OPEN

Can Biomarkers Correctly Predict Ventilator-associated Pneumonia in Patients Treated With Targeted Temperature Management After Cardiac Arrest? An Exploratory Study of the Multicenter Randomized Antibiotic (ANTHARTIC) Study

IMPORTANCE: Ventilator-associated pneumonia (VAP) frequently occurs in patients with cardiac arrest. Diagnosis of VAP after cardiac arrest remains challenging, while the use of current biomarkers such as C-reactive protein (CRP) or procalcitonin (PCT) is debated.

OBJECTIVES: To evaluate biomarkers' impact in helping VAP diagnosis after cardiac arrest.

DESIGN, SETTING, AND PARTICIPANTS: This is a prospective ancillary study of the randomized, multicenter, double-blind placebo-controlled ANtibiotherapy during Therapeutic HypothermiA to pRevenT Infectious Complications (ANTHARTIC) trial evaluating the impact of antibiotic prophylaxis to prevent VAP in out-of-hospital patients with cardiac arrest secondary to shockable rhythm and treated with therapeutic hypothermia. An adjudication committee blindly evaluated VAP according to predefined clinical, radiologic, and microbiological criteria. All patients with available biomarker(s), sample(s), and consent approval were included.

MAIN OUTCOMES AND MEASURES: The main endpoint was to evaluate the ability of biomarkers to correctly diagnose and predict VAP within 48 hours after sampling. The secondary endpoint was to study the combination of two biomarkers in discriminating VAP. Blood samples were collected at baseline on day 3. Routine and exploratory panel of inflammatory biomarkers measurements were blindly performed. Analyses were adjusted on the randomization group.

RESULTS: Among 161 patients of the ANTHARTIC trial with available biological sample(s), patients with VAP ($n = 33$) had higher body mass index and Acute Physiology and Chronic Health Evaluation II score, more unwitnessed cardiac arrest, more catecholamines, and experienced more prolonged therapeutic hypothermia duration than patients without VAP ($n = 121$). In univariate analyses, biomarkers significantly associated with VAP and showing an area under the curve (AUC) greater than 0.70 were CRP (AUC = 0.76), interleukin (IL) 17A and 17C (IL17C) (0.74), macrophage colony-stimulating factor 1 (0.73), PCT (0.72), and vascular endothelial growth factor A (VEGF-A) (0.71). Multivariate analysis combining novel biomarkers revealed several pairs with p value of less than 0.001 and odds ratio greater than 1: VEGF-A + IL12 subunit beta (IL12B), Fms-related tyrosine kinase 3 ligands (Flt3L) + C–C chemokine 20 (CCL20), Flt3L + IL17A, Flt3L + IL6, STAM-binding protein (STAMBP) + CCL20, STAMBP + IL6, CCL20 + 4EBP1, CCL20 + caspase-8 (CASP8), IL6 + 4EBP1, and IL6 + CASP8. Best AUCs were observed for CRP + IL6 (0.79), CRP + CCL20 (0.78), CRP + IL17A, and CRP + IL17C.

CONCLUSIONS AND RELEVANCE: Our exploratory study shows that specific biomarkers, especially CRP combined with IL6, could help to better diagnose or predict early VAP occurrence in cardiac arrest patients.

Nicolas Deye, MD, PhD[1]

Amelie Le Gouge, MSc[2]

Bruno François, MD[3]

Camille Chenevier-Gobeaux, MD, PhD[4]

Thomas Daix, MD[3]

Hamid Merdji, MD, PhD[5]

Alain Cariou, MD, PhD[6]

Pierre-François Dequin, MD, PhD[7]

Christophe Guitton, MD[8]

Bruno Mégarbane, MD, PhD[9]

Jacques Callebert, PharmD, PhD[10]

Bruno Giraudeau, PhD[2]

Alexandre Mebazaa, MD, PhD[11,12]

Nicolas Vodovar, PhD[11]

for the Clinical Research in Intensive Care and Sepsis-TRIal Group for Global Evaluation and Research in SEPsis (TRIGGERSEP) Network and the ANtibiotherapy during Therapeutic HypothermiA to pRevenT Infectious Complications (ANTHARTIC) Study Group

DOI: 10.1097/CCE.0000000000001104

KEY POINTS

Question: Can biomarkers predict ventilator-associated pneumonia (VAP) in patients treated with targeted temperature management after cardiac arrest?

Findings: The prospective randomized multicenter ANTHARTIC (ANtibiotherapy during Therapeutic HypothermiA to pRevenT Infectious Complications) trial included 161 out-of-hospital cardiac arrest patients from shockable rhythm treated with therapeutic hypothermia and with available biomarkers blindly measured from outcome and VAP diagnosis (blindly adjudicated). To diagnose VAP occurring within 48 hours after sampling, C-reactive protein (CRP) appears the most performant biomarker in a mono-biomarker strategy, and CRP + interleukin-6 (IL6) is the best bimodal combination.

Meaning: Using CRP and IL6, biomarkers both clinically available, could help clinicians to better diagnose VAP after cardiac arrest, and possibly better adapt treatments, especially antibiotics.

KEYWORDS: biomarker; cardiac arrest; chemokine/interleukin; C-reactive protein/procalcitonin; ventilator-assisted pneumonia

Infectious events particularly pneumonia frequently occur in cardiac arrest patients treated with targeted temperature management, possibly with a higher frequency when mild therapeutic hypothermia is used (1–3). Outside cardiac arrest, performing routine bedside clinical assessment for ventilator-associated pneumonia (VAP) or hospital-acquired pneumonia management represents good practice, whereas performing serial biomarker determinations in addition to bedside clinical assessment is not recommended (4). In some circumstances such as cardiac arrest, especially in therapeutic hypothermia-treated patients, biomarkers could help the pneumonia diagnostic process. However, the usefulness of C-reactive protein (CRP) or procalcitonin (PCT) to correctly diagnose or predict VAP occurrence remains debated especially after cardiac arrest (2, 5–11). Besides their potential prognostic value, these two biomarkers could preferentially represent a surrogate of the frequent systemic inflammatory response (SIRS) rather than detecting an actual underlying infection such as pneumonia. Differentiating isolated postcardiac arrest inflammation syndrome without pneumonia from a true infection related to pneumonia with these biomarkers seems particularly difficult in cardiac arrest patients treated with targeted temperature management experiencing a frequent sepsis-like syndrome (12). Other biomarkers such as novel cytokines, chemokines, or interleukins (ILs), have also been described in sepsis, in several inflammatory conditions including bacterial or viral pneumonia or other respiratory diseases such as chronic obstructive pulmonary disease, COVID-19, or cystic fibrosis (13–18). Consequently, these novel biomarkers of interest could be helpful in the VAP diagnostic process in cardiac arrest patients treated with targeted temperature management.

The ANtibiotherapy during Therapeutic HypothermiA to pRevenT Infectious Complications (ANTHARTIC) study is a randomized, multicenter, double-blind placebo-controlled trial in patients hospitalized for out-of-hospital successfully resuscitated cardiac arrest secondary to shockable rhythm and therapeutic hypothermia-treated (19). In this study, patients were treated with amoxicillin-clavulanic acid versus placebo, and VAP was blindly adjudicated according to a predefined clinical, radiologic, and microbiological score. As a prospective substudy of the ANTHARTIC study, our main objective was to evaluate multiple biomarkers in their ability to correctly discriminate VAP patients from non-VAP patients. We hypothesized that standard and novel biomarkers could diagnose or predict VAP with high accuracy as soon as the immediate post-cardiac arrest phase.

