



# Impact of Hypothermic Temperature Control on Plasma and Soft Tissue Pharmacokinetics of Penicillin/Beta-Lactamase Inhibitor Combinations in Patients Resuscitated After Cardiac Arrest

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## Abstract

**Background and Objectives** Penicillin/beta-lactamase inhibitors are often used to treat aspiration pneumonia in patients resuscitated after cardiac arrest (CA). The impact of hypothermic temperature control on the pharmacokinetics of amoxicillin/clavulanate (AMO/CLAV) and ampicillin/sulbactam (AMP/SULB) has not been studied. Our objective was to evaluate the effects of hypothermic temperature control on the plasma and soft tissue pharmacokinetics of AMO/CLAV and AMP/SULB, including pulmonary concentrations of AMP/SULB, in patients resuscitated after CA.

**Methods** This prospective clinical study involved ten adult patients after CA receiving either AMO/CLAV 2 g/0.2 g or AMP/SULB 2 g/1 g intravenously every 8 h. Patients underwent hypothermic temperature control ( $33 \pm 1$  °C) for 24 h, followed by normothermia. Plasma, urine, muscle, and subcutaneous pharmacokinetics were measured and plasma protein-binding assessed for each subject. Microdialysis determined unbound drug concentrations in soft tissues. The pulmonary concentration of AMP/SULB was analyzed in the epithelial lining fluid.

**Results** No significant differences in plasma pharmacokinetics or renal excretion of AMO/CLAV and AMP/SULB were observed between the two temperature conditions. Soft tissue concentrations showed no consistent trend. Pharmacokinetic/pharmacodynamic targets (time that the unbound plasma concentrations were above the minimal inhibitory concentration [MIC] for MIC up to 8 mg/L) were met but not for 16 mg/L. Pulmonary concentrations of AMP/SULB in the epithelial lining fluid showed no clear trend.

**Conclusion** This study indicates that hypothermic temperature control does not significantly affect plasma concentrations, soft tissue concentrations, or renal excretion of AMO/CLAV and AMP/SULB in patients resuscitated after CA. However, pulmonary concentrations of AMP/SULB exhibited interindividual variability.

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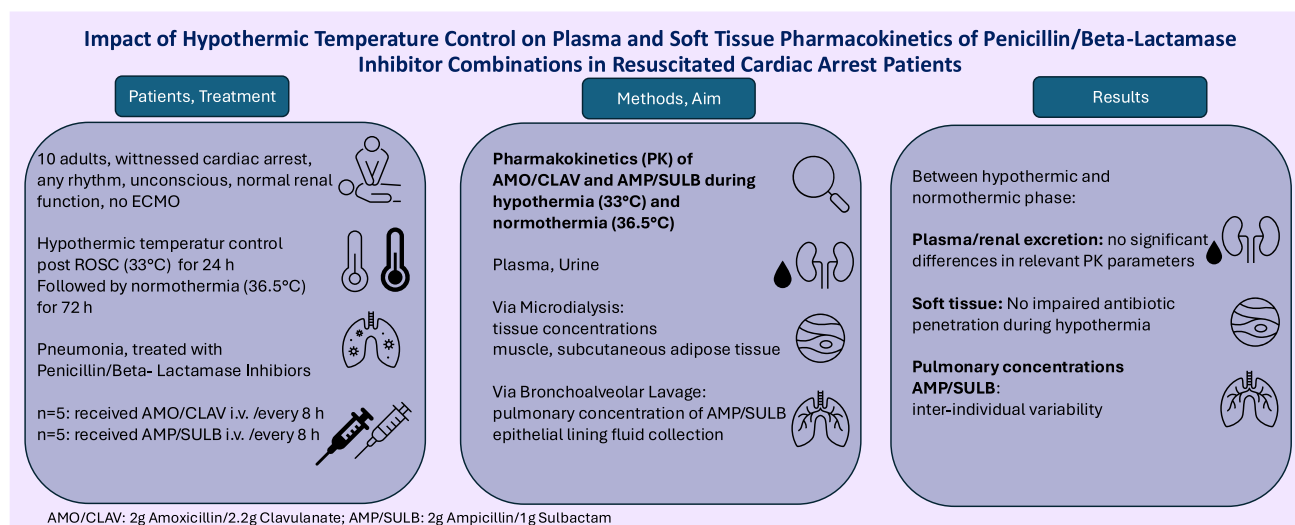
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## Graphical Abstract



## Key Points

Hypothermic temperature control did not significantly alter plasma or soft tissue pharmacokinetics of amoxicillin/clavulanate or ampicillin/sulbactam.

Pharmacokinetic/pharmacodynamic targets (including time that the unbound plasma concentrations were above the minimal inhibitory concentration) were met for minimal inhibitory concentrations up to 8 mg/L but not for 16 mg/L.

Pulmonary concentrations of ampicillin/sulbactam in epithelial lining fluid showed interindividual variability.

## 1 Introduction

Sudden cardiac arrest (CA), particularly out-of-hospital CA remains a major global health issue and a leading cause of adult death [1]. In Europe, resuscitation attempts average 56 per 100,000 individuals annually, but survival rates to hospital discharge are only around 10% [2].

