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Early-Onset Pneumonia in Non-Traumatic Out-of-Hospital Cardiac Arrest Patients with Special Focus on Prehospital Airway Management

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Manuscript Preparation E
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Background: More than half of all non-traumatic out-of-hospital cardiac arrest (OHCA) patients die in the hospital. Early-onset pneumonia (EOP) has been described as one of the most common complications after successful cardiopulmonary resuscitation. However, the expanded use of alternative airway devices (AAD) might influence the incidence of EOP following OHCA.



Material/Methods: We analyzed data from all OHCA patients admitted to our hospital between 1 January 2008 and 31 December 2014. EOP was defined as proof of the presence of a pathogenic microorganism in samples of respiratory secretions within the first 5 days after hospital admission.

Results: There were 252 patients admitted: 155 men (61.5%) and 97 women (38.5%), with a mean age of 69.1 ± 13.8 years. Of these, 164 patients (77.6%) were admitted with an endotracheal tube (ET) and 62 (27.4%) with an AAD. We found that 36 out of a total of 80 respiratory secretion samples (45.0%) contained pathogenic microorganisms, with *Staphylococcus aureus* as the most common bacteria. Neither bacterial detection ($p=0.765$) nor survival rates ($p=0.538$) differed between patients admitted with ET and those with AAD.

Conclusions: Irrespective of increasing use of AAD, the incidence of EOP remains high.

MeSH Keywords: **Cardiopulmonary Resuscitation • Diagnostic Techniques, Respiratory System • Out-of-Hospital Cardiac Arrest**

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Background

Non-traumatic out-of-hospital cardiac arrest (OHCA) is one of the leading causes of death, with an estimated risk-adjusted incidence of 76/100 000 inhabitants per year in the United States [1]. However, despite a tendency towards better survival rates, overall mortality is still enormously high – only 10.6% of all OHCA patients survive until hospital discharge [2].

Unfortunately, more than half of all OHCA patients die after hospital admission, with an in-hospital mortality of 57.8% in the year 2009 [3]. At present, there are still only 2 main in-hospital techniques that have been shown to improve survival rates of OHCA victims: targeted temperature management and (at least in patients with suspected cardiac cause of death) early cardiac catheterization [4]. Therefore, both techniques are recommended in the current guidelines of the European Resuscitation Council [5].

However, as early-onset pneumonia (EOP) has been described as one of the most common complication after successful cardiopulmonary resuscitation [6], we initiated this study to learn more about the incidence of EOP and its clinical importance in OHCA patients with special regard to the increasing use of alternative airway devices.

Material and Methods

Patient data collection

All non-traumatic out-of-hospital cardiac arrest patients who were admitted to our hospital between 1 January 2008 and 31 December 2014 were identified by analysis of our central admission registry.

Data on out-of-hospital airway management were taken from the emergency physician's reports and further in-hospital data were collected from the patient's health records. All data were anonymously stored on a central database and the study design adhered to all criteria of the WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects [7].

Microbiological sampling

Klompas et al. reported a median time of 6 days to the onset of ventilator-associated pneumonia [8]. Therefore, we classified microbiological samples of tracheal secretions between admission and day 5 as “early” and regarded detection of pathogenic microorganisms in these early samples as proof of early-onset pneumonia.

Endotracheal aspirate specimens were collected with a sputum suction trap and the procedure was repeated if the aspirate fluid was less than 3 milliliters (ml). Bronchoscopic bronchoalveolar lavage was performed with a fiberoptic bronchoscope. Fifty ml of saline 0.9% was instilled to the terminal bronchioles and then recollected for analysis.

Samples were immediately transported for bacteriological examination, centrifuged for 30 s, and Gram stained. The bacterial cultures were processed with the microorganisms quantified by an experienced microbiologist using standard serial dilutions and the results are expressed as colony-forming units (cfu/ml) [9]. The cut-off point for significant growth was 10^4 cfu/ml [10,11].

Statistical analysis

Statistical analysis was performed with the Statistical Package of Social Science (SPSS 22.0, IBM, Armonk, NY, USA). Continuous variables are expressed as the mean \pm standard deviation; comparisons of categorical variables among groups were conducted using chi-square tests or *t* test. P-values ≤ 0.05 were viewed as statistically significant.