MATERIALS AND METHODS

Study Design and Ethics

This study is a prospective ancillary study of the ANTHARTIC trial already published (19) which received ethical approval as part of the ANTHARTIC global regulatory process. This study was approved by the regional ethics committee ("Comité de Protection des Personnes du Sud Ouest Outre Mer IV," Reference CPP14-012/2014-000202-35 on February 13, 2014) and was authorized by the "Agence Nationale de la Sécurité du Médicament" on June 27, 2014.

Procedures were in accordance with the ethical standards of the committee on human experimentation and with the 1975 Helsinki Declaration. This research entitled "Antibiotherapy during therapeutic hypothermia to prevent infectious complications" was registered in the European EudraCT database (no. 2014-000202-35) and in the National Clinical Trial Registry (NCT02186951). Written informed consent was obtained from a relative of each patient or through an emergency consent procedure for the main study, and a specific additional written informed consent was obtained for this substudy from a relative of each patient or through an emergency consent procedure.

Inclusion Criteria

Inclusion criteria were both the participation of the patient in the main study and the participation of the center in this biomarker study (13 participating centers among the 16 ICUs). Exclusion criteria were unavailability of biomarkers (absence of sampling, incorrect sampling or storage) and consent withdrawal.

Sample Scheme and Measurements

Two blood samples were collected during the study period for each included patient: at baseline (before placebo or antibiotic administration: D0), and at day 3 (D3) after cardiac arrest, during normothermia (**eFig. S1**, http://links.lww.com/CCX/B358). EDTA plasma samples were obtained by centrifugation within 30 minutes of blood collection (2500 g for 10 min at 4°C), aliquoted, and frozen at −80°C until use. Samples were transferred in dry ice to the core laboratory (Inserm UMR-S 942 unit, Lariboisière University Hospital, 75010 Paris, France), and stored at the Center des Ressources Biologiques (CRB, Lariboisière University Hospital, 75010, Paris, France).

As "routine" biomarkers, CRP and PCT were measured at Cochin University Hospital using available methods. CRP was measured using the immunoturbidimetric assay on a C701-module integrated into a Cobas 8000 analyzer (Roche Diagnostics, Meylan, France). The range of the assays extends from 0.5 to 350 mg/L and the detection limit was 5 mg/L. PCT was measured using the Roche immunochemiluminescent assays performed on an E801 module integrated into the Cobas 8000 analyzer. The range of the assays extends from 0.02 to 80 µg/L and the detection limit was 0.046 µg/L. Tryptophan (TRP) and kynurenine (KYN) measurements were performed by high-performance liquid chromatography at Lariboisière University Hospital as previously described (20). Indoleamine 2, 3 oxygenase (IDO) activity was estimated by the KYN/TRP ratio. Reference values for TRP, KYN, and IDO activity are 35–90 µM, 1.0–2.75 µM, and less than 5%, respectively. The exploratory panel of inflammatory biomarkers including novel chemokines, cytokines, and ILs was performed by Olink Proteomics (Uppsala, Sweden). The complete list of exploratory biomarkers and other details regarding biochemical parameters are available in the **Supplemental material** (http://links.lww.com/CCX/B358). All measurements were blindly and simultaneously performed.

Aims

Our primary objective was to evaluate the ability of biomarkers, measured at baseline and on D3, to diagnose or predict VAP occurring within 48 hours after sampling. Our secondary objective was to study the combination of two biomarkers as a multimodal strategy to accurately diagnose or predict early VAP.

VAP Definition

According to the ANTHARTIC study, VAP was blindly defined by three physicians in a standardized approach with the use of criteria from 2010 Food and Drug Administration guidance for diagnosis and confirmation of VAP (21). This relies on clinical (Clinical Pulmonary Infection Score [CPIS]), radiologic, and microbiological criteria (patients had to meet all three types of criteria), without the use of biological criteria except the total peripheral WBC count (19). The adjudication committee, unaware of the trial-group assignments (i.e., antibiotics or not), reviewed all patients' medical charts and adjudicated all respiratory tract infections, defining two different subgroups according to VAP occurrence or not.

Statistical Analyses

All patients were followed until the first event occurred: VAP occurrence within 48 hours after sampling (or

not) or death. Details regarding statistical analyses are available in the Supplemental material (http://links.lww.com/CCX/B358). Briefly, VAP was considered when diagnosed within 48 h after D0 and D3 samplings, whereas surviving patients without VAP as those with VAP occurring at D5 or thereafter were included in the nonpneumonia group. In our pooled analysis, we considered both observed values at baseline to study VAP at D1 and D2 and biomarkers measured at D3 for VAP occurring at D3 and D4. Baseline characteristics were described using numbers and percentages for categorical data, and median and interquartile intervals for continuous data. Baseline characteristics were compared between VAP and non-VAP using chi-square tests for categorical data (or Fisher tests) and Wilcoxon tests for continuous data. Correlations between biomarkers were studied using a correlation plot with the estimation of Spearman coefficients. Associations between biomarkers and VAP were analyzed using mixed logistic regression models with a random effect on the patient to take into account correlation data (i.e., each patient had several measures), after log transformation for CRP, PCT, IDO, TRP, and KYN values. The area under the curve (AUC) and its 95% CIs were estimated directly from these models as an odds ratio (OR). Adjustment was performed according to the group of randomization (i.e., antibiotic vs. placebo group). A p value of 0.05 was considered statistically significant. Statistical analyses were performed with the use of SAS software, version 9.4 (SAS Institute, Cary, NC), and R software, version 3.3.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Among the 194 patients analyzed in the ANTHARTIC study, 161 patients with at least one available sample were included in the biomarker substudy (**Fig. 1**). Seven patients without VAP who died within the first 2 days were excluded, resulting in 154 patients for the analysis. among the 52 patients with a diagnosis of VAP occurring within the first 7 days after cardiac arrest, 18 patients experienced VAP on day 5 or thereafter, and one patient with VAP occurring at D3 had a blood sample only available at D0 but not at D3. Finally, the main characteristics of the 154 patients (33 patients with analyzable VAP vs. 121 without VAP) are described in **Table 1**. Patients with VAP had a higher body mass index and Acute Physiology and Chronic Health Evaluation II score, presented more