Current joint guidelines from the European Resuscitation Council and the European Society of Intensive Care Medicine recommend continuous core temperature monitoring and fever prevention ( $> 37.7^{\circ}\text{C}$ ) for at least 72 h in comatose patients after return of spontaneous circulation (ROSC). The ideal temperature target is debated and

ranges from 32 to 36 °C or fever prevention above 37.7 °C [3, 4]. If initiated early after ROSC, hypothermic temperature control with a target of 32–34 °C primarily acts by lowering metabolic demand in ischemic tissue and can reduce cerebral reperfusion injury in comatose patients after CA [4, 5].

However, hypothermia can alter peripheral blood flow and organ metabolism, potentially affecting drug pharmacokinetics, making standard dosing less effective [6].

Early-onset and ventilator-associated pneumonia are common complications in survivors of CA admitted to the intensive care unit (ICU). Although post-ROSC hypothermia can dampen inflammatory responses, it may increase lung susceptibility to infections, potentially contributing to a greater pneumonia risk [7].

Empiric treatments for early-onset pneumonia in intubated survivors of CA often include broad-spectrum penicillin/beta-lactamase inhibitors such as amoxicillin/clavulanate (AMO/CLAV) and ampicillin/sulbactam (AMP/SULB) [8, 9]. In clinical practice, empiric antibiotics are frequently started early in cooled survivors of CA to prevent aspiration pneumonia, although European guidelines recommend antibiotics only when pneumonia is confirmed [10]. A trial showed that early prophylactic antibiotics in survivors of CA under hypothermic temperature control reduced early ventilator-associated pneumonia but not mortality [9]. Consequently, the American Heart Association and Neurocritical Care Society recommend early, short-term antibiotic prophylaxis [11].

Microdialysis is often used to measure unbound drug concentrations in tissues such as plasma, muscles, and

subcutaneous tissue [12, 13]. Although a comprehensive understanding of plasma and tissue pharmacokinetics of commonly used antibiotics under normothermic conditions has been obtained, their pharmacokinetic behavior during hypothermia in resuscitated adults remains largely unexplored [14–18]. Understanding tissue pharmacokinetics of antibiotics is key for optimizing treatment in critically ill patients, as altered renal and liver function, capillary leakage, and hypoalbuminemia all affect drug distribution and clearance. Adequate drug levels at infection sites are crucial for effective treatment and preventing resistance, especially in patients in the ICU who require adjusted dosing [19].

This study aimed to investigate the pharmacokinetic profiles of AMO/CLAV and AMP/SULB in the plasma, muscle, subcutaneous adipose tissue, urine, and epithelial lining fluid (ELF) of patients resuscitated after CA during hypothermia and normothermia.

## 2 Material and Methods

### 2.1 Ethics

This prospective, open-labelled, single-center study was approved by the ethics committee of the Medical University of Vienna (EC: 1348/2015) and the Austrian Agency for Health and Food Safety. It was registered at the European Union Drug Regulating Authorities Clinical Trials Database (EUDRACT 2015-001793-18) and conducted according to International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use good clinical practice guidelines and the Declaration of Helsinki. Since the participants were unconscious, consent was obtained from survivors once they could understand the study. The treating team informed patients' relatives about their inclusion in the study, but the ethics committee did not mandate this as a requirement. The study procedures were conducted at the Department of Emergency Medicine (ED) and the ICU at the Medical University of Vienna from April 2016 to June 2022.

### 2.2 Study Population and Procedure

We included comatose, intubated patients aged  $\geq 18$  years who experienced witnessed CA of any rhythm, were eligible for hypothermic temperature control, and received AMO/CLAV or AMP/SULB for suspected or confirmed aspiration pneumonia. Exclusion criteria included pregnancy, unwitnessed CA, non-sustained ROSC, body mass index (BMI) outside the range of 18–40 kg/m<sup>2</sup>, significant coagulopathies or hemorrhagic conditions (platelet count  $< 50$  G/L), a glomerular filtration rate  $< 50$  mL/min/1.73 m<sup>2</sup>, advanced

malignancies, terminal illnesses, or signs of impending clinical deterioration.

All patients underwent the same procedures during two study phases: the hypothermic phase and the subsequent normothermic phase. During each study period, plasma, microdialysate, and urine were collected at predetermined intervals after antibiotic steady state. In the AMP/SULB group, bronchial mucosa ELF was collected in both phases.

#### 2.2.1 Hypothermic Temperature Control

Hypothermic temperature control procedures followed ED guidelines targeting  $33 \pm 1$  °C for 24 h after sustained ROSC, followed by rewarming at 0.5 °C/h [20]. Normothermia ( $36.5 \pm 1$  °C) was maintained for at least 72 h using physical or pharmacological methods. Cooling was achieved noninvasively with Arctic Sun® 5000 (Bard Medical Division, C.R. Bard, Inc., Louisville, CO, USA) or external surface cooling pads (EMCOOL-Spad®, EMCOOLS AG, Pfaffstatten, Austria, and TTcool-pad 302, Everynear GmbH, Baden, Austria) or invasively with Thermogard® XP (ZOLL Medical, Cologne; Germany). Body temperature was monitored with an esophageal temperature probe.

#### 2.2.2 Study Medication

Patients received either 2 g amoxicillin/0.2 g clavulanate (Curam® 2.2 g powder for infusion solution, Sandoz GmbH, Vienna, Austria) or 2 g ampicillin/1 g sulbactam (Unasyn 3g Dry Vials®, Pfizer Corporation Austria Ges.m.b.H, Vienna, Austria). Antibiotics were prepared in 100 mL 0.9% saline solution (physiological saline solution “Fresenius”- Infusions Solution, Fresenius Kabi Austria GmbH., Graz, Austria) and administered via infusion pump intravenously over 15 min every 8 h. The line was flushed with 50 mL 0.9% saline after infusion. Antibiotics were given at least twice before sampling to ensure steady-state conditions.

