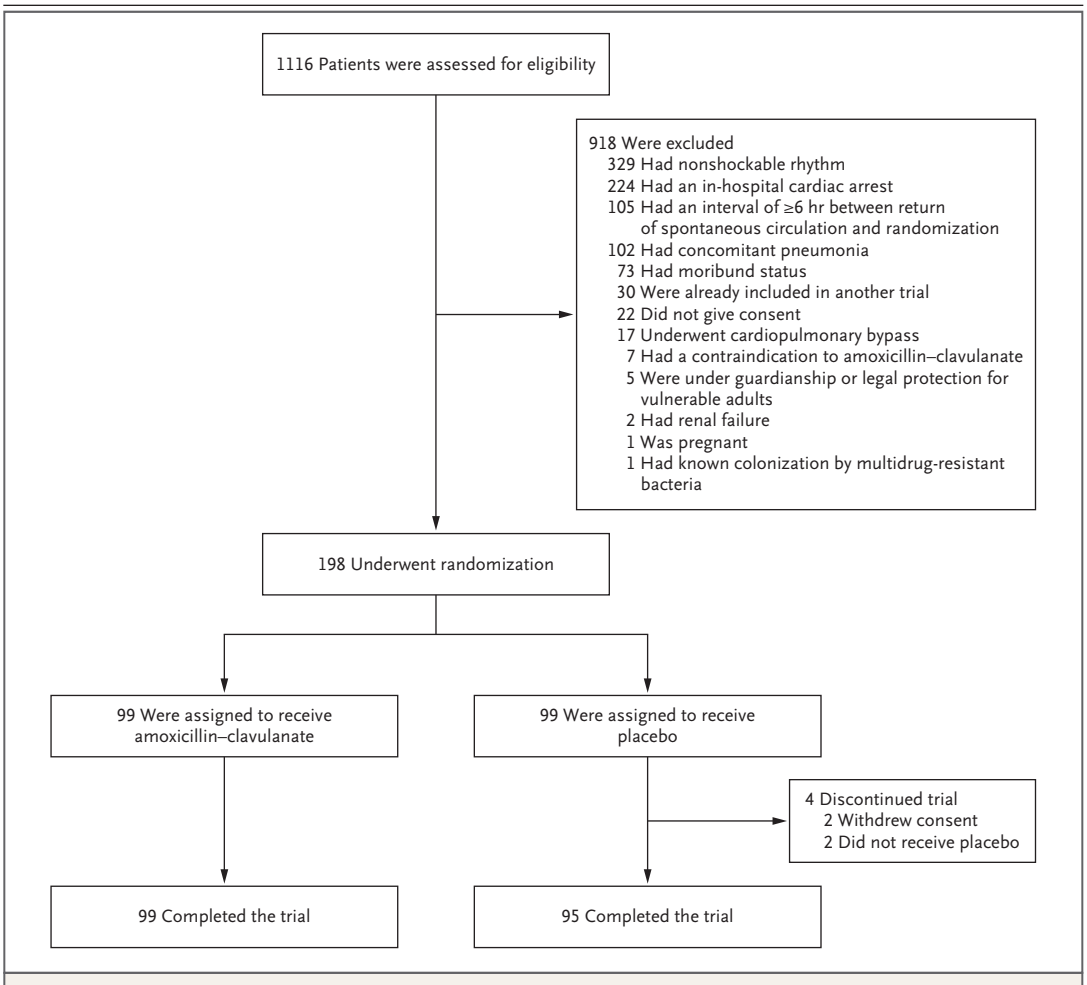

Figure 1. Screening and Randomization.

CLINICAL OUTCOME

A total of 80 cases of ventilator-associated pneumonia were reported by the investigators (31 [31% of the patients] in the antibiotic group and 49 [52%] in the control group), of which 60 cases were assessed as ventilator-associated pneumonia by the adjudication committee (23 [23%] in the antibiotic group and 37 [39%] in the control group). The adjudication committee only reported cases with pathogen documentation. Respiratory sampling was performed with the use of bronchoalveolar lavage and mini–bronchoalveolar lavage in 31 patients and endotracheal aspiration in 29 patients. The initial rate of agreement between the two adjudicators was 78%, and for the remaining cases with disagreement, a decision was made by the referee adjudicator. There were 51 cases of early ventilator-associated pneumonia and 9 cases of late ventilator-associated pneumonia.