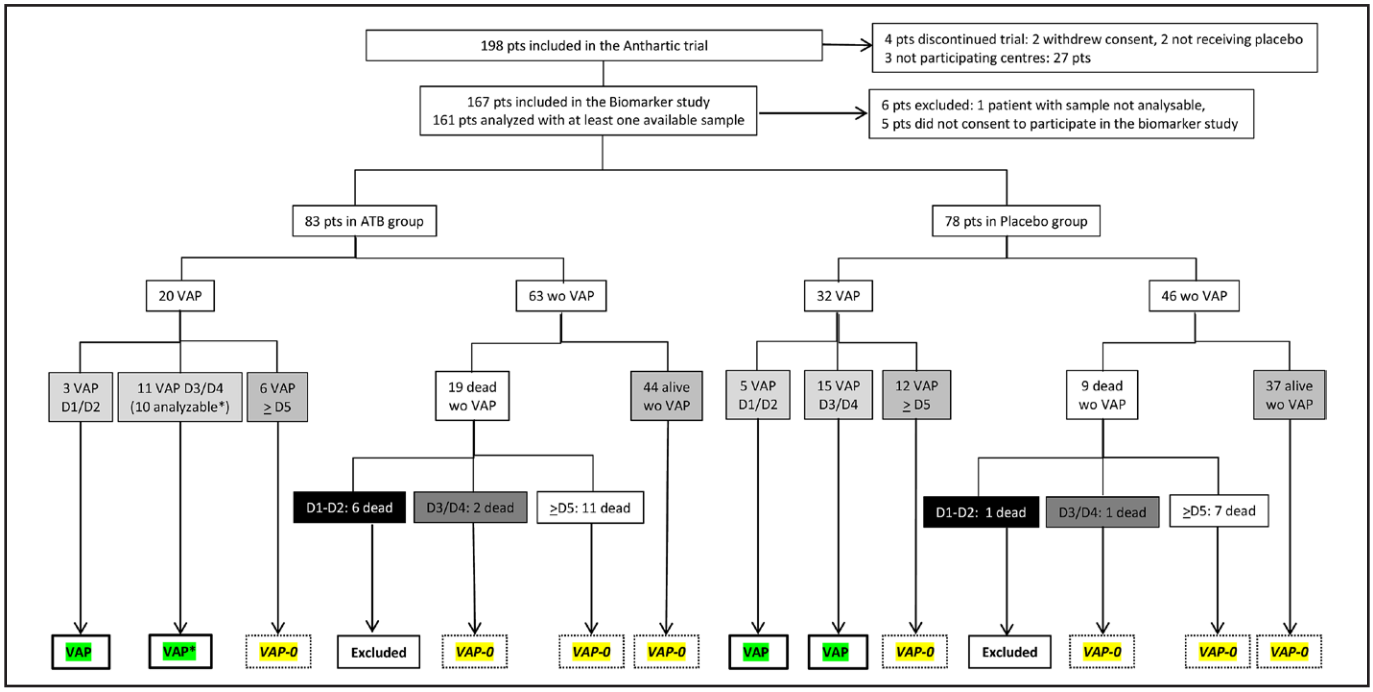

Figure 1. Flowchart. ATB = antibiotic, D = day after inclusion, pts = patients, VAP = ventilator-associated pneumonia occurring within 2 days after sampling (*green* group), VAP-0 = no ventilator-associated pneumonia diagnosed within 2 days after sampling (*yellow* group), wo = without. *: one patient, with only one blood sample available at baseline (D0) but not at D3, did not experience VAP at D1-D2 but VAP occurred at D3-D4.

TABLE 1.
Baseline Characteristics of Patients According to Pneumonia Occurrence (Ventilator-Associated Pneumonia)

Characteristic	Patients (*N* = 154)	VAP (*N* = 33)	No VAP (*N* = 121)	*P*
Age, yr	59.5 (49.0–70.6)	57.9 (53.0–70.6)	59.9 (48.6–70.0)	0.98
Male sex	126 (81.8)	27 (81.8)	99 (81.8)	1
Body mass index, kg/m², *n* = 147	26.1 (24.1–29.0)	27.7 (25.0–30.7)	25.9 (24.1–28.4)	0.03
Charlson score	2.0 (1.0–3.0)	2.0 (1.0–3.0)	2.0 (1.0–3.0)	0.97
Chronic lung disease	10 (6.5)	3 (9.1)	7 (5.8)	0.45
Immunosuppression	2 (1.3)	0 (0.0)	2 (1.7)	1
Chronic heart disease	35 (22.7)	8 (24.2)	27 (22.3)	0.81
Diabetes	14 (9.1)	5 (15.2)	9 (7.4)	0.18
Witnessed OHCA	147 (95.5)	29 (87.9)	118 (97.5)	0.04
No flow, min, *n* = 150	2.0 (0.0–5.0)	2.0 (0.0–5.0)	2.0 (0.0–5.0)	0.57
Low flow, min, *n* = 150	20.0 (11.0–25.0)	20.0 (13.0–25.0)	20.0 (10.0–25.0)	0.33
Time to intubation, min, *n* = 144	22 (13–32.5)	20 (12.0–32.0)	22 (14.0–33.0)	0.71
Initial shockable rhythm				0.45
Ventricular fibrillation	121 (78.6)	26 (78.8)	95 (78.5)	
Pulseless ventricular tachycardia	21 (13.6)	3 (9.1)	18 (14.9)	
Other	12 (7.8)	4 (12.1)	8 (6.6)	
Number of electric shocks	3 (1–4)	2 (2–4)	3 (1–4)	0.65
Catecholamine support	110 (71.4)	29 (87.9)	81 (66.9)	0.02
Anti-arrhythmic drugs	61 (39.6)	15 (45.5)	46 (38.0)	0.44
Suspected aspiration	10 (6.5)	1 (3.0)	9 (7.4)	0.69
Baseline temperature, °C, *n* = 152	35.7 (34.7–36.5)	35.9 (35.4–36.5)	35.6 (34.6–36.5)	0.17
Glasgow Coma Scale	3.0 (3.0–3.0)	3.0 (3.0–3.0)	3.0 (3.0–3.0)	0.92
Sequential Organ Failure Assessment score	8.0 (6.0–11.0)	9.0 (7.0–11.0)	8.0 (6.0–11.0)	0.24
Acute Physiology and Chronic Health Evaluation II score, *n* = 152	24.0 (20.0–27.5)	27.0 (22.5–28.0)	24.0 (20.0–26.5)	0.03
Time lag between OHCA and hypothermia, hr, *n* = 148	5.4 (4.5–6.1)	5.4 (4.7–6.4)	5.5 (4.3–6.1)	0.74
Duration of hypothermia, hr	29.5 (24.0–34.0)	31.5 (26.5–36.4)	29.0 (23.0–33.0)	0.01
Target temperature, °C	33.3 (33.0–34.0)	33.0 (33.0–34.0)	33.5 (33.0–34.8)	0.20

OHCA = out-of-hospital cardiac arrest, VAP = ventilator-associated pneumonia (occurring within the 2 d after sampling).
Data are expressed as either median (interquartile range) or *n* (%).

unwitnessed cardiac arrest, needed more catecholamines, and experienced longer hypothermia duration than patients without VAP.

Univariate analyses evaluating associations between all biomarkers and VAP occurrence adjusted on the randomization group are described in **Table 2** and **eTable S1** (http://links.lww.com/CCX/B358). As "routine" biomarkers (**Fig. 2**; and **eTable S2** http://links.lww.com/CCX/B358), CRP and PCT were significantly associated with early VAP occurrence (OR 1.71, 95% CI [1.28–2.27], $p = 0.0002$; OR 1.46, 95% CI [1.19–1.80], $p = 0.003$, respectively). Regarding the exploratory study (Table 2 and additional eTable S1 http://links.lww.com/CCX/B358), significant differences were observed for Eukaryotic translation initiation factor 4E-binding protein 1 (4E-BP1), caspase-8 (CASP8), C–C chemokine 19-20-23 (CCL19-20-23), macrophage colony-stimulating

TABLE 2.
Significant Associations in Univariate Analysis Between Biomarkers and Ventilator-Associated Pneumonia Occurrence Adjusted on Randomization Group