#### 2.2.3 Clinical Pneumonia Surveillance

C-reactive protein levels (normal:  $\leq 0.49$  mg/dL) were measured daily. Chest X-rays or computed tomography scans were performed at the physician's discretion, and pneumonia signs were evaluated by the attending radiologist.

### 2.3 Sampling

#### 2.3.1 Plasma Sampling

Blood samples (4 mL) were collected via an arterial catheter into lithium–heparin tubes. To measure total drug concentrations in plasma, samples were drawn at baseline (before the next antibiotic administration) and at 0.5, 1, 1.5, 2, 3, 4,

and 6 h after start of drug infusion. The sample collection schedule was identical for both study periods. Samples were refrigerated immediately, centrifuged at +4 °C, 2600g, 10 min, and the plasma was frozen at –20 °C within 1 h.

### 2.3.2 Urine Sampling

Urine was collected at 0–2, 2–4, and 4–6 h after drug administration. About 5 mL per sample was refrigerated and frozen at –20 °C within 1 h.

### 2.3.3 Bronchoalveolar Lavage, ELF Collection

To investigate antibiotic distribution in the bronchial mucosa, ELF was collected via bronchoscopy from endotracheally intubated patients. This procedure was conducted exclusively in the AMP/SULB group as part of an exploratory approach to assess target site antibiotic penetration. A single bronchoalveolar lavage (BAL) was performed at 2, 4, or 6 h after starting antibiotic administration during each study period. Up to three 20 mL saline aliquots were instilled and aspirated. BAL samples were mixed, filtered, and centrifuged at 2000g, 4 °C, 10 min, and the supernatant was frozen at –20 °C within 1 h.

Bronchoscopies were performed using a flexible video bronchoscope (EB-1970K by Pentax®, HOYA Corporation, Tokyo, Japan). To determine the dilution factor of ELF in BAL, the urea method was applied as described previously [21].

### 2.3.4 Microdialysis

In the present study, two microdialysis probes were inserted into one of the patient's thighs. The microdialysis catheters (63 Microdialysis Catheter 60/10, M Dialysis AB, Solna, Sweden) with a membrane length of 10 mm and a molecular weight cut-off of 20 kDa, were inserted into the subcutaneous adipose tissue and into the quadriceps muscle. Throughout the entire study (both sampling periods), microdialysis probes were perfused with 0.9% saline solution at a flow rate of 2 µL/min. Following an equilibration period of 30 min, microdialysis samples were collected at baseline (before antibiotic drug administration) and at 0–1, 1–2, 3–4, 4–5, and 5–6 h after drug administration. All microdialysis samples were immediately placed in a portable refrigerator box and frozen at –20 °C within 1 h from collection.

After the last sample of each study day, each probe was calibrated using the retrodialysis method to calculate the concentration in the interstitial space fluid, as previously described [22]. For this part of the experiment, the perfusion medium for calibration contained a known concentration of the respective antibiotics and beta-lactamase inhibitor, and the relative loss rate was determined.

### 2.3.5 Sample Handling and Storage

At the end of the study day, plasma, microdialysate, ELF, and urine samples were transferred from –20 °C to –80 °C and stored at –80 °C until analysis.

### 2.3.6 Sample Analysis: High-Performance Liquid Chromatography Method and Ultrafiltration

The high-performance liquid chromatography equipment consisted of a Shimadzu Prominence modular system with a three-channel degasser (DGU 20A3R), quaternary solvent pump (LC 20AD), autosampler (SIL 20AC HT, set to 6 °C), column oven (CTO 20AC, set to 40 °C), photodiode array detector (SPD M30A, detection wavelengths: AMP/SULB 205 nm, AMO 227 nm, CLAV 215 nm) equipped with cells of 10 mm or 85 mm optical path length, system controller CBM 20A, and LabSolution software (all from Shimadzu Europe, Duisburg, Germany). The flow rate was 0.4 mL/min, and the injection volume was 1–2 µL, for BAL 5 µL. Separation was performed isocratically using a Cortecs T3 2.7 µ 100 × 3 mm analytical column (Waters, Eschborn, Germany) preceded by a guard column (Nucleoshell RP18 2.7 µ 4 × 3 mm, Macherey-Nagel, Düren, Germany). The mobile phase consisted of 0.1 M sodium phosphate buffer/ acetonitrile 90:10 (v/v), pH 3.1, for the determination of AMP/SULB, and 97:3 (v/v), pH 3.3, for the determination of AMO/CLAV. SULB and CLAV were eluted after 2.1 min, AMP and AMO after 4.2 min.

Total drug concentrations were analyzed according to a published protocol [23]. In brief, serum (100 µL) was buffered with 25 mM sodium phosphate buffer (pH 6.0, 200 µL) and deproteinized with acetonitrile (500 µL). The precipitated protein was separated by centrifugation, the acetonitrile was extracted into dichloromethane (1.5 mL), and an aliquot of the aqueous layer was injected. The free concentrations were measured using a published ultrafiltration method [24]. In brief, plasma (300 µL) was mixed with 10 µL potassium phosphate (3M, pH 7.43 ± 0.02) in a Vivafree™ 500 30 kD Hydrosart® centrifugal ultrafiltration device (Vivaproducts Inc., Littleton, MA, USA) before ultrafiltration at 37 °C. Microdialysate or BAL were injected directly, and urine after dilution 1:50 with 10 mM sodium phosphate buffer, pH 6.0.