Results

Patient characteristics

Overall, 252 patients (155 men [61.5%] and 97 women [38.5%]) were admitted to our hospital following OHCA between 1 January 2008 and 31 December 2014. The mean age was 69.1 ± 13.8 years (range 18–98 years). There were 183 witnessed arrests (72.6%), 122 patients received bystander resuscitation (48.4%), and 90 patients (35.7%) presented with an initial shockable rhythm.

On hospital admission, 21 patients (8.3%) breathed spontaneously and 226 patients (89.7%) had some kind of airway device. In the remaining 5 patients (2.0%), data concerning the airway management on hospital admission were imprecise.

Coronary angiography was done on 112 OHCA patients (44.4%) and 75 (29.8%) underwent percutaneous coronary intervention.

Overall, 102 patients (40.5%) were treated with targeted temperature management and 76 patients (30.2%) survived until hospital discharge. All data are summarized in Table 1.

Out-of-hospital airway management between 2008 and 2014

Between 1 January 2008 and 31 December 2014 there were 164 out-of-hospital cardiac arrest patients (77.6%) who were

Table 1. Characteristics of all victims of out-of-hospital cardiac arrest.

| All patients (n=252) | |
|--|-------------------|
| Male gender | 155 (61.5%) |
| Age (years) [range] | 69.1±13.8 [18–98] |
| Witnessed cardiac arrest | 183 (72.6%) |
| Bystander resuscitation | 122 (48.4%) |
| Initial shockable rhythm | 90 (35.7%) |
| Spontaneous breathing at admission | 21 (8.3%) |
| Airway protection | 226 (89.7%) |
| Endotracheal tube | 164 (72.6%) |
| Combitube | 12 (4.8%) |
| Laryngeal tube | 41 (16.3%) |
| Laryngeal mask | 9 (3.6%) |
| Targeted temperature management (TTM) | 102 (40.5%) |
| Coronary angiography (CA) | 112 (44.4%) |
| Percutaneous coronary intervention (PCI) | 75 (29.8%) |
| Survival until hospital discharge | 76 (30.2%) |

admitted with an endotracheal tube (ET) and 62 patients (27.4%) who presented with an alternative airway device (AAD).

Specifically, there were 20 OHCA patients (95.2%) in the year 2008 who received an ET and 1 patient (4.8%) who was treated with an AAD. In 2009, 15 patients (88.2%) received an ET and 2 patients (11.8%) an AAD. In 2010, 26 OHCA patients (72.2%) received an ET and 10 patients (27.8%) an AAD. In the year 2011, 18 patients (66.7%) were admitted with an ET and 9 patients (33.3%) with an AAD. In 2012, 19 OHCA patients (70.4%)

presented with an ET and 8 (29.6%) with an AAD. In the year 2013 we recorded 41 OHCA patients (74.5%) with an ET and 14 patients (25.4%) with an AAD. In 2014 there were 25 patients (58.1%) admitted with an ET and 18 patients (41.9%) who presented with an AAD. All data are shown in Figure 1.

Microbiological samples and antibiotic regimen in out-of-hospital cardiac arrest patients

Samples of tracheal secretions (n=47 patients [18.7%]) or bronchial lavage (n=34 patients [13.5%]) were taken in 81 patients (32.1%) within the first 5 days after hospital admission (mean 1.2±1.4 days, range 0–5 days). On average, microbiological results were returned in 36 patients (14.3%) 3.3±1.8 days after hospital admission [range 0–6 days].

During the same period, 134 patients (53.2%) received antibiotic therapy 0.5±0.8 days after hospital admission [range 0–4 days]. An antibiotic switch was prescribed in 44 patients (17.5%) 2.8±1.0 days after hospital admission (range 1–5 days). All data are summarized in Table 2.

Microbiological findings in out-of-hospital cardiac arrest patients

Altogether, there were 14 detections of *Staphylococcus aureus* (5.6%), 1 patient with MRSA (0.4%), 3 findings of *Streptococcus pneumoniae* (1.2%), 1 of *Enterococcus faecalis* (0.4%), and 1 of *Streptococcus agalactiae* (0.4%).