Biomarker	OR (95% CI)	*P*
Log C-reactive protein[a]	1.706 (1.283–2.269)	0.0002
Log procalcitonin[a]	1.463 (1.192–1.796)	0.0003
Eukaryotic translation initiation factor 4E-binding protein 1	0.718 (0.546–0.944)	0.0178
Caspase-8	0.687 (0.495–0.954)	0.0249
CCL19	1.401 (1.038–1.890)	0.0275
CCL20	1.264 (1.059–1.509)	0.0096
CCL23	2.035 (1.195–3.466)	0.0089
Macrophage colony-stimulating factor 1	18.738 (5.722–61.361)	< 0.0001
Protein S100-A12	1.625 (1.151–2.292)	0.0057
Fms-related tyrosine kinase 3 ligand	0.419 (0.243–0.723)	0.0018
IL12B	0.536 (0.372–0.770)	0.0008
IL17A	1.447 (1.092–1.917)	0.0101
IL17C	1.910 (1.433–2.545)	< 0.0001
IL6	1.243 (1.052–1.469)	0.0108
IL6/IL10 ratio	6.308 (1.692–23.522)	0.0061
Monocyte chemotactic protein 4	0.537 (0.343–0.841)	0.0066
Matrix metalloproteinase-10	1.973 (1.325–2.936)	0.0008
Stem cell factor	0.438 (0.252–0.762)	0.0035
Sulfotransferase 1A1	0.756 (0.616–0.927)	0.0071
STAM-binding protein	0.707 (0.550–0.907)	0.0065
TNF-beta	0.563 (0.339–0.937)	0.0269
TNF ligand superfamily 14	2.264 (1.426–3.595)	0.0005
TNF-related apoptosis-inducing ligand	0.484 (0.306–0.767)	0.0020
TWEAK	0.568 (0.341–0.946)	0.0296
Vascular endothelial growth factor A	2.561 (1.487–4.409)	0.0007
Log kynurenine[a]	2.796 (1.279–6.111)	0.0100
Log indoleamine 2, 3 oxygenase[a]	2.450 (1.134–5.295)	0.0227

CCL19-20-23 = C–C chemokine 19-20-23, Flt3L = Fms-related tyrosine kinase 3 ligand, IL12B = interleukin 12 subunit beta, IL17A and IL17C = interleukin 17A and 17C, IL6 = interleukin-6, KYN = kynurenine, OR = odds ratio, STAM = endosome-associated ubiquitin isopeptidase, TNF = tumor necrosis factor, TWEAK = TNF (ligand) superfamily, member 12.

[a]C-reactive protein, procalcitonin, indoleamine 2, 3 oxygenase, tryptophan, and kynurenine values were analyzed after log transformation.

factor 1 (CSF1), protein S100-A12 (EN-RAGE), Fms-related tyrosine kinase 3 ligand (Flt3L), tumor necrosis factor-ligand superfamily 12 and 14 (TWEAK and TNF-SF14), TNF-related apoptosis-inducing ligand (TRAIL), vascular endothelial growth factor A (VEGF-A), IL12 subunit beta (IL12B), IL6, IL17A and 17C (IL17A and IL17A and 17C [IL17C]), monocyte chemotactic protein 4 (MCP4), matrix metalloproteinase-10 (MMP10), stem cell factor (SCF), Sulfotransferase 1A1 (ST1A1), endosome-associated ubiquitin isopeptidase-binding protein (STAMBP), TNF-beta (TNF-B), KYN, and IDO. Correlation matrices between these biomarkers at baseline and on D3 are depicted in **eFigures S2** and **S3** (http://links.lww.com/CCX/B358).

In the multivariate analyses adjusted on the randomization group, associations between two biomarkers and early VAP occurrence are described in

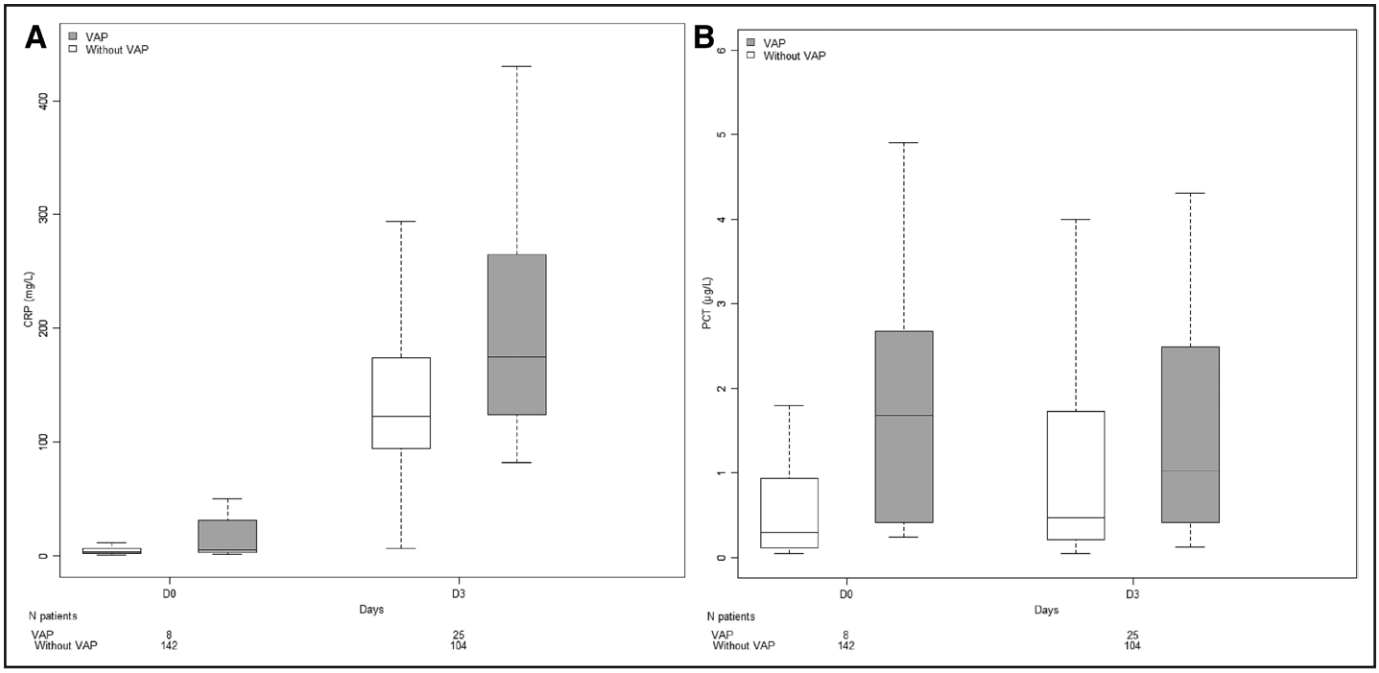

Figure 2. Association between "routine" biomarkers and ventilator-associated pneumonia occurrence adjusted on randomization group. **A**, C-reactive protein (CRP). **B**, Procalcitonin (PCT). See also eTable S2 (http://links.lww.com/CCX/B358) for corresponding values. CRP and PCT are expressed as logarithmic values. D0 = sampling at baseline, D3 = sampling at D3 after inclusion. VAP = ventilator-associated pneumonia within 2 days after sampling (*gray box plots*).

eTable S3 (http://links.lww.com/CCX/B358). When using a bimodal biomarker strategy including CRP as a first-line biomarker and one additional biomarker, CSF1, CCL20, IL17A, and IL6 showed a preserved significant value, whereas PCT and all other biomarkers were no longer significant. When using a bimodal biomarker strategy using PCT as a first-line biomarker and one additional biomarker, TNF-SF14, Flt3L, SCF, STAMBP, ST1A1, 4E-BP1, and CASP8 showed a preserved significant value. Irrespectively of CRP and PCT, the combinations of the two following biomarkers showed a significant *p* value of less than 0.001 and an OR greater than 1: VEGF-A + IL12, Flt3L + CCL20, Flt3L + IL17A, Flt3L + IL6, STAMBP + CCL20, STAMBP + IL6, CCL20 + eukaryotic translation initiation factor 4E-binding protein 1 (4EBP1), CCL20 + CASP8, IL6 + 4EBP1, and IL6+CASP8 (**Table 3**; and **eFig. S4**, http://links.lww.com/CCX/B358).

Main AUC for CRP and its combination with other biomarkers are depicted in Table 3, **Figure 3**; and **eFigure S5** (http://links.lww.com/CCX/B358): the best AUC using a single-biomarker strategy was observed for CRP (AUC = 0.76), whereas best AUCs using a bimodal strategy were observed for CRP + IL6 (0.79), CRP + CCL20 (0.78), CRP + IL17A (0.78), and CRP + IL17C (0.78).