The incidence of early ventilator-associated pneumonia was lower among patients who received amoxicillin–clavulanate than among those who received placebo (cumulative incidence on day 7, 19% vs. 34%; hazard ratio, 0.53; 95% confidence interval [CI], 0.31 to 0.92; P=0.03) (Fig. 2A), whereas the occurrence of late ventilator-associated pneumonia was similar in the two groups (4 of 99 patients and 5 of 95 patients, respectively). Similar results were obtained when we used the 5-day cutoff value to distinguish early from late ventilator-associated pneumonia (cumulative incidence on day 5, 17% in the antibiotic group vs. 31% in the control group; haz-

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Antibiotic Group (N=99)	Control Group (N=95)
Median age (IQR) — yr	61 (50–73)	60 (51–72)
Male sex — no. (%)	76 (77)	80 (84)
Median body-mass index (IQR)†	26 (24–29)	27 (24–29)
Medical history		
Median score on the Charlson Comorbidity Index (IQR)‡	2 (1–4)	2 (1–4)
Chronic lung disease — no. (%)	6 (6)	9 (9)
Immunosuppression — no. (%)	3 (3)	0
Chronic heart disease — no. (%)	23 (23)	28 (29)
Diabetes — no. (%)	10 (10)	6 (6)
Out-of-hospital cardiac arrest		
Witnessed — no. (%)	94 (95)	90 (95)
Median no-flow time (IQR) — min§	2 (0–5)	3 (0–6)
Median low-flow time (IQR) — min§	20 (10–28)	18 (12–25)
Median time to intubation (IQR) — min	20 (12–34)	22 (13–33)
Initial shockable rhythm — no. (%)		
Ventricular fibrillation	84 (85)	74 (78)
Ventricular tachycardia without pulse	13 (13)	10 (11)
Other	2 (2)	11 (12)
Median no. of electric shocks (IQR)	3 (2–4)	2 (1–3)
Catecholamine support — no. (%)	73 (74)	67 (71)
Antiarrhythmic drugs — no. (%)	39 (39)	45 (47)
Suspected aspiration — no. (%)	3 (3)	8 (8)
Median baseline temperature (IQR) — °C	35 (35–36)	36 (35–36)
Median score on the Glasgow Coma Scale (IQR)¶	3 (3–3)	3 (3–3)
Median SOFA score (IQR)‖	8 (7–12)	9 (6–11)
Median APACHE II score (IQR)**	24 (22–28)	24 (20–28)
Mild therapeutic hypothermia		
Median interval between out-of-hospital cardiac arrest and hypothermia (IQR) — hr	6 (4–6)	5 (5–6)
Median duration of hypothermia (IQR) — hr	30 (24–34)	29 (23–33)
Median target temperature (IQR) — °C	34 (33–35)	34 (33–34)

* Percentages may not total 100 because of rounding. IQR denotes interquartile range.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ Scores on the Charlson Comorbidity Index range from 0 to 37, with higher scores indicating more coexisting conditions.
§ No-flow time refers to the period without any cardiopulmonary resuscitation procedure, and low-flow time refers to the total period with active cardiopulmonary resuscitation but without sustained spontaneous circulation.
¶ Scores on the Glasgow Coma Scale range from 3 to 15, with lower scores indicating a reduced level of consciousness.
‖ Scores on the Sequential Organ Failure Assessment (SOFA) range from 0 to 24 (from 0 to 4 for each of six organ systems), with higher scores indicating more severe organ dysfunction.
** Scores on the Acute Physiology and Chronic Health Evaluation (APACHE) II range from 0 to 71, with higher scores indicating a higher risk of death.