The lower limit of quantification (LLOQ) for AMP/SULB and AMO/CLAV was 0.3/0.5 and 0.3/0.2 mg/L, respectively, in plasma, and 0.03/0.05 and 0.03/0.02 mg/L, respectively, in saline, which was used as a surrogate for the other matrices. Based on in-process quality controls (high/low), the relative standard deviation (SD) for precision was <3%/≤7% for AMP/SULB and <3%/<5% for AMO/CLAV, respectively; the inaccuracy was <3% for all substances. The estimated LLOQ (signal-to-noise ratio = 5) in BAL (injection volume 5 µL) was 0.02/0.01 for AMP/SULB and

0.01/0.01 mg/L for AMO/CLAV; the LLOQ in urine was estimated at <30/50 and <30/20 mg/L, respectively. The accuracy of the determination of free drug in plasma cannot be specified, as the extent of protein binding in a particular sample is not known. The precision was assessed by analyzing spiked pooled plasma of healthy subjects; in these samples, the mean  $\pm$  SD unbound fraction of AMP/SULB and AMO/CLAV was  $80.6 \pm 6.9\%$ / $91.7 \pm 6.9\%$  and  $87.3 \pm 1.9\%$ / $81.7 \pm 3.4\%$ , respectively.

## 2.4 Pharmacokinetic Analysis

The pharmacokinetic data were analyzed using Phoenix<sup>®</sup> WinNonlin<sup>®</sup> Build 8.0 (Certara USA, Inc., Princeton, NJ, USA). We employed a non-compartmental analysis for this study to determine the pharmacokinetic parameters.

### 2.4.1 Plasma Protein Binding

Plasma protein binding was assessed for each subject at three distinct timepoints using ultrafiltration. Mean plasma protein binding per subject was used to calculate unbound drug concentrations, which were used for pharmacokinetic analysis.

### 2.4.2 Pharmacokinetic Parameters

We determined key plasma pharmacokinetic parameters, including maximum plasma concentration, elimination half-life, apparent volume of distribution, total body clearance, and area under the concentration–time curve from 0 to 6 h.

We also calculated the duration that unbound plasma concentrations exceeded the minimal inhibitory concentration [MIC] ( $fT_{>MIC}$ ) for AMO and AMP, using MIC values of 4 mg/L, 8 mg/L, and 16 mg/L, representing the upper range for relevant pathogens per European Committee on Antimicrobial Susceptibility Testing MIC distributions [25]. Calculations of the  $fT_{>MIC}$  were based on the individual concentrations from each study subject.

### 2.4.3 Exposure Comparison

To compare drug exposure between the normothermic and hypothermic states, we calculated concentration ratios (individual concentration at each timepoint in normothermia divided by the concentration at the same time point in hypothermia) for plasma, muscle, and subcutaneous tissue.

## 2.5 Data Analysis

### 2.5.1 Urine Excretion

The amount of drug excreted in urine within the first 6 h after infusion initiation at the targeted temperature (hypo- or

normothermia) was quantified based on concentration measurements at various urine sampling intervals. This was expressed as a percentage of the administered drug dose for one dosing interval.

## 2.6 Statistical Methods

Data presentation included mean values  $\pm$  SDs or geometric means with 95% confidence intervals, as appropriate. A paired, parametric *t* test was used to test for statistical significance of differences, at a two-sided *p* value of <0.05.

## 3 Results

### 3.1 Study Population

The study included 10 patients (nine males, one female). Demographics and resuscitation details are available in Tables 1 and 2 in the electronic supplementary material (ESM). Causes of CA and post-resuscitation care specifics are detailed in Table 3 in the ESM. Laboratory results for both phases are in Tables 1 and 4 in the ESM. Mean  $\pm$  SD C-reactive protein increased from  $4.7 \pm 8.4$  mg/dL (AMO/CLAV group) and  $1.1 \pm 1.2$  mg/dL (AMP/SULB group) during hypothermia to  $15.1 \pm 6.1$  mg/dL and  $8.5 \pm 4.9$  mg/dL, respectively, in normothermia. Medical history and relevant pharmacotherapy are in Tables 5 and 6, respectively, in the ESM.

In the AMO/CLAV group (one female, four males, age  $62 \pm 16$  years, weight  $93 \pm 12$  kg, BMI  $30 \pm 5$  kg/m<sup>2</sup>), four of the five developed aspiration pneumonia on day 1. The remaining patient, who had hypoxic CA from grape aspiration, had the obstruction removed bronchoscopically after ROSC. In the AMP/SULB group (five males, age  $56 \pm 13$  years, weight  $103 \pm 21$  kg, BMI  $29 \pm 7$  kg/m<sup>2</sup>), all five showed pneumonia signs from aspiration on day 1.

One minor adverse event—a small skin bleed after removal of the microdialysis probe—occurred, with no further complications. No allergic reactions to antibiotics were observed.