DISCUSSION

CRP and PCT are statistically discriminant to diagnose or predict VAP occurrence within 48 hours after sampling in this cohort of out-of-hospital cardiac arrest patients using a blinded diagnosis of VAP. However, the levels of these two biomarkers overlapped with patients who did not develop VAP, especially for PCT. Other exploratory biomarkers also associated with VAP in univariate analyses are IL12, IL17, IL6/10 ratio, CSF1, MCP4, MMP10, CCL20/CCL23, EN-RAGE, Flt3L, SCF, ST1A1, STAMBP, TNF SF14, TRAIL, and VEGF-A. In multivariate analysis outside CRP and PCT, a strategy using a combination of two biomarkers revealed several pairs of interest, with VEGF-A, CCL20, Flt3L, IL6/12B/17A, STAMBP, 4EBP1, and CASP8 being associated with the most significant *p* values and best OR. Adding PCT to CRP measurements did not add any interest in helping VAP diagnosis. CRP shows the best AUC using a mono-marker strategy (0.76) and CRP + IL6 the best AUC in a bimodal strategy (0.79).

VAP After Cardiac Arrest and Biomarkers

The percentage of pneumonia after cardiac arrest has been largely discussed in the literature, ranging from 40% to 65% (1, 3, 22, 23). The lower-than-expected

TABLE 3.

Main Areas Under the Curve for Single or Combined[a] Biomarkers to Diagnose or Predict Ventilator-Associated Pneumonia Adjusted on Randomization Group

Biomarkers With AUC > 0.7		Biomarkers With AUC ≤ 0.7	
CRP + IL6[a]	0.79	TNF-related apoptosis-inducing ligand	0.70
CRP + CCL20[a]	0.78	Flt3L	0.70
CRP + IL17C[a]	0.78	TNF ligand superfamily 14	0.70
CRP + IL17A[a]	0.78	Stem cell factor	0.69
CRP + CSF1[a]	0.77	Matrix metalloproteinase-10	0.69
IL6 + Flt3L[a]	0.77	IL12B	0.69
CRP	0.76	Monocyte chemotactic protein 4	0.68
IL17A + Flt3L[a]	0.76	CCL19	0.68
IL12B + VEGF[a]	0.76	Protein S100-A12	0.67
CCL20 + Flt3L[a]	0.75	CCL23	0.66
IL17C	0.74	STAMBP	0.66
CSF1	0.73	4EBP1	0.65
IL6 + CASP8[a]	0.73	TNF-beta	0.65
IL6 + STAMBP[a]	0.73	IL6/IL10 ratio[a]	0.65
IL6 + 4EBP1[a]	0.72	Log KYN	0.64
PCT	0.72	Sulfotransferase 1A1	0.64
CCL20 + STAMBP[a]	0.72	TWEAK	0.64
CCL20 + 4EBP1[a]	0.72	IL17A	0.64
VEGF-A	0.71	CCL20	0.63
CCL20 + CASP8[a]	0.71	IL6	0.63
		CASP8	0.63
		Log indoleamine 2, 3 oxygenase	0.61

4EBP1 = eukaryotic translation initiation factor 4E-binding protein 1, AUC = area under the curve, CRP = C-reactive protein, CASP8 = caspase-8, CCL19-20-23 = C–C chemokine 19-20-23, CSF1 = macrophage colony-stimulating factor 1, Flt3L = Fms-related tyrosine kinase 3 ligand, IL12B = interleukin 12 subunit beta, IL17A and IL17C = interleukin 17A and 17C, IL6 = interleukin-6, KYN = kynurenine, PCT = procalcitonin, STAM = endosome-associated ubiquitin isopeptidase, STAMBP = STAM-binding protein, TNF = tumor necrosis factor, TWEAK = TNF (ligand) superfamily, member 12, VEGF-A = vascular endothelial growth factor A.[a] Combination of two biomarkers.

overall 31% frequency of VAP observed in the original ANTHARTIC study has already been discussed (19). According to the design of our ancillary study, we also excluded late VAP (> D4) and early deaths within the 52 patients with VAP, limiting the total number of analyzable patients (VAP was diagnosed here in 21% of patients with available biomarkers). Furthermore, other factors could explain our low VAP rate: exclusion of overt aspirations, systematic use of bundles decreasing VAP frequency, complex diagnosis of VAP with its heterogeneous definition, our blinded adjudication committee that finally confirmed only 75% of suspected VAP, and the possible eradication of microorganisms in the antibiotic-treated group. However, a recent study using strict clinical and radiologic criteria showed that 23% of patients developed VAP after out-of-hospital cardiac arrest, close to our VAP frequency (24). This difference between suspected and adjudicated VAP reinforces the need for biomarkers to better diagnose VAP.

CRP and PCT

The association of increased CRP and PCT values with postcardiac arrest pneumonia is largely debated. These two biomarkers can preferentially be a marker of the SIRS

