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ORIGINAL ARTICLE

Prevention of Early Ventilator-Associated Pneumonia after Cardiac Arrest

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Background

- Targeted temperature management (TTM) 32-36 °C is recommended for patients with out-of hospital cardiac arrest an initial shockable rhythm
- TTM is associated with an increased risk of pneumonia

Study aim

- Effect of an 48h empiric therapy with CoAmoxicillin regarding
- Primary Outcome:
  - Onset of early ventilator associated pneumonia (VAP)
- Secondary main outcome:
  - Onset of late VAP
  - Other nosocomial infections
  - Mortality on day 28
  - Intestinal acquisition of multidrug-resistant bacteria on day 7
  - Percentage of days with antibiotic use in ICU (outside trial)
  - Length of stay in ICU
  - Ventilator-free days (until day 28)

Methods: Trial design

- randomized
- double-blind
- placebo- controlled
- conducted in 16 ICUs in France (university and nonuniversity hospitals)

Methods: Patients

- Inclusion criteria
  - >18 years of age
  - hospitalized in the ICU after an out-of-hospital cardiac arrest with shockable rhythm
  - Treatment with 32-to-34°C
- Exclusion criteria
  - Non-shockable rhythm
  - Ongoing pneumonia or gross aspiration
  - Ongoing antibiotic therapy (or during 7 days before admission)
  - Chronic colonization with multidrug-resistenat bacteria
  - Prevoius lung disease precluding accurate interpretations of chest radiographs
  - Moribund status or predictable decision of early care limitations (7 days)
  - Pregnancy
  - Participation in another trial within previous 30 days

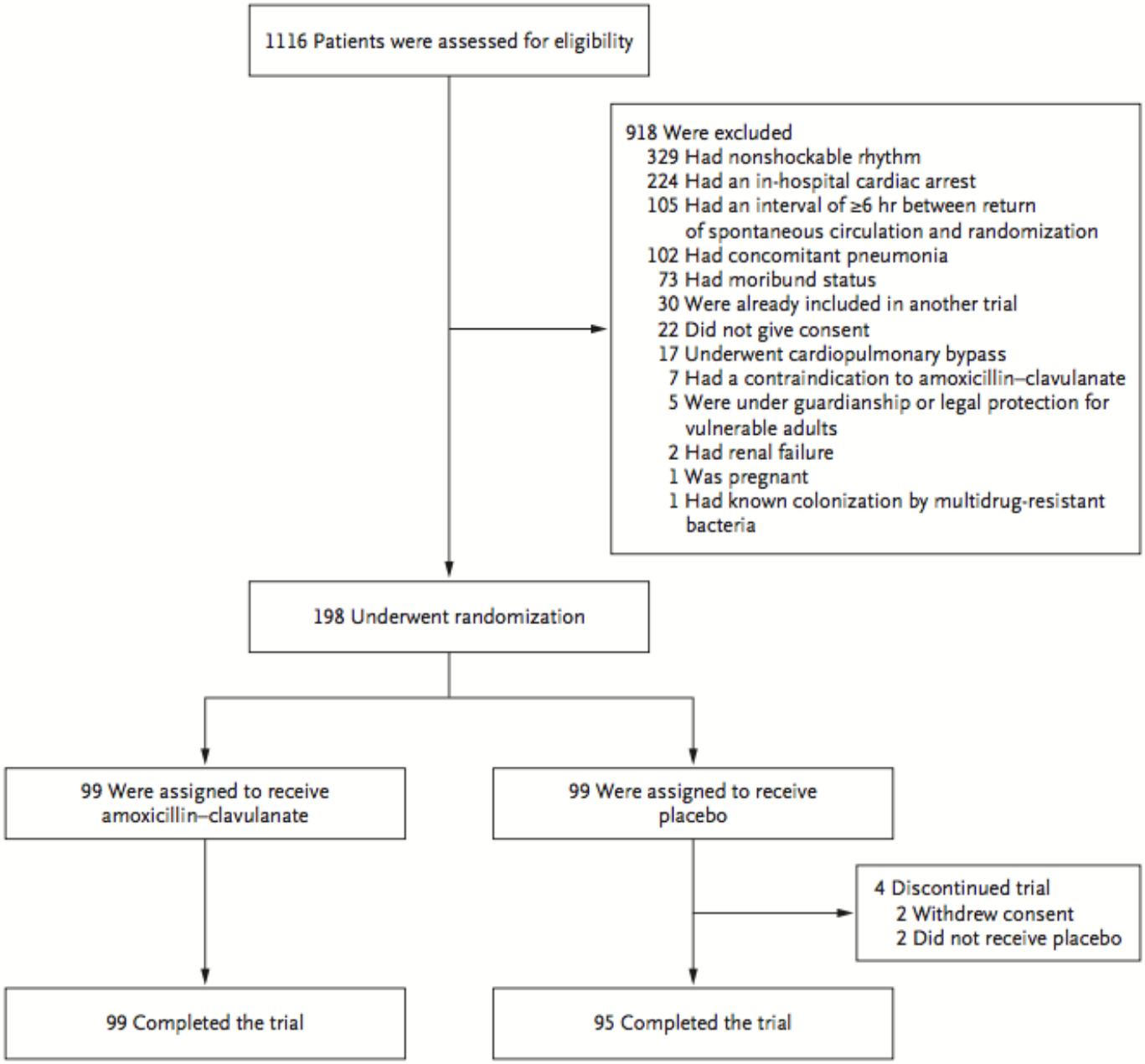
Methods: Randomization & Intervention

- Randomization was performed within 6 hours after return of spontaneous circulation
- 1:1 Ratio
- TTM was performed with 32-34°C for 24-36h
- Antibiotic group
  - CoAmoxicillin 1200 mg 3x/d
  - 48h treatment