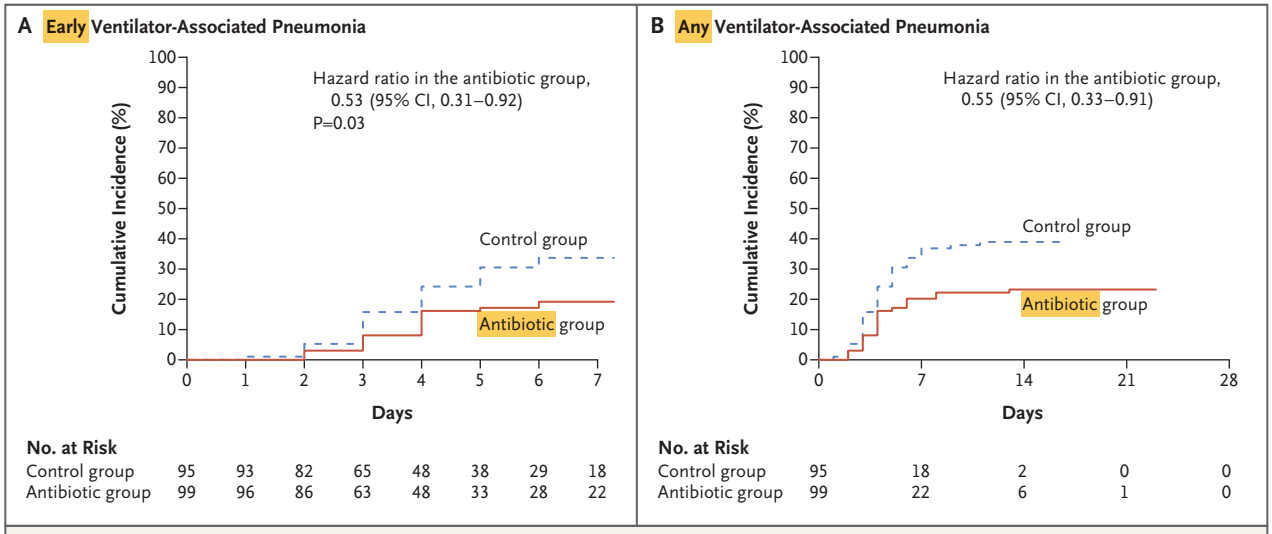

Figure 2. Cumulative Incidence of Ventilator-Associated Pneumonia.

Cumulative incidence curves of early ventilator-associated pneumonia (during the first 7 days of hospitalization) (Panel A) and any ventilator-associated pneumonia (Panel B) were compared with the use of the Fine–Gray approach between patients assigned to receive amoxicillin–clavulanate (1 g and 200 mg, respectively) three times a day for 2 days (antibiotic group) and those assigned to receive placebo (control group).

ard ratio, 0.53; 95% CI, 0.30 to 0.95; P=0.03). No significant difference in the incidence of ventilator-associated pneumonia was observed when the method of targeted temperature management was considered (P=0.49 for interaction), and no effect of trial center was noted. Overall, the risk of ventilator-associated pneumonia was lower among patients who received antibiotics than those who received placebo (hazard ratio, 0.55; 95% CI, 0.33 to 0.91) (Fig. 2B).

Nonpulmonary secondary infectious complications were equally distributed between the two groups (Table 2). The median percentage of days with antibiotic use (outside the trial intervention) during the ICU stay tended to be lower in the antibiotic group than in the control group (23% [interquartile range, 0 to 64] vs. 50% [0 to 70]; median difference, 0 days; 95% CI, –15 to 0). The trial procedure did not significantly influence the median number of ventilator-free days (21 [interquartile range, 0 to 26] and 19 [interquartile range, 0 to 25], respectively; median difference, 0 days; 95% CI, 0 to 0). The median ICU length of stay did not differ significantly between the two groups, regardless of whether patients were discharged (5 days [interquartile range, 3.5 to 8.5] in the antibiotic group and 8 days [interquartile range, 3 to 11] in the control group) or had died (7 days [interquartile range, 4 to 12] and 7 days [interquartile range, 5 to 9], respectively). Mortality at day 28 was 39% and did not differ significantly between the two groups (41% in the antibiotic group and 37% in the control group; difference, 4 percentage points; 95% CI, –10 to 18) (Table S1 in the Supplementary Appendix). No death was attributable to ventilator-associated pneumonia or sepsis. More than half the patients who were enrolled had a good neurologic outcome (Cerebral Performance Category of 1 or 2, on a scale from 1 [good cerebral performance] to 5 [death or brain death]) on day 28. This percentage was similar at 3 months and 12 months (Table S2).

MICROBIOLOGIC FINDINGS

Microbiologic documentation of early and late ventilator-associated pneumonia in each group is presented in Table 3 and Table S3, respectively. Colonization cases were excluded from the analysis by the adjudication committee and are not reported. Most cases of ventilator-associated pneumonia were polymicrobial (60%), with

Table 2. Infectious Complications.*

Complication	Antibiotic Group (N=99)	Control Group (N=95)	Hazard Ratio (95% CI)	P Value
	number (percent)			
Ventilator-associated pneumonia†‡	23 (23)	37 (39)	0.55 (0.33–0.91)	
Early‡	19 (19)	32 (34)	0.53 (0.31–0.92)	0.03
Late	4 (4)	5 (5)		
Catheter-related bloodstream infection	1 (1)	1 (1)		
Urinary tract infection	4 (4)	3 (3)		
Other infections§	0	2 (2)		