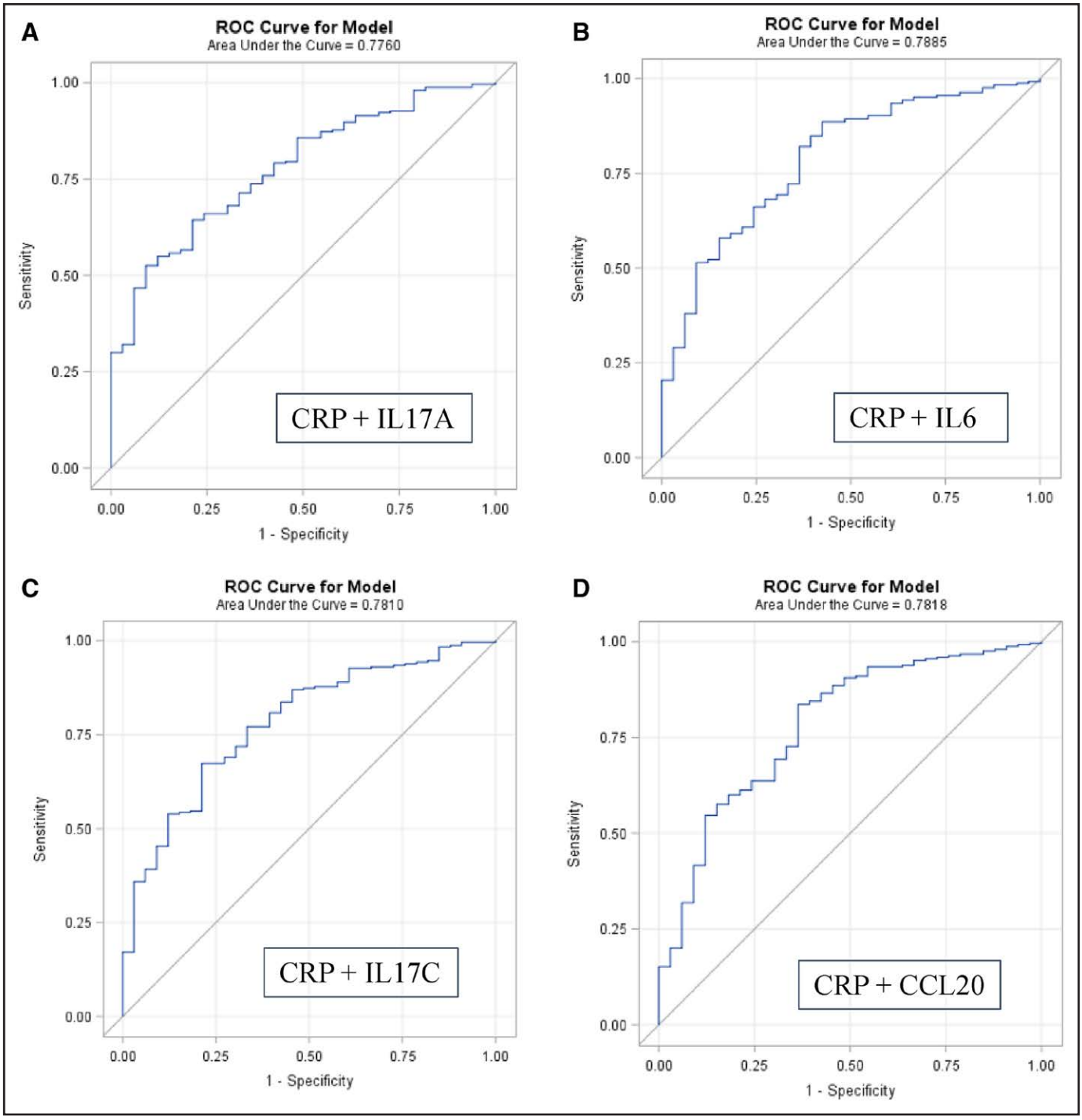

Figure 3. Best areas under the curve for significant combinations of two biomarkers, including C-reactive protein (CRP) and adjusted on group randomization, to predict ventilator-associated pneumonia (VAP) within 2 days after sampling. **A**, CRP and interleukin (IL)17A. **B**, CRP and IL6. **C**, CRP and IL17C. **D**, CRP and C–C chemokine 20 (CCL20). ROC = receiver operating characteristic.

rather than pneumonia in most studies evaluating successfully resuscitated cardiac arrest patients (4–9, 25). Conversely, these current biomarkers have been associated with a true underlying infection such as pneumonia in other studies (2, 10). Using a blinded methodology in contrast to all previous studies, we suggest that these two biomarkers can predict pneumonia within 48 hours after sampling. However, we observed a consequent overlap between groups with and without VAP, particularly for PCT but to a lesser extent for CRP at admission.

These discrepancies can be explained by several factors. First, these biomarkers were used in practice

in most studies to diagnose pneumonia suggesting a possible risk of self-fulfilling prophecy. Second, diagnoses of pneumonia were mostly unblinded to physicians by contrast to our study where adjudication was blinded. Additionally, in contrast to all published studies, our study was prospective and focused on VAP occurring within 2 days after sampling outside aspiration syndromes that could introduce biases (26). Third, temperature as a component of the CPIS is faked when using therapeutic hypothermia and could slightly modify CRP values at H24 after cardiac arrest, but not later at H48-72, nor PCT values (27). Fourth, with an earlier release of PCT over CRP, their kinetics are clearly different, suggesting that the historical idea of CRP describing inflammation and PCT infection probably does not stand anymore (8). Fifth, the delay between occurrence and diagnosis of VAP, and the time of blood sampling could also play a role in altering the relationship between the biomarker value and true pneumonia. The contribution of SIRS that could mask the discriminative biomarker value to diagnose pneumonia remains to be evaluated.

Interestingly, our results are close to those published in the large Targeted Temperature Management 1 (TTM_1) trial, with CRP and PCT being increased in patients with infections at all times (from H24 to H48) with important overlap (27). However, several major differences can be noted: no sample was performed at admission; pneumonia, septic shock, and sepsis were included for biomarker comparisons; pneumonia was recorded up to day 7 and during ICU hospitalization to compare the infected versus the noninfected groups; and diagnosis of VAP by the treating physician was considered as definitive.

Finally, adding PCT to CRP measurement did not add any value, suggesting the requirement of only one routine biomarker -if any-, according to hospital facilities. Consequently, considering its lower cost, we suggest using CRP to help with VAP diagnosis, especially during the first days after admission, as CRP was not outperformed by any other biomarkers used alone.

Exploratory Study

Our study is the first to enlighten the contribution of several biomarkers to diagnose VAP occurrence within 48 hours after sampling in cardiac arrest patients. If CRP is used as the first-line biomarker, IL6 as a second-line biomarker could add a modest but interesting diagnostic value. New biomarkers of interest in our multivariate analyses are VEGF-A, CCL20, Flt3L, IL6, IL12B, IL17A, STAMBP, 4EBP1, and CASP8. This is consistent with several studies describing similar ILs and chemokines candidates to better define septic, inflammatory, and infectious conditions, especially in patients with pneumonia or respiratory diseases (14–18, 28–31). These biomarkers probably reflect the importance of all inflammatory processes, frequent in successfully resuscitated cardiac arrest patients, especially if associated with aspiration pneumonia or VAP (12, 32). However, differentiating inflammation from infection still remains challenging in such patients, contrasting with PCT's contribution to diagnosing sepsis in noncardiac arrest patients (32). SIRS severity after cardiac arrest possibly limits significant differences in the range of biomarker increase between VAP and non-VAP patients. Furthermore, the presence of early VAP probably increments the usual values of all inflammatory biomarkers. The exact thresholds to rule out or confirm VAP after cardiac arrest using CRP+IL17 or CRP+IL6 for instance remains to be determined.

IL6 is one of the most cited candidates in our study. IL6, a short half-life pyrogenic cytokine that enhances T cell differentiation through IL-2 induction, has an immediate response to infection or inflammation and is a very sensitive biomarker of localized infection (16). As increasingly used since the COVID-19 epidemic (18, 33, 34), IL6 may help more accurately to diagnose VAP occurring within 48 hours after sampling in cardiac arrest patients in addition to usual biomarkers such as CRP. Finally, some postcardiac arrest patients experiencing a major inflammation even if triggered by VAP, confirmed by an important increase in inflammatory biomarkers, may potentially benefit from steroids or IL6 receptor antibodies besides antibiotics (31, 35, 36).

Practical Aspects and Applicability of Our Results

The novelty of our study is its specific design: to our best knowledge, this is the first study where biomarkers were designed to diagnose or predict pneumonia occurrence within 48 h after sampling. We here focused on the importance of inflammatory biomarkers to help physicians introduce earlier justified antibiotic

therapy. Second, 25% of VAP initially reported by investigators in the ANTHARTIC study were not subsequently confirmed during adjudication, highlighting the importance of precise VAP diagnosis where biomarker(s) could help to better identify VAP earlier (19). This could possibly save some patients from useless antibiotic therapy. Third, the ANTHARTIC study showed that antibiotic therapy (vs. placebo) decreases the frequency of early VAP but not mortality, a result that cannot firmly justify systematic antibiotic therapy after cardiac arrest. Whereas international guidelines dos not support antibiotic prophylaxis in such patients (37), good clinical practices of antibiotic prescription should be largely driven by firm pneumonia diagnosis using clinical, microbiological, radiographic parameters but also biomarkers increases. Finally, despite no microbiota modification being observed in the ANTHARTIC study until day 7, potential long-term ecological issues and antibiotic sparing in this population should be further evaluated. These assertions highlight the importance of giving antibiotics only when VAP is precisely diagnosed, potentially with the additional help of a clear biomarker strategy considering the difficult VAP diagnosis.

Fever prevention rather than other temperature control strategies in postcardiac arrest could limit the applicability of our results here obtained using a 33°C-hypothermia strategy. Indeed, most recent studies, meta-analyses, and guidelines has challenged the benefit of using therapeutic hypothermia versus normothermia and fever prevention to improve survival or favorable outcome (38–43). Furthermore, therapeutic hypothermia attenuates general inflammatory response, potentially leads to more infectious complications, requires prolonged sedation and mechanical ventilation, was identified as a single independent risk factor of early-onset pneumonia in several studies, and might be a VAP contributor besides loss of airway protection, coma, pulmonary contusion, emergency airway access, and mechanical ventilation (1, 22, 24). However, the clear causality of hypothermia in inducing VAP after cardiac arrest remains debatable, with this association not being observed in all studies and most meta-analyses (24, 27, 39, 41, 44).