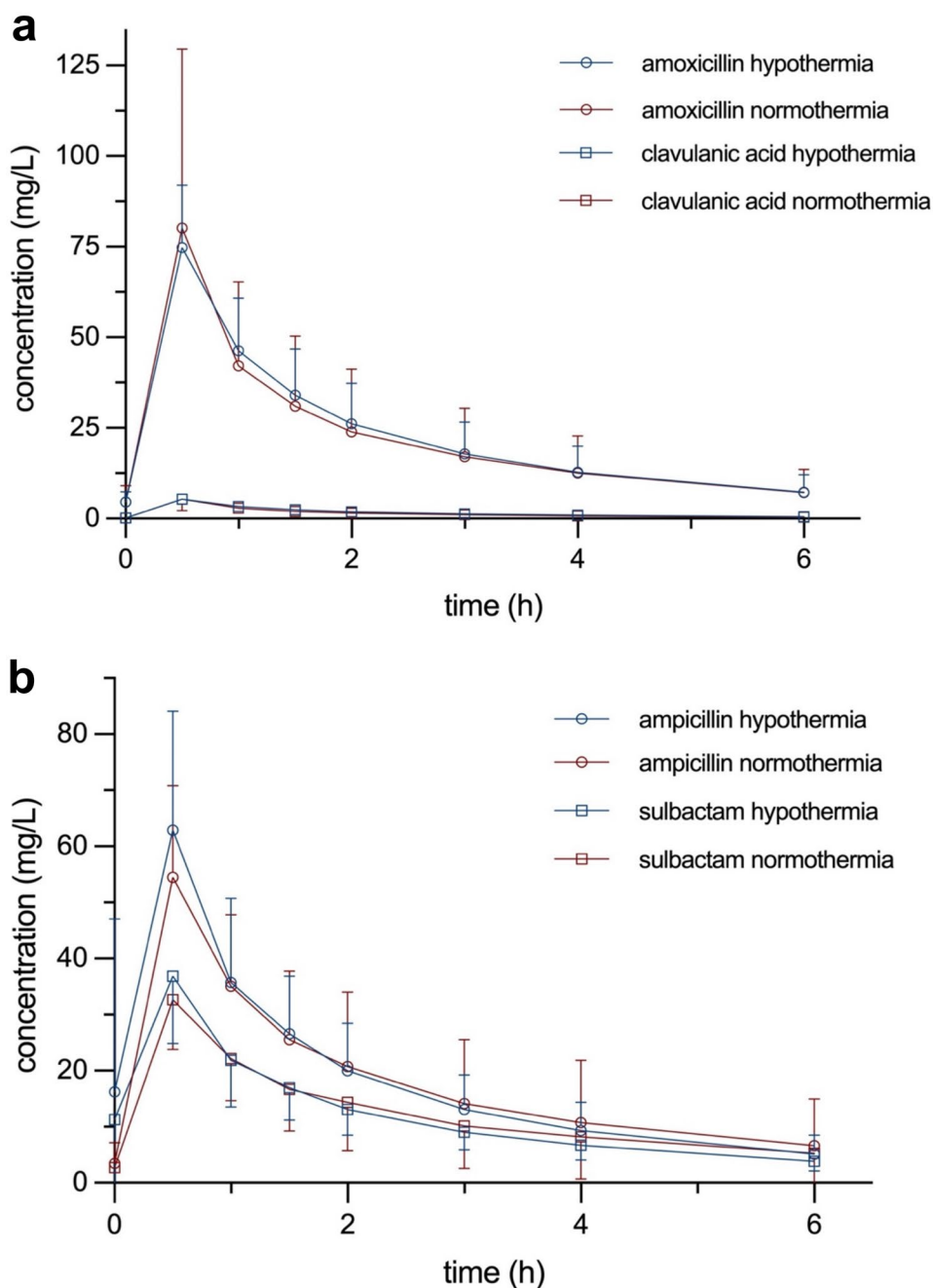
### 3.2 Pharmacokinetic Analysis

#### 3.2.1 Steady-State Concentration–Time Profiles

Figure 1 illustrates the mean unbound plasma concentration–time profiles for hypothermic and normothermic states. CLAV levels were nearly identical in both conditions. AMO peaked within the first hour, slightly higher during normothermia, and AMP and SULB had higher concentrations during hypothermia. However, no significant differences were observed.



**Fig. 1** Steady-state concentration–time profiles of unbound plasma concentrations of (a) amoxicillin/clavulanic acid and (b) ampicillin/sulbactam in hypothermic and normothermic patient states



### 3.2.2 Comparison of Plasma Pharmacokinetic Parameters

The plasma pharmacokinetic parameters and drug amounts excreted in urine for AMO/CLAV and AMP/SULB during hypothermia and normothermia are detailed in Tables 1 and 2, respectively. No statistically significant differences between the two temperature states were observed.

### 3.2.3 Concentration Ratios

Table 3 presents the ratios of normothermic to hypothermic concentrations in plasma, muscle tissue, and subcutaneous adipose tissue. Notably, there was a trend indicating higher plasma concentrations of AMO/CLAV during hypothermia, with mean ratios of 0.87 for AMO and 0.76 for CLAV. Conversely, the plasma exposure of AMP/

**Table 1** Unbound plasma pharmacokinetic (PK) parameters for amoxicillin and clavulanic acid at hypothermic and normothermic patient states