* Unless otherwise indicated, no statistical test was performed, owing to small sample size.
† Ventilator-associated pneumonia that occurred during the first 7 days of hospitalization was defined as early, and ventilator-associated pneumonia that occurred after the first 7 days of hospitalization was defined as late.
‡ Outcomes that are reported as cumulative incidence were analyzed with the use of a competing-risk approach.
§ In the control group, infectious endocarditis occurred in one patient, and purulent pleural effusion occurred in another patient.

two bacteria per sample and a majority of gram-negative bacilli. In the control group, the main causative microorganisms were *Haemophilus influenzae* (16 cases [24% of the pathogens in this group]) and *Escherichia coli* (8 cases [12%]) with respect to gram-negative bacilli, and *S. aureus* (8 cases [12%]) and *Streptococcus pneumoniae* (6 cases [9%]) with respect to gram-positive cocci. In the antibiotic group, *S. aureus* had the highest incidence for gram-positive cocci (4 cases [10%]). The main relevant difference in terms of microbiologic pattern was for gram-negative bacilli, with more cases of enterobacteria such as *Serratia marcescens* (4 cases [10%]), *Hafnia alvei* (3 cases [7%]), and klebsiella species (4 cases [10%]) in the antibiotic group than in the control group.

Two strains were resistant to the third-generation medication cephalosporin, one *Enterobacter cloacae* in the control group and one *Klebsiella pneumoniae* in the antibiotic group among patients with early ventilator-associated pneumonia. *Pseudomonas aeruginosa* was documented in 6 (6%) of the samples, half of them from patients who had late ventilator-associated pneumonia. The microbiologic pattern of late ventilator-associated pneumonia was predominantly gram-negative bacilli (13 cases [81%]) and especially enterobacteria. Rectal swabbing before and after the trial intervention did not show an emergence of multidrug-resistant bacteria, with seven patients documented with such bacteria (five in the control group and two in the antibiotic group) at day 0 and eight patients (seven in the control group and one in the antibiotic group) at day 7.

SAFETY

Of 309 adverse events reported, 107 (35%) were reported as serious, without a significant difference between the antibiotic group and the control group (55 serious adverse events in 48 patients and 52 serious adverse events in 42 patients, respectively; difference in incidence, 4 percentage points; 95% CI, –10 to 18). Most serious adverse events involved the nervous system (59 events), with the majority of such events being postanoxic encephalopathy (37). A total of 10 recurrences of cardiac arrest and 7 cases of multiple organ failure were also reported. None of the serious adverse events was considered by investigators to be related to the trial intervention (Table S4).

DISCUSSION

In patients treated with targeted temperature management after resuscitation of out-of-hospital cardiac arrests with shockable rhythm, we found that a 2-day treatment with amoxicillin–clavulanate resulted in a lower incidence of early ventilator-associated pneumonia than placebo. The overall 31% incidence of ventilator-associated

Table 3. Microbiologic Documentation of Confirmed Early Ventilator-Associated Pneumonia.*

Pathogen	Antibiotic Group (N=33)	Control Group (N=59)	Total (N=92)
	number of cases (percent of pathogens)		
Gram-negative bacilli			
Haemophilus influenzae	5 (15)	15 (25)	20 (22)
Escherichia coli	3 (9)	7 (12)	10 (11)
Citrobacter koseri	2 (6)	1 (2)	3 (3)
Citrobacter freundii	2 (6)	0	2 (2)
Klebsiella pneumoniae	2 (6)	2 (3)	4 (4)
Klebsiella oxytoca	0	1 (2)	1 (1)
Enterobacter cloacae	1 (3)	2 (3)	3 (3)
Enterobacter aerogenes	1 (3)	1 (2)	2 (2)
Serratia marcescens	3 (9)	0	3 (3)
Hafnia alvei	3 (9)	0	3 (3)
Pseudomonas aeruginosa	1 (3)	2 (3)	3 (3)
Proteus vulgaris	1 (3)	1 (2)	2 (2)
Proteus mirabilis	0	1 (2)	1 (1)
Raoultella species	0	2 (3)	2 (2)
Acinetobacter species	0	1 (2)	1 (1)
Other	1 (3)	3 (5)	4 (4)
Gram-positive cocci			
Staphylococcus aureus	3 (9)	8 (14)	11 (12)
Streptococcus pneumoniae	0	6 (10)	6 (7)
Streptococcus species	0	3 (5)	3 (3)
Gram-negative cocci			
Neisseria species	1 (3)	1 (2)	2 (2)
Moraxella species	1 (3)	0	1 (1)
Gram-positive bacilli: corynebacterium species	0	2 (3)	2 (2)
Fungi: candida species	3 (9)	0	3 (3)