Finally, it would seem reasonable to treat widely postcardiac arrest patients with antibiotics when therapeutic hypothermia is used and try to identify at-risk patients for VAP with biomarkers specific to VAP (not all infections in general). Further prospective studies evaluating CRP + IL6 for instance should be performed to better discriminate VAP from non-VAP patients, whatever the temperature control strategy. Our results regarding the VAP diagnosis could interestingly be evaluated when a normothermic or a fever prevention strategy is preferred after cardiac arrest. Indeed, while CRP is not drastically modified by temperature (27), our biomarker measurements were performed outside the therapeutic hypothermia window in both VAP and non-VAP groups.

Limitations

First, although scarce (1, 3, 22, 23), we cannot exclude that infections from other organs than the lungs could have influenced our results. However, only four patients in our cohort developed extrapulmonary infection without VAP within the first 4 days after inclusion. This could have decreased the significance and AUC values found for the biomarkers of interest pointed out in our cohort, but it does not drastically change our conclusions about their discriminative value. At last, pneumonia is the most commonly observed infectious complication in out-of-hospital cardiac arrest patients but does not seem to affect mortality (1, 3, 22, 24). Second, the lower-than-expected number of VAP observed in the ANTHARTIC study and the design of our study did not allow us to investigate longitudinal biomarker variations and subgroup analyses (patients with vs. without antibiotics, sampling performed at admission vs. D3). However, our results bring new possibilities to correctly diagnose early VAP occurring within 2 days after sampling using biomarkers in hypothermic or normothermic cardiac arrest patients.

CONCLUSIONS

The diagnosis of VAP remains challenging after cardiac arrest especially when targeted temperature management is used, as most scores are unsuitable or imperfect. Some biomarkers could help to better diagnose or predict VAP occurring within 48 hours after sampling, especially by combining IL6 and CRP. Whether these biomarkers could help to decrease antibiotic use or modify outcomes warrants new studies.

ACKNOWLEDGMENTS

The authors would like to thank Philippe Manivet, PhD, Claire Pernin, and Lydia Suarez for the "Center

des Ressources Biologiques" (CRB), Lariboisiere University Hospital, APHP, Paris, France; Nathalie Debarle, for the Medical and Toxicological ICU; AnnaLotta Schiller Vestergren, PhD, Bertrand Caetano, MD, and Jamal Fakir, Business Development Manager France for Olink Proteomics AB, Upsala, Sweden; Malha Sadoune, Karima Chabane, Jane-Lise Samuel, PhD, Claude Delcayre, PhD, and Feriel Azibani, PhD, for the Inserm UMR-S 942 MASCOT, Paris, France; Cecile Duchiron, Sandrine Naturel, for the "center d'Investigation Clinique" 1435, center Hospitalier Universitaire, Limoges, France.

1 *Medical ICU, Lariboisiere University Hospital, Inserm UMR-S 942, APHP, Paris, France.*

2 *Inserm CIC 1415, CHU de Tours, Tours, France.*

3 *Réanimation Polyvalente, INSERM CIC 1435 and UMR 1092, CHU Limoges, Limoges, France.*

4 *Biochemical Laboratory, Cochin University Hospital, APHP, Paris, France.*

5 *Service de Médecine Intensive–Réanimation, Nouvel Hôpital Civil, Hôpitaux Universitaires de Strasbourg, INSERM UMR 1260, Regenerative NanoMedicine, FMTS, Strasbourg, France.*

6 *Medical ICU, Cochin University Hospital, AP-HP Centre Université Paris Cité, Paris, France.*

7 *INSERM UMR 1100 and Médecine Intensive–Réanimation, Tours, France.*

8 *Medecine Intensive Réanimation, Center Hospitalier Universitaire, Nantes, France.*

9 *Department of Medical and Toxicological Critical Care, Paris Cité University, Lariboisiere University Hospital, Inserm UMR-S 1144, Paris, France.*

10 *Biochemical Laboratory, Lariboisiere University Hospital, Inserm UMR-S 1144, Paris, France.*

11 *Université de Paris, Inserm UMR-S 942 MASCOT, Paris, France*

12 *Department of Anaesthesiology and Intensive Care, Lariboisière University Hospital, APHP, Paris, France.*

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (http://journals.lww.com/ccejournal).

Drs. Deye and Vodovar contributed equally.

A list of all investigators participating in the ancillary study of the ANTHARTIC Study Group is provided in the Supplementary material (http://links.lww.com/CCX/B358).

The study was funded and granted by the French Ministry of Health (Programme Hospitalier de Recherche Clinique 2013/number Direction Générale de l'Offre de Soins, 13-0081).

The authors have disclosed that they do not have any potential conflicts of interest.

For information regarding this article, E-mail: nicolas.deye@aphp.fr

Clinical Trial Registration Number: NCT02186951.

REFERENCES

1. Perbet S, Mongardon N, Dumas F, et al: Early-onset pneumonia after cardiac arrest: Characteristics, risk factors and influence on prognosis. *Am J Respir Crit Care Med* 2011; 184:1048–1054
2. Pabst D, Römer S, Samol A, et al: Predictors and outcome of early-onset pneumonia after out-of-hospital cardiac arrest. *Respir Care* 2013; 58:1514–1520
3. Nielsen N, Sunde K, Hovdenes J, et al; Hypothermia Network: Adverse events and their relation to mortality in out-of-hospital cardiac arrest patients treated with therapeutic hypothermia. *Crit Care Med* 2011; 39:57–64
4. Torres A, Niederman MS, Chastre J, et al: International ERS/ESICM/ESCMID/ALAT guidelines for the management of hospital-acquired pneumonia and ventilator-associated pneumonia. TASK FORCE REPORT ERS/ESICM/ESCMID/ALAT GUIDELINES. *Eur Respir J* 2017; 50:1700582–1700526
5. Fries M, Kunz D, Gressner AM, et al: Procalcitonin serum levels after out-of-hospital cardiac arrest. *Resuscitation* 2003; 59:105–109
6. Hayashida H, Kaneko T, Kasaoka S, et al: Comparison of the predictability of neurological outcome by serum procalcitonin and glial fibrillary acidic protein in postcardiac-arrest patients. *Neurocrit Care* 2010; 12:252–257
7. Schuetz P, Affolter B, Hunziker S, et al: Serum procalcitonin, C-reactive protein and white blood cell levels following hypothermia after cardiac arrest: A retrospective cohort study. *Eur J Clin Invest* 2010; 40:376–381
8. Annborn M, Dankiewicz J, Erlinge D, et al: Procalcitonin after cardiac arrest—an indicator of severity of illness, ischemia-reperfusion injury and outcome. *Resuscitation* 2013; 84:782–787
9. Engel H, Ben Hamouda N, Portmann K, et al: Serum procalcitonin as a marker of post-cardiac arrest syndrome and long-term neurological recovery, but not of early-onset infections, in comatose post-anoxic patients treated with therapeutic hypothermia. *Resuscitation* 2013; 84:776–781
10. Oppert M, Reinicke A, Müller C, et al: Elevations in procalcitonin but not C-reactive protein are associated with pneumonia after cardiopulmonary resuscitation. *Resuscitation* 2002; 53:167–170
11. Fluri F, Morgenthaler NG, Mueller B, et al: Copeptin, procalcitonin and routine inflammatory markers-predictors of infection after stroke. *PLoS One* 8309; 12:e4
12. Adrie C, Laurent I, Monchi M, et al: Postresuscitation disease after cardiac arrest: A sepsis-like syndrome? *Curr Opin Crit Care* 2004; 10:208–212
13. Christ-Crain M, Opal Steven M: Clinical review: The role of biomarkers in the diagnosis and management of community acquired pneumonia. *Crit Care* 2010; 14:203
14. Yende S, Tuomanen EI, Wunderink R, et al: Preinfection systemic inflammatory markers and risk of hospitalization due to pneumonia. *Am J Respir Crit Care Med* 2005; 172:1440–1446