PK parameter	Amoxicillin			Clavulanic acid		
	Hypothermia	Normothermia	<i>p</i> value	Hypothermia	Normothermia	<i>p</i> value
$t_{1/2}$ (h)	2.16 ± 0.50	2.18 ± 0.64	0.957	2.39 ± 0.76	2.30 ± 1.25	0.782
$C_{max}$ (mg/L)	74.8 ± 17.2	80.2 ± 39.2	0.670	5.32 ± 1.02	5.33 ± 2.40	0.929
$AUC_{last}$ (h*mg/L)	142.6 ± 54.8	146.7 ± 88.7	0.619	10.11 ± 2.47	9.14 ± 4.43	0.595
CL (L/h)	14.5 ± 7.70	16.1 ± 6.78	0.659	17.7 ± 5.22	24.3 ± 10.5	0.183
<i>V</i> (L)	41.6 ± 13.8	43.7 ± 18.9	0.949	59.2 ± 19.9	70.4 ± 36.5	0.645
Amount in urine (%)	64.7 ± 32.5	56.6 ± 17.2	0.631	42.5 ± 39.9	32.9 ± 14.9	0.562

The amount of drug excreted in urine in the first 6 h at the targeted temperature is given as the percentage of dose administered. Values are expressed as mean ± standard deviation

$AUC_{last}$  area under the concentration–time curve from time point 0 to 6 h, CL total body clearance,  $C_{max}$  maximum plasma concentration,  $t_{1/2}$  elimination half-life, *V* apparent volume of distribution

**Table 2** Unbound plasma pharmacokinetic (PK) parameters for ampicillin (AMP) and sulbactam (SULB) at hypothermic and normothermic patient states

PK parameter	Ampicillin			Sulbactam		
	Hypothermia	Normothermia	<i>p</i> value	Hypothermia	Normothermia	<i>p</i> value
$t_{1/2}$ (h)	2.07 ± 0.58	2.19 ± 1.12	0.821	2.45 ± 0.56	2.76 ± 1.76	0.711
$C_{max}$ (mg/L)	63.3 ± 21.4	54.5 ± 16.3	0.397	37.3 ± 12.2	32.6 ± 8.79	0.448
$AUC_{last}$ (h*mg/L)	112.2 ± 48.7	109.5 ± 65.8	0.928	72.6 ± 26.2	74.3 ± 43.3	0.932
CL (L/h)	20.0 ± 12.7	21.0 ± 12.2	0.865	13.2 ± 5.65	14.3 ± 7.95	0.765
<i>V</i> (L)	56.3 ± 34.5	53.3 ± 18.1	0.867	47.2 ± 27.8	43.5 ± 13.9	0.781
Amount in urine (%)	80.4 ± 16.7 <sup>a</sup>	63.7 ± 19.7 <sup>b</sup>	0.468 <sup>a</sup>	95.6 ± 27.0 <sup>a</sup>	71.4 ± 19.9 <sup>b</sup>	0.460 <sup>a</sup>

The amount of drug excreted in urine in the first 6 h is given as the percentage of dose administered. Values are expressed as mean ± standard deviation

$AUC_{last}$  area under the concentration–time curve from time point 0 to 6 h, CL total body clearance,  $C_{max}$  maximum plasma concentration,  $t_{1/2}$  elimination half-life, *V* apparent volume of distribution

<sup>a</sup>Data from only two subjects were available

<sup>b</sup>Data from only four subjects were available

**Table 3** Geometric means (95% confidence interval) of concentration ratios (normothermia/hypothermia) of amoxicillin, clavulanic acid, ampicillin, and sulbactam for plasma, muscle, and subcutaneous adipose tissue

Plasma/Tissue	Amoxicillin	Clavulanic acid	Ampicillin	Sulbactam
Plasma	0.87 (0.76–0.99)	0.76 (0.67–0.86)	0.89 (0.72–1.11)	0.86 (0.68–1.10)
Muscle	1.0 (0.79–1.3)	0.93 (0.68–1.3)	1.2 (1.0–1.4)	1.2 (1.0–1.3)
Subcutis	0.99 (0.65–1.5)	0.58 (0.42–0.8)	0.86 (0.63–1.2)	0.85 (0.64–1.1)

SULB remained comparable across the two temperature conditions.

### 3.2.4 Tissue Concentration Differences

Significant differences in tissue concentrations between hypothermic and normothermic states were observed for AMO and CLAV in subcutaneous tissue, with *p* values of 0.029 and 0.012, respectively. However, the overall analysis of the remaining soft tissue concentrations revealed no consistent trend between the hypothermic and normothermic states (Table 3).

### 3.2.5 Pharmacokinetic/Pharmacodynamic Targets

Table 4 displays the  $fT_{>MIC}$  values for MICs of 4 mg/L, 8 mg/L, and 16 mg/L for both AMO and AMP. For MICs up to 8 mg/L, the mean  $fT_{>MIC}$  exceeded 50% of the dosing interval for both antimicrobial agents, indicating adequate exposure. The comparison between hypothermia and normothermia in terms of pharmacokinetic/pharmacodynamic target attainment ( $\%fT_{>MIC}$ ) did not show statistically significant differences.