Methods: Diagnosis of VAP

- Clinical, radiologic and microbiologic criteria
- Clinical
  - Fever/hypothermia, Leukozytosis/-penia, new purulent sputum
  - *auscultary findings and or changes in ventilator support system to enhance ventilation
- Radiographic
  - New/progressive infiltrates or new consolidation
- Microbiologic
  - Positive respiratory culture
- Clinical Pulmonary Infection Score > 6 (0-10)
- Adjudication through 3 senior intensivists

Results:
Screening and Randomization



Results:
Patients Characteristics

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)

Results: VAP

- 80 reported and 60 confirmed cases of VAP
- 23 cases in the antibiotic group; 37 cases in the control group
- 51 cases of early VAP; 9 cases of late VAP

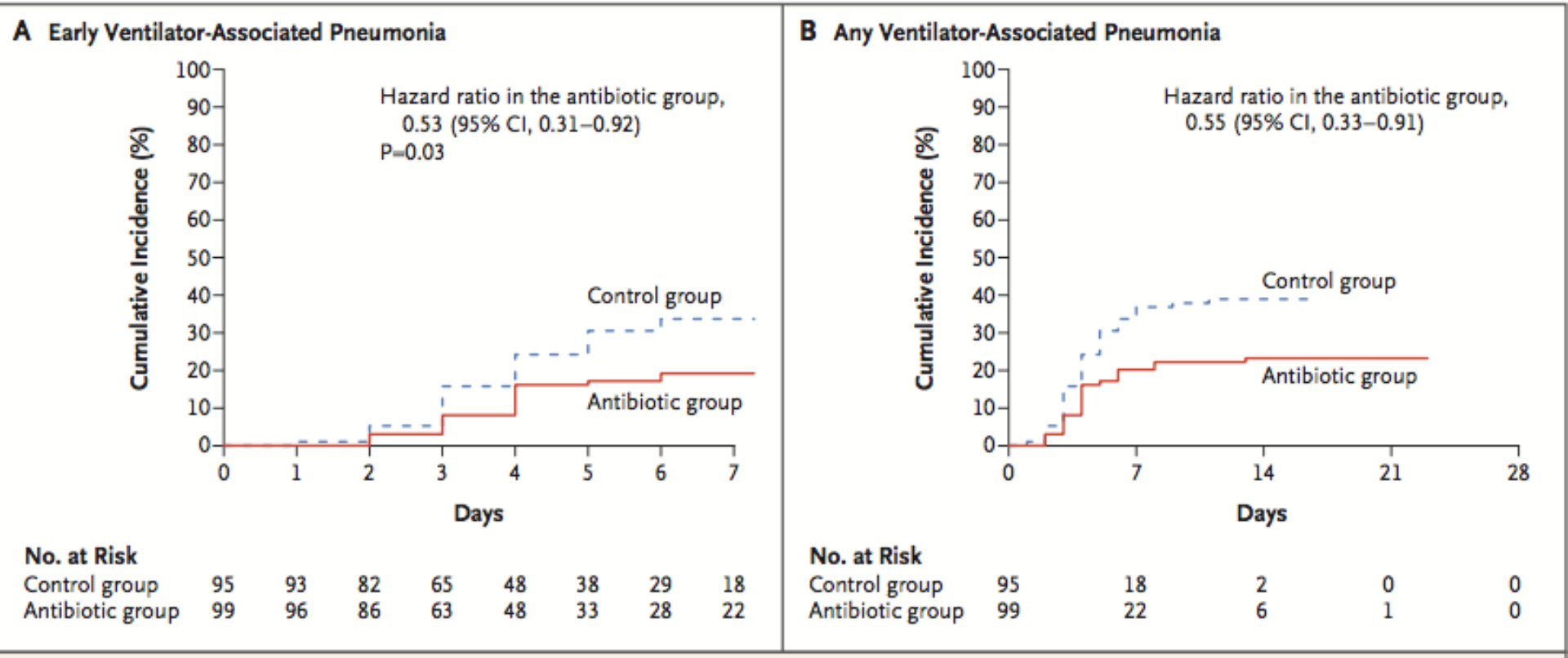


Figure 2. Cumulative Incidence of Ventilator-Associated Pneumonia.

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).

Results: VAP/Non-pulmonary infections

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)		

Results:
Pathogens

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)

Results: other secondary outcomes

- No significant difference regarding
  - median number of ventilator-free days (21 vs. 19 days)
  - median ICU length of stay, regardless of whether patients
    - were discharged (5 vs. 8 days)
    - had died (7 vs. 7 days)
  - Mortality at day 28 (41% vs. 37%)
  - Emergence of multidrug-resistant bacteria (rectal swabbing)

- The median percentage of days with antibiotic use during the ICU stay tended to be lower in the antibiotic group than in the control group

Limitations

- Exclusion of patients with overt aspiration
- Exclusion of patients with non-shockable rhythm
- Analysis concerning multi-resistent bacteria was only performed once on day 7

Danke für die Aufmerksamkeit