15. Heper Y, Akalin EH, Mistik R, et al: Evaluation of serum C-reactive protein, procalcitonin, tumor necrosis factor alpha, and interleukin-10 levels as diagnostic and prognostic parameters in patients with community-acquired sepsis, severe sepsis, and septic shock. *Eur J Clin Microbiol Infect Dis* 2006; 25:481–491
16. Karakioulaki M, Stolz D: Biomarkers in pneumonia—beyond procalcitonin. *Int J Mol Sci* 2019; 20:2004
17. Giacalone VD, Moncada-Giraldo D, Margaroli C, et al; the IMPEDE-CF Program: Pilot study of inflammatory biomarkers in matched induced sputum and bronchoalveolar lavage of 2-year-olds with cystic fibrosis. *Pediatr Pulmonol* 2022; 57:2189–2198
18. Kermalia M, Kaur Khalsaa R, Pillaia K, et al: The role of biomarkers in diagnosis of COVID-19—a systematic review. *Life Sci* 2020; 254:117788
19. François B, Cariou A, Clere-Jehl R, et al; CRICS-TRIGGERSEP Network and the ANTHARTIC Study Group: Prevention of early ventilator-associated pneumonia after cardiac arrest. *N Engl J Med* 2019; 381:1831–1842
20. Laugeray A, Launay JM, Callebert J, et al: Evidence for a key role of the peripheral kynurenine pathway in the modulation of anxiety- and depression-like behaviours in mice: Focus on individual differences. *Pharmacol Biochem Behav* 2011; 98:161–168
21. Center for Drug Evaluation and Research, Food and Drug Administration (November 2010). Guidance for industry—hospital acquired bacterial pneumonia and ventilator-associated bacterial pneumonia: Developing drugs for treatment. *Silver Spring, MD, Center for Drug Evaluation and Research, Food and Drug Administration, 2010*
22. Mongardon N, Perbet S, Lemiale V, et al: Infectious complications in out-of-hospital cardiac arrest patients in the therapeutic hypothermia era. *Crit Care Med* 2011; 39:1359–1364
23. Nielsen N, Hovdenes J, Nilsson F, et al; Hypothermia Network: Outcome, timing and adverse events in therapeutic hypothermia after out-of-hospital cardiac arrest. *Acta Anaesthesiol Scand* 2009; 53:926–934
24. Hasslacher J, Steinkohl F, Ulmer H, et al: Increased risk of ventilator-associated pneumonia in patients after cardiac arrest treated with mild therapeutic hypothermia. *Acta Anaesthesiol Scand* 2022; 66:704–712
25. Mongardon N, Lemiale V, Perbet S, et al: Value of procalcitonin for diagnosis of early onset pneumonia in hypothermia-treated cardiac arrest patients. *Intensive Care Med* 2010; 36:92–99
26. El-Sohl AA, Vora H, Knight PR, et al: Diagnostic use of serum procalcitonin levels in pulmonary aspiration syndromes. *Crit Care Med* 2011; 39:1251–1256
27. Dankiewicz J, Nielsen N, Linder A, et al; TTM Trial Investigators: Infectious complications after out-of-hospital cardiac arrest—a comparison between two target temperatures. *Resuscitation* 2017; 113:70–76
28. Happel KI, Zheng M, Young E, et al: Cutting edge: Roles of Toll-like receptor 4 and IL-23 in IL-17 expression in response to *Klebsiella pneumoniae* infection. *J Immunol* 2003; 170:4432–4436
29. Eide HA, Halvorsen AR, Sandhu V, et al: Non-small cell lung cancer is characterised by a distinct inflammatory signature in serum compared with chronic obstructive pulmonary disease. *Clin Transl Immunology* 2016; 5:e109
30. Björkander S, Klevebro S, Hernandez-Pacheco N, et al: Obese asthma phenotypes display distinct plasma biomarker profiles. *Clin Transl Allergy* 2023; 13:e12238
31. Hui Tan L, Lin C, Ungerer H, et al: Steroid affected cytokines in aspirin-exacerbated respiratory disease. *Int Forum Allergy Rhinol* 2022; 12:1232–1241
32. Shin H, Kim JG, Kim W, et al: Procalcitonin as a prognostic marker for outcomes in post-cardiac arrest patients: A systematic review and meta-analysis. *Resuscitation* 2019; 138:160–167
33. Liu F, Li L, Xu MD, et al: Prognostic value of interleukin-6, C-reactive protein, and procalcitonin in patients with COVID-19. *J Clin Virol* 2020; 127:104370
34. Keddie S, Ziff O, Chou MKL, et al: Laboratory biomarkers associated with COVID-19 severity and management. *Clin Immunol* 2020; 221:108614
35. Meyer MAS, Wiberg S, Grand J, et al: Treatment effects of interleukin-6 receptor antibodies for modulating the systemic inflammatory response after out-of-hospital cardiac arrest (the IMICA Trial): A double-blinded, placebo-controlled, single-center, randomized, clinical trial. *Circulation* 2021; 143:1841–1851
36. Penn J, Douglas W, Curran J, et al: Efficacy and safety of corticosteroids in cardiac arrest: A systematic review, meta-analysis and trial sequential analysis of randomized control trials. *Crit Care* 2023; 27:12
37. Nolan JP, Sandroni C, Böttiger BW, et al: European Resuscitation Council and European Society of Intensive Care Medicine Guidelines 2021: Post-resuscitation care. *Resuscitation* 2021; 161:220–269
38. Dankiewicz J, Cronberg T, Lilja G, et al; TTM2 Trial Investigators: Hypothermia versus normothermia after out-of-hospital cardiac arrest. *N Engl J Med* 2021; 384:2283–2294
39. Fernando SM, Di Santo P, Sadeghirad B, et al: Targeted temperature management following out-of-hospital cardiac arrest: A systematic review and network meta-analysis of temperature targets. *Intensive Care Med* 2021; 47:1078–1088
40. Granfeldt A, Holmberg MJ, Nolan JP, et al; International Liaison Committee on Resuscitation ILCOR Advanced Life Support Task Force: Temperature control after adult cardiac arrest: An updated systematic review and meta-analysis. *Resuscitation* 2023; 191:109928
41. Taccone FS, Dankiewicz J, Cariou A, et al: Hypothermia vs normothermia in patients with cardiac arrest and nonshockable rhythm: A meta-analysis. *JAMA Neurol* 2024; 81:126–133
42. Holgersson J, Meyer MAS, Dankiewicz J, et al: Hypothermic versus normothermic temperature control after cardiac arrest. *NEJM evidence* 2022; 1:1–13
43. Wyckoff MH, Greif R, Morley PT, et al; ILCOR Summary Statement: 2022 International consensus on cardiopulmonary resuscitation and emergency cardiovascular care science with treatment recommendations: Summary from the basic life support; advanced life support; pediatric life support; neonatal life support; education, implementation, and teams; and first aid task forces. *Circulation* 2022; 146:e48–e557
44. Arrich J, Schütz N, Oppenauer J, et al: Hypothermia for neuroprotection in adults after cardiac arrest (review). *Cochrane Database Systemat Reviews* 2023; 2023:CD004128