In addition, we identified 4 patients with *Klebsiella pneumoniae* (1.6%), 3 with *Enterobacter cloacae* (1.2%), 3 with *Haemophilus influenzae* (1.2%), 2 with *Escherichia coli* (0.8%), 1 with *Citrobacter koseri* (0.4%), 1 with *Enterobacter aerogenes* (0.4%), 1 of *Proteus vulgaris* (0.4%), and 1 with *Serratia marcescens* (0.4%).

Furthermore, there were 4 proven identifications of *Pseudomonas aeruginosa* (1.6%), 1 of *Stenotrophomonas*

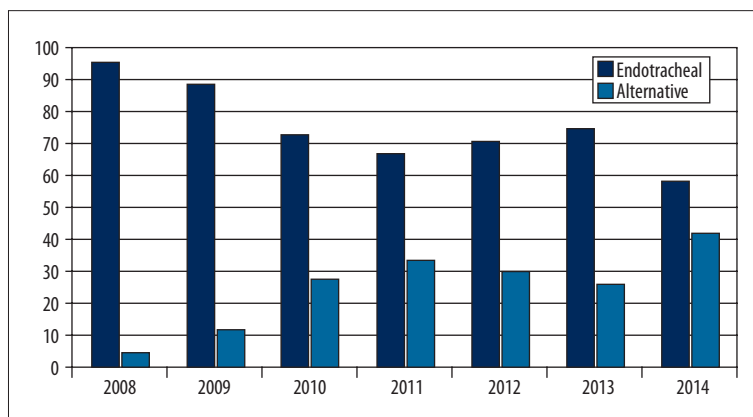


Figure 1. Percentage changes in the chosen airway management at hospital admission in out-of-hospital cardiac arrest patients between 2008 and 2014.

Table 2. Microbiological samples and antibiotic regime in victims of out-of-hospital cardiac arrest.

| | All patients (n=252) |
|--|----------------------|
| Microbiological investigation | 81 (32.1%) |
| Tracheal secretion | 47 (18.7%) |
| Bronchial lavage | 34 (13.5%) |
| Day of microbiological sampling [range] | 1.2±1.4 [0–5] |
| Bacterial detection | 36 (14.3%) |
| Day of microbiological results reporting [range] | 3.3±1.8 [0–6] |
| Antibiotic therapy | 134 (53.2%) |
| Day of first antibiotic application [range] | 0.5±0.8 [0–4] |
| Antibiotic switch | 44 (17.5%) |
| Day of antibiotic switch [range] | 2.8±1.0 [1–5] |

maltophilia (0.4%), and 1 of *Acinetobacter baumannii* (0.4%). All data are summarized in Table 3.

Differences between out-of-hospital cardiac arrest patients treated with an endotracheal tube compared with those who received an alternative airway device

OHCA patients treated with an ET and those who received an AAD did not differ with regards to sex (p=0.073), age (p=0.145), rate of witnessed arrests (p=0.206), rate of bystander resuscitation (p=0.380), or rate of initial shockable rhythm (p=0.458).

However, on admission, partial oxygen pressure was significantly higher in patients with an endotracheal tube (p=0.008), whereas partial pressure of carbon dioxide was significantly lower in these patients (p=0.016), but arterial oxygen saturation did not differ between the groups (p=0.814).

Analysis of further in-hospital therapy showed no differences in the use of targeted temperature management (p=0.843), rate of coronary angiography (p=0.801), or necessity of percutaneous coronary interventions (p=0.745) between patients fitted with ET or AAD.

In addition, there were no differences with regard to the rate of microbiological samples (p=0.503), the rate of bacterial detection (p=0.765), leucocyte levels at admission (p=0.700), rate of early antibiotic therapy (p=0.812), time to first antibiotic application after admission (p=0.189), or rate of antibiotic switch (p=0.510) between the groups.