* A total of 33 pathogens were observed in samples from the antibiotic group, and 59 pathogens were observed in samples from the control group. Percentages may not total 100 because of rounding.

pneumonia that was observed in the current trial was lower than that previously reported in similar ICU populations.[5,20,25,26] It is important that patients with overt aspiration were not enrolled in our trial and that systematic implementation of bundles known to decrease the incidence of ventilator-associated pneumonia in the ICU was highly recommended.[27]

The diagnosis of ventilator-associated pneumonia remains complex owing to considerable heterogeneity in its definition,[28,29] especially in patients with out-of-hospital cardiac arrest receiving targeted temperature management. To minimize a potential reporting bias, a central adjudication committee whose members were unaware of the trial-group assignments diagnosed ventilator-associated pneumonia on the basis of predefined criteria. One fourth of the cases of ventilator-associated pneumonia that were initially reported by investigators were not subsequently confirmed during adjudication. Despite the potential eradication of microorganisms in the treatment group (complicating the diagnosis of ventilator-associated pneumonia), the between-group

difference in the incidence of ventilator-associated pneumonia after adjudication tended to be smaller than the difference in the incidence of pneumonia reported by investigators during the trial period (16 percentage points after adjudication vs. 20 percentage points before adjudication). Overall, these specific factors presumably account for the lower incidence of ventilator-associated pneumonia in this trial than in previous trials, despite the fact that the characteristics were similar among the trial populations.

A randomized trial has previously shown that short-term treatment with amoxicillin–clavulanate failed to prevent ventilator-associated pneumonia in patients with out-of-hospital cardiac arrest as compared with placebo (50% in both groups).[30] Nevertheless, this single-center trial was underpowered and limited by the absence of adjudication of secondary infections. Less than 10% of screened ICU patients were excluded for having an interval of 6 hours or longer between the return of spontaneous circulation and randomization. In the present trial, the absence of effects of short-term antibiotic therapy on the incidence of other secondary infections (the incidence of which increases with targeted temperature management[4,20]) may have been related to the sample size and the lower incidence of these complications.

Microbiologic documentation of ventilator-associated pneumonia in the control group was similar to that previously described in European ICUs,[5,10,20,25,30,31] with a predominance of gram-negative bacteria susceptible to amoxicillin–clavulanate.[32] Some authors suggested that such a therapeutic strategy could alter the microbiota and the epidemiology of secondary infections.[33,34] In our limited sampling, we noted a higher frequency of enterobacteria among patients who received amoxicillin–clavulanate than among those who received placebo; however, the implications are unclear (e.g., similar incidence of *P. aeruginosa* and methicillin-resistant *S. aureus*).[9,35] No *Clostridium difficile* infection was reported. In our trial, the 2-day course of amoxicillin–clavulanate that was used was not associated with the emergence of difficult-to-treat microorganisms, as suggested previously,[36] although the number of events was fairly limited.

The trial treatment did not affect mortality at day 28 or the number of ventilator-free days, findings that are consistent with that of previous research.[7] This is presumably related to the low mortality attributable to ventilator-associated pneumonia (<10%) among ICU patients.[37,38] As expected, the prognosis of our population was mainly driven by neurologic outcome due to hypoxic ischemic brain injury[39,40]; most of the deaths were related to care withdrawal. Nevertheless, more than 50% of the patients had a good neurologic outcome (Cerebral Performance Category of 1 or 2 at month 12). The incidence of late ventilator-associated pneumonia was not influenced by our intervention, a finding consistent with that of previous studies,[8,9] since late ventilator-associated pneumonia is mostly driven by prolonged mechanical ventilation with a distinct microbiologic epidemiology.

Our trial has some limitations. First, even if risk factors for the development of ventilator-associated pneumonia are not related to initial rhythm,[5,6] we cannot extend the benefit of the trial treatment to patients with an in-hospital cardiac arrest or out-of-hospital cardiac arrest with nonshockable rhythm. Second, patients with overt aspiration were not included in the trial. Third, microbiota analysis was designed to detect multidrug-resistant bacteria only and was not repeated after day 7. It could be informative to better analyze the consequences of a short-term antibiotic treatment on microbiota that play a role in the protective, structural, and metabolic gut function. Fourth, whether the present results apply to patients with out-of-hospital cardiac arrest whose condition is managed with a different targeted temperature remains to be determined.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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APPENDIX

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