**Table 4** The time that the unbound plasma concentrations were above the minimal inhibitory concentration ( $fT_{>MIC}$ ) for amoxicillin and ampicillin in hypothermia and normothermia

MIC	Amoxicillin ( $fT_{>MIC}$ in %)			Ampicillin ( $fT_{>MIC}$ in %)		
	Hypothermia	Normothermia	<i>p</i> value	Hypothermia	Normothermia	<i>p</i> value
4 mg/L	84.8 ± 21.6	78.1 ± 23.1	0.382	74.7 ± 23.7	69.8 ± 25.7	0.317
8 mg/L	65.7 ± 25.7	61.6 ± 26.8	0.871	54.9 ± 24.7	53.1 ± 29.7	0.576
16 mg/L	41.7 ± 19.6	35.4 ± 23.3	0.635	30.5 ± 16.5	37.3 ± 32.7	0.363

Three different MIC values were used for the calculations.  $fT_{>MIC}$  is presented as a percentage of the dosing interval (8 h) ± standard deviation

### 3.2.6 Pulmonary Concentrations of AMP and SULB

Pulmonary AMP and SULB concentrations were measured in the ELF of five patients at 2, 4, or 6 h (±1 h) after antibiotic administration. AMP was detectable in all BAL samples, and SULB was undetectable in one due to interference. Two patients missed BAL sampling after transfer from the ED to the ICU, leading to missing AMP/SULB data for one patient in the normothermic phase and another in the hypothermic phase. In one patient, BAL was performed at different time points during the two phases for organizational reasons: during hypothermia (2 h after antibiotic administration) and during normothermia (6 h after antibiotic administration). ELF concentrations are shown in Fig. 2.

## 4 Discussion

This is the first study to examine the effects of hypothermia on the pharmacokinetics of AMO/CLAV and AMP/SULB in plasma, muscle, subcutaneous tissue, and ELF in

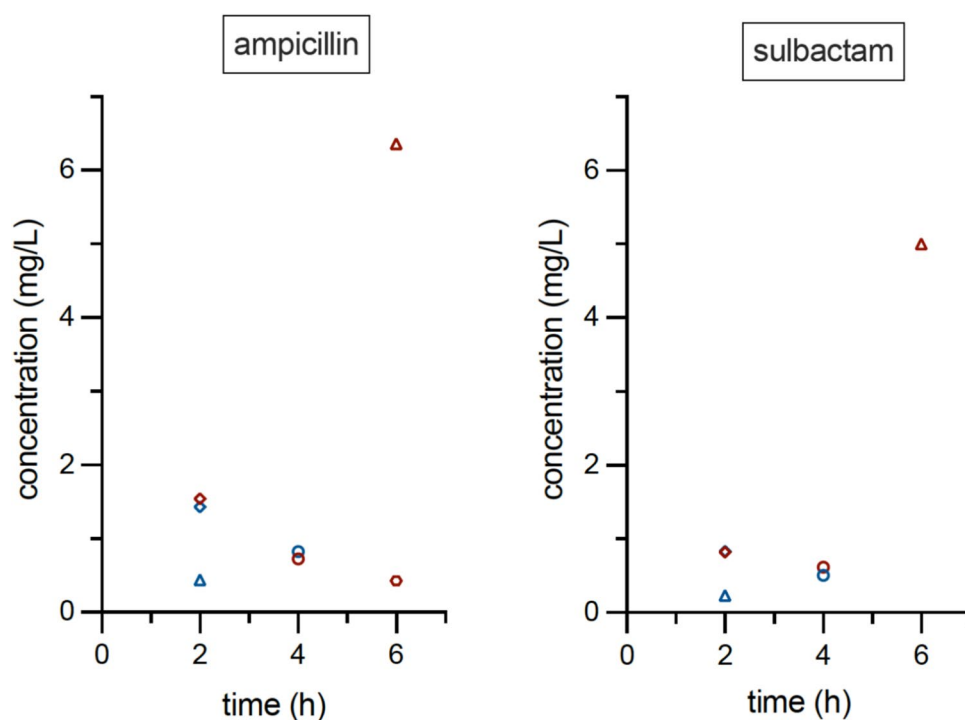
resuscitated adults. It aimed to assess how controlled hypothermia ( $33 \pm 1^\circ\text{C}$ ) affects pharmacokinetics and antibiotic efficacy in treating aspiration pneumonia after ROSC.

The plasma pharmacokinetic parameters of AMP/SULB aligned with those from previous studies in healthy individuals and patients with normal renal function [15, 26, 27]. Similarly, AMO/CLAV pharmacokinetic parameters were consistent with published data [28, 29].

We expected altered antibiotic pharmacokinetics between the two temperature phases in our cohort of hypothermic, critically ill patients receiving multiple medications after surviving CA.

In a large multinational study on beta-lactams (including AMO and AMP) in critically ill patients, plasma concentrations varied significantly, leading to inconsistent achievement of pharmacokinetic targets [30]. Hypothermia may slow drug absorption, especially for oral drugs, and reduce the volume of distribution, potentially increasing toxicity because of altered perfusion, blood pH, and drug properties [31]. Most research, which is particularly lacking in antibiotics, relies on animal studies, indicating a gap in the understanding of the full impact

**Fig. 2** Concentrations (mg/L) of ampicillin and sulbactam measured in epithelial lining fluid. Blue indicates concentrations that were measured in the hypothermic phase, and red indicates those measured in the normothermic phase. The different symbols indicate different subjects





of hypothermia on drug pharmacokinetics and pharmacodynamics in humans [31, 32].

In the present study, we could not identify statistically significant differences in plasma concentrations, pharmacokinetic parameters, or the amount of drug excreted in urine of AMO/CLAV and AMP/SULB between the hypothermic and normothermic phases.

Antibiotic penetration into peripheral soft tissues was not impaired during the hypothermic state. Although no consistent trend was observed between hypothermic and normothermic conditions, AMO and CLAV showed significantly higher subcutaneous tissue concentrations during hypothermia. These findings suggest that although hypothermia does not broadly affect antibiotic penetration into soft tissues, it may influence the distribution of specific antibiotics.