Table 3. Microbiological findings in victims of out-of-hospital cardiac arrest.

| n (%) | Microorganism |
|---|--|
| Gram-positive, cocci, facultatively anaerobic | |
| 13 (5.2%) | <i>Staphylococcus aureus</i> |
| 1 (0.4%) | Methicillin-resistant <i>Staphylococcus aureus</i> |
| 3 (1.2%) | <i>Streptococcus pneumoniae</i> |
| 1 (0.4%) | <i>Enterococcus faecalis</i> |
| 1 (0.4%) | <i>Streptococcus agalactiae</i> |
| Gram-negative, rod-shaped, facultatively anaerobic | |
| 4 (1.6%) | <i>Klebsiella pneumoniae</i> |
| 3 (1.2%) | <i>Enterobacter cloacae</i> |
| 3 (1.2%) | <i>Haemophilus influenzae</i> |
| 2 (0.8%) | <i>Escherichia coli</i> |
| 1 (0.4%) | <i>Citrobacter koseri</i> |
| 1 (0.4%) | <i>Enterobacter aerogenes</i> |
| 1 (0.4%) | <i>Proteus vulgaris</i> |
| 1 (0.4%) | <i>Serratia marcescens</i> |
| Gram-negative, rod-shaped, aerobic | |
| 4 (1.6%) | <i>Pseudomonas aeruginosa</i> |
| 1 (0.4%) | <i>Stenotrophomonas maltophilia</i> |
| 1 (0.4%) | <i>Acinetobacter baumannii</i> |

Finally, there were comparable rates of survival until hospital discharge between patients admitted with ET and patients treated with AAD. All data are summarized in Table 4.

Differences between OHCA patients with proven microbiological findings in their tracheal secretions and OHCA patients without microbiological findings

OHCA patients with proven bacteria in their tracheal secretions were significantly more often intubated at admission to our hospital than those patients with investigated tracheal secretions but without proven microbiological findings (p=0.039). Furthermore, we observed a significantly higher percentage of antibiotic switch in OHCA patients with proven microorganisms (p=0.010).

No differences could be detected with regard to sex, age, rate of witnessed arrests, bystander resuscitation, or initial shockable rhythm.

Table 4. Differences between victims of out-of-hospital cardiac arrest treated with an endotracheal tube in comparison to those who received alternative airway management.

| | Endotracheal tube (n=164) | Alternative airway management (n=62) | p |
|--|------------------------------|--|--------------|
| Male gender | 106 (64.6%) | 32 (51.6%) | 0.073 |
| Age (years) | 70.5±13.0 | 67.6±13.7 | 0.145 |
| Witnessed cardiac arrest | 119 (72.6%) | 42 (67.7%) | 0.206 |
| Bystander resuscitation | 75 (45.7%) | 29 (46.8%) | 0.380 |
| Initial shockable rhythm | 60 (36.6%) | 19 (30.6%) | 0.458 |
| Partial oxygen pressure (pO ₂) | 205.6±171.2 | 138.5±123.4 | 0.008 |
| Partial pressure of carbon dioxide (pCO ₂) | 56.9±25.3 | 67.1±29.7 | 0.016 |
| Arterial oxygen saturation at admission (%) | 86.2±25.8 | 87.1±19.8 | 0.814 |
| Targeted temperature management (TTM) | 72 (43.9%) | 26 (41.9%) | 0.843 |
| Coronary angiography (CA) | 71 (43.3%) | 28 (45.2%) | 0.801 |
| Percutaneous coronary intervention (PCI) | 50 (30.5%) | 19 (30.6%) | 0.745 |
| Microbiological samples | 51 (31.1%) | 25 (40.3%) | 0.503 |
| Bacterial detection | 25 (15.2%) | 11 (17.7%) | 0.765 |
| Day of microbiological results reporting | 3.2±1.8 | 3.4±1.6 | 0.802 |
| Leucocytes (/nl) | 15.2±6.5 | 15.7±8.8 | 0.700 |
| Antibiotic therapy | 88 (53.7%) | 34 (54.8%) | 0.812 |
| Duration until first antibiotic application (days) | 0.5±0.7 | 0.3±0.6 | 0.189 |
| Antibiotic switch | 30 (18.3%) | 14 (22.6%) | 0.510 |
| Survival until hospital discharge | 41 (25.0%) | 18 (29.0%) | 0.538 |

Partial oxygen pressure, partial pressure of carbon dioxide, and arterial oxygen saturation at admission also did not differ between the groups. Likewise, rates of targeted temperature management, coronary angiography, percutaneous coronary intervention, and antibiotic therapy did not differ between the groups. Leucocyte levels at admission were comparable, as was the time to first antibiotic application. Finally, survival until hospital discharge was also comparable between the groups. All data are summarized in Table 5.