The pulmonary ELF concentration of AMP and SULB in our small cohort showed no clear trend for reliable interpretation. However, in two patients, concentrations of AMP and SULB were similar at the respective sampling time points during both the hypothermia and the normothermia phases. In one patient, low concentrations were observed in the 2-h BAL (hypothermia) and high concentrations in the 6-h BAL (normothermia). No relevant clinical reason could be identified for these extreme values compared with the other available samples at the respective time points. Previous studies have reported a significant variability in ELF exposure. A comprehensive review highlighted this variability, especially in critically ill patients with lower respiratory tract infections, and emphasized the need for further research to optimize dosing regimens and understand the relationship between ELF concentrations and clinical outcomes [33].

Literature indicates that the causative micro-organisms in early-onset pneumonia after ROSC of patients resuscitated from out-of-hospital CA are most frequently *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Streptococcus* spp., *Haemophilus influenzae*, *Escherichia coli*, and *Klebsiella pneumoniae* [34, 35].

According to our data, bactericidal  $fT_{>MIC}$  of AMO and of AMP in plasma was  $\geq 50\%$ , but  $< 100\%$  (of the dosing interval) for MIC values of 4 mg/L and 8 mg/L, and  $< 50\%$  for a MIC of 16 mg/L. There was no statistically significant difference in achievement of pharmacokinetic/pharmacodynamic targets, expressed as  $\% fT_{>MIC}$ , between normothermia and hypothermia in the ten patients analyzed.

## 5 Limitations

Our study has several limitations that must be considered.

First, the small sample size and predominantly male, exclusively white demographic may limit the generalizability of the findings. However, this aligns with evidence that sudden CA more frequently affects men because of higher cardiovascular disease incidences and mortality rates [36]. Additionally,

critically ill patients, particularly those who undergo resuscitation, often develop acute kidney injury within the first 48 h after CA [37, 38], necessitating antibiotic dose adjustments. Our study included only patients with normal renal function and excluded those with renal impairment, which limits the data on how renal dysfunction affects antibiotic pharmacokinetics during hypothermia, an important area for future research. We also excluded patients who underwent extracorporeal cardiopulmonary resuscitation or veno-arterial extracorporeal membrane oxygenation (ECMO) following ROSC. As the use of ECMO in resuscitation is growing, this exclusion is significant, particularly given the impact of ECMO on beta-lactam pharmacokinetics, underscoring the need for tailored drug monitoring and further research in ECMO settings [39, 40]. Lastly, the antibiotics were administered via short infusions, which contrasts with guidelines recommending prolonged or continuous infusions in critically ill patients, especially those with septic shock or high severity scores, to optimize therapeutic outcomes [41]. Continuous infusions are more commonly used in the ICU setting, whereas short infusions are typically used in emergency contexts such as in the ED.

## 6 Conclusion

Our study showed no significant differences in relevant pharmacokinetic parameters of AMP/SULB and AMO/CLAV for plasma and renal excretion between hypothermia and normothermia. Antibiotic penetration into peripheral soft tissues remained unaffected during hypothermia. In our small cohort, the pulmonary ELF concentrations of AMP and SULB showed no clear trend. Pharmacokinetic/pharmacodynamic targets ( $fT_{>MIC}$ ) for MICs up to 8 mg/L were met but not for 16 mg/L.

Further research in larger cohorts and with other antibiotics is needed to better understand the impact of controlled hypothermia on antibiotic therapy in patients resuscitated after CA.

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## Declarations

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**Conflict of interest** Markus Zeitlinger is an editorial board member of *Clinical Pharmacokinetics* and was not involved in the selection of peer reviewers for the manuscript nor any of the subsequent editorial decisions. The other authors have no competing interests to declare that are relevant to the content of this article.

**Availability of data and materials** The datasets generated during the current study are available from the corresponding author upon reasonable request.

**Author contributions** Alexandra-Maria Stommel: conceptualization, validation, formal analysis, investigation, data curation, writing—original draft, writing—review and editing, and visualization. Peter Matzneller: conceptualization, investigation, and writing—review and editing. Valentin al Jalali: formal analysis, data curation, visualization, and writing—review and editing. Beatrix Wulkersdorfer: investigation, data curation, writing—review and editing, and project administration. Edith Lackner: investigation, writing—review and editing, and project administration. Matthias Mueller: investigation and writing—review and editing. Christoph Dorn: methodology, validation, formal analysis, investigation, resources, data curation, and writing—review and editing. Michael Holzer: writing—review and editing and supervision. Markus Zeitlinger: conceptualization, methodology, validation, resources, writing—review and editing, supervision, project administration, and funding acquisition.

**Ethics approval** The study was approved by the ethics committee of the Medical University of Vienna, Austria (EC: 1348/2015) and the Austrian Agency for Health and Food Safety. It was registered in the European Union Drug Regulating Authorities Clinical Trials Database (EUDRACT 2015-001793-18) and conducted according to International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use good clinical practice guidelines and the Declaration of Helsinki.

**Consent to participate** Since the participants were unconscious, informed written consent was obtained from survivors once they were able to comprehend the study. The treating team informed patients' relatives about their inclusion in the study, but the ethics committee did not mandate this as a requirement.

**Consent for publication** Not applicable.

**Code availability** Not applicable.

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