In-hospital survival and antibiotic treatment during the first 5 days after hospital admission

Immediately after hospital admission, 84 OHCA patients (33.3%) received antibiotic treatment. On the first day after hospital admission, 158 patients (62.7%) were still alive and 112 of them (70.9%) received antibiotic therapy. On the second day, 132 patients (52.4%) were alive and 113 of them (85.6%) were

treated with antibiotics. On the third day, 105 OHCA patients (89.7%) out of the 117 surviving patients (46.4%) received antibiotics, and on the fourth day 107 patients (42.5%) were still alive and 97 of them (90.7%) received antibiotic therapy. On the fifth day, 91 (91.0%) of a total of 100 survivors (39.7%) were treated with antibiotics. All data are shown in Figure 2.

Discussion

Incidence of early-onset pneumonia

In this study, 36 of a total of 81 respiratory secretion samples (44.4%) from patients following out-of-hospital cardiac arrest showed the presence of pathogenic microorganisms (Table 2). This is in line with previous study results that described an enormously high incidence of pneumonia, occurring in about half of all OHCA patients [12,13].

Table 5. Differences between victims of OHCA with proven microbiological findings in their tracheal secretions and victims of OHCA without microbiological findings.

| | Sampled with microbiological findings (n=36) | Sampled without microbiological findings (n=45) | p |
|--|--|---|--------------|
| Male gender | 19 (52.8%) | 27 (60.0%) | 0.514 |
| Age (years) | 65.6±12.2 | 68.8±13.2 | 0.264 |
| Witnessed cardiac arrest | 28 (77.8%) | 34 (75.6%) | 0.917 |
| Bystander resuscitation | 17 (47.2%) | 20 (44.4%) | 0.497 |
| Initial shockable rhythm | 10 (27.8%) | 20 (44.4%) | 0.146 |
| Airway device | 36 (100.0%) | 40 (88.9%) | 0.039 |
| Endotracheal | 25 (69.4%) | 26 (57.8%) | |
| Alternative | 11 (30.6%) | 14 (31.1%) | |
| Partial oxygen pressure (pO ₂) | 204.2±152.8 | 219.7±181.4 | 0.687 |
| Partial pressure of carbon dioxide (pCO ₂) | 50.1±18.7 | 55.4±23.5 | 0.281 |
| Arterial oxygen saturation at admission (%) | 95.0±7.1 | 93.4±11.3 | 0.458 |
| Targeted temperature management (TTM) | 22 (61.1%) | 34 (75.6%) | 0.162 |
| Coronary angiography (CA) | 21 (58.3%) | 25 (55.6%) | 0.802 |
| Percutaneous coronary intervention (PCI) | 13 (36.1%) | 16 (35.6%) | 0.803 |
| Leucocytes (/nl) | 15.4±7.1 | 13.2±4.7 | 0.117 |
| Antibiotic therapy | 36 (100.0%) | 41 (91.1%) | 0.067 |
| Duration until first antibiotic application (days) | 3.8±2.5 | 3.4±3.0 | 0.554 |
| Antibiotic switch | 19 (52.8%) | 10 (22.2%) | 0.010 |
| Survival until hospital discharge | 21 (58.3%) | 18 (40.0%) | 0.101 |

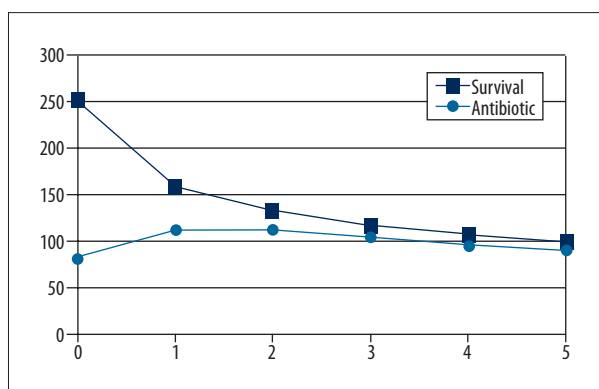


Figure 2. Absolute numbers of in-hospital surviving patients and antibiotic treatment during the first 5 days after hospital admission.

To date, only targeted temperature management has been identified as an independent risk factor for this infectious complication [6,14], but it is unlikely that physicians would dispense with targeted temperature management in post-resuscitation care. Other procedures, like early endotracheal tube exchange, failed to show a reduction of EOP rates [15]. Therefore, and considering the worldwide increase in the use of targeted temperature management cooling devices, we assume that EOP will become even more important in post-resuscitation therapy during the coming years.

Clinical implications of early-onset pneumonia

Several studies have failed to show an influence of EOP on survival and neurological outcome [6,12,13,15]. Nevertheless, the onset of EOP has the capability to increase the duration of mechanical ventilation, the tracheotomy rate, and the length of intensive care unit stay [6,15], which are factors that in turn

increase the risk of ventilator-associated events and cause higher hospital mortality risk *per se* [8].

We therefore wondered whether these missing influences of EOP on survival rates are really reproducible for all OHCA patients, because study designs have focused mainly on OHCA patients treated with targeted temperature management [12,13,15], which excludes all those patients with unstable cardiopulmonary conditions at hospital admission [16] and increases the incidence of EOP [6] and therefore might lead to a general shift towards better survival rates of OHCA patients with EOP. However, our data, consisting of a heterogeneous real-life collective, also failed to show an effect of EOP on survival until hospital discharge (Table 5).

In our opinion, this surprising lack of differences between the groups might be caused by general broad empiric antibiotic use in OHCA patients admitted to a hospital. Pabst et al., for example, found pathogenic microorganisms in respiratory secretions of 24% of all OHCA patients but treated 75% of those patients with antibiotics [15]. Also, in our data, we found a broad use of antibiotics, with 91% of all survivors of OHCA treated with antibiotics on day 5 after hospital admission (Figure 2).

Such a broad use of antibiotics might be prompted by previous findings that 135 of a total of 138 OHCA patients (97.8%) had at least 1 positive marker of infection within 72 h of hospital admission and also reported a significant reduction in mortality in OHCA patients who received prophylactic antibiotics compared with patients who did not [17].

Overall, due to inconsistent findings about the clinical importance of early-onset pneumonia, as well as early empiric antibiotic treatment in OHCA patients [6,12,13,15,17], we see an urgent need for further studies that focus on this topic.

Microbiological findings

It has been shown that *Staphylococcus aureus* is the most common microorganism that causes ventilator-associated pneumonia in general [8], but also early-onset pneumonia in OHCA patients in particular [15]. This is in line with our findings; nevertheless, antibiotic therapy that only focuses on *Staphylococcus aureus* might fail in a clinically relevant proportion of cases, because almost two-thirds (65.9%) of all detected microorganisms were species other than *Staphylococcus aureus* (Table 3).

However, with regard to the currently common empirical early use of antibiotics in OHCA patients (Figure 2) [6,17], we

doubt that microbiological sampling of respiratory secretions will ever really regain its value in the decision to initiate antibiotic treatment in these patients. Nevertheless, we would support a call for early microbiological sampling of respiratory secretions in all OHCA patients, because we can show that for 44.4% of positive samples in our data (Table 2) it allows an early reevaluation of the chosen antibiotic therapy and possibly an early switch or de-escalation in a significant percentage of all OHCA patients (Table 5).

Influence of the chosen airway device on the rate of early-onset pneumonia

Although the incidence of advanced pre-hospital difficult airway management has been reported to be only 3.2% [18], our data show an increasing use of AAD far beyond this percentage (Figure 1), with a current maximum in the year 2014 of more than 40% of all OHCA patients receiving an AAD in the preclinical setting (Figure 1).

One of the main reasons for this increasing use of AAD is probably the reduced emphasis in the current guidelines on early tracheal intubation unless it is performed by highly skilled individuals with minimal interruption of chest compressions [19].

Although the current evidence does not conclusively support the superiority of either ET or AAD with regard to the return of spontaneous circulation or survival [20], rates of aspiration and pneumonia following resuscitation might be influenced by the chosen airway management method. Honold et al., for example, reported higher rates of aspiration and pneumonia after pre-hospital endotracheal intubation in general, and in victims of OHCA in particular [21]. However, our study failed to show any influence of the chosen airway device on the subsequent clinical course, either on early-onset pneumonia or survival (Table 4).

Conclusions

Early-onset pneumonia is a frequent finding in out-of-hospital cardiac arrest patients, but its clinical importance is unclear. According to our data, the incidence of EOP remains high despite increasing use of alternative airway devices.

Conflict of interest

No conflicts of interest to declare.

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