# Early detection of patient deterioration in patients with infection or sepsis

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# Chapter 5

# Trends in vital signs and routine biomarkers in patients with sepsis during resuscitation in the emergency department: a prospective observational pilot study.

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## ABSTRACT

### OBJECTIVES
Sepsis lacks a reliable and readily available measure of disease activity. Thereby, it remains unclear how to monitor response to treatment. Research on numerous (new) biomarkers associated with sepsis provided disappointing results and little is known about changes in vital signs during sepsis resuscitation. We hypothesized that trends in vital signs together with routine biomarker levels during resuscitation might provide information about the response to treatment at a very early stage of sepsis in the emergency department (ED). We therefore explore trends in vital signs and routine biomarker levels during sepsis resuscitation in the ED.

### DESIGN
Prospective observational pilot study.

### SETTING
ED of a tertiary care teaching hospital.

### PARTICIPANTS
99 Adult non-trauma patients with suspected infection and 2 or more systemic inflammatory response syndrome criteria admitted to the ED.

### PRIMARY AND SECONDARY OUTCOME MEASURES
Vital signs and biomarker levels at admittance ($T_0$) and after 3 h in the ED ($T_1$).

### RESULTS
In total, data of 99 patients were analyzed. Of these patients, 63 presented with sepsis, 30 with severe sepsis and 6 with septic shock. All vital signs decreased, except for peripheral oxygen saturation which increased. Almost all routine biomarker levels decreased during resuscitation, except for C reactive protein, bands, potassium, troponin T and direct bilirubin which remained stable. Sodium, chloride and N-terminal prohormone of brain natruretic peptide increased slightly.

### CONCLUSIONS
Vital signs and biomarker levels showed descending trends during resuscitation, except for parameters directly affected by treatment modalities. Despite these trends, most patients improved clinically. Trends in vital signs and routine biomarkers might be helpful in predicting clinical course and response to treatment in patients with sepsis during early resuscitation.

## INTRODUCTION

Early and aggressive resuscitation is an important factor to reduce mortality of sepsis[1,2]. It appears that early recognition of patients with sepsis and timely and aggressive resuscitation are more important than the specific kind of treatment provided[1,3,4]. Sepsis lacks a reliable measure of disease activity, similar to the viral load in HIV or left ventricle function in cardiology[5,6]. Therefore, it remains unclear how response to treatment can be monitored[6,7]. One known approach to monitor this is to monitor the patient's vital signs. However, there is little information about changes in vital signs in sepsis and their relation to treatment during early resuscitation in the emergency department (ED). Furthermore, numerous biomarkers associated with sepsis have been studied for this purpose, generally with disappointing results. Their sensitivity and specificity are too low to be of real clinical value and they are often not readily available[7,8].

Up to 50% of all patients with sepsis are admitted through the ED[9]. Patients are usually transferred from the ED to either the intensive care unit (ICU) or nursing wards within 4 h[10,11]. Within these 4 h, early resuscitation is initiated, preferably as soon as possible[6]. We hypothesized that trends in vital signs together with routine biomarker levels during the resuscitation of patients with sepsis in the ED might provide information about the response to treatment. This information is useful to guide treatment at a very early stage of sepsis, while the patient is still in the ED. The response to treatment could be used to tailor the patient's treatment and monitoring and, at the same time, prevent doing harm to patients with mild sepsis with too aggressive treatment. It could furthermore serve as a feasible and accurate way to recognize the patients with a great chance to deteriorate and potentially provide an early warning of deterioration[12]. To the best of our knowledge, there are no data available about trends in vital signs and biomarkers during resuscitation in the ED. Therefore, we performed a pilot study within the 4 h time frame that the patient is in the ED.

## METHODS

### STUDY DESIGN AND SETTING

We performed a prospective observational pilot study in the ED of the University Medical Center Groningen, a tertiary care teaching hospital with over 34 000 visits to the ED annually. The pilot study was aimed to establish power calculations and feasibility of a full-scale study on the use of trends in vital signs and biomarkers as response to treatment parameter. The pilot aimed to include a convenience sample of 100 patients within a limited 6-month time frame. Data were collected between October 2013 and April 2014. To prevent selection bias, taking blood samples in patients with an altered mental status due to sepsis was also approved by the review board. In these cases, informed consent was obtained from the next of kin or from the patient during their stay in hospital.

## STUDY POPULATION AND PROTOCOL

Adult non-trauma patients visiting the ED with presumed infection or sepsis were screened for inclusion. Inclusion criteria were: age ≥18 years, presumed or confirmed infection, and two or more systemic inflammatory response syndrome (SIRS) criteria as defined by the International Sepsis Definitions Conference[13].

Patients are usually transferred from the ED to either the ICU or nursing ward within 4 h. To detect trends in vital signs and biomarker levels, we took measurements at two points within this time frame: at admittance to the ED ($T_0$) and after 3 h ($T_1$). At $T_0$, a nurse measured the patient's vital signs and took a routine blood sample. Vital signs were measured with a patient monitor (IntelliVue MP30 System with Multi-Measurement Module, Philips, Eindhoven, The Netherlands), except for temperature which was measured using an electronic tympanic ear thermometer (Genius 2; Mountainside Medical Equipment, Marcy, New York, USA). Simultaneously with the routine blood sample, the nurse took a number of additional blood vials for this study. These additional vials were temporarily stored until informed consent was obtained. This procedure ensured that treatment was not delayed for patients participating in the study. The vials for the routine blood sample were immediately sent to the hospital's central laboratory and were analyzed for the routine biomarkers listed in Table 1.

Patients or their healthcare proxies had to provide written informed consent before $T_1$; otherwise, the patient was excluded from the study and the stored vials were destroyed. The stored vials were sent to the central laboratory for analysis immediately after obtaining

**TABLE 1. Overview of the measured biomarkers and their characteristics**

| Name | Unit | CV (%) | Reference values | |
|---|---|---|---|---|
| Routine biomarkers | | | | |
| Albumin | g/L | 1.4 | 35-50 | |
| Alkaline phosphatase (ALP) | U/L | 2.2 | Male: <115 | Female: <98 |
| Aspartate transaminase (AST) | U/L | 1.4 | Male: <35 | Female: <31 |
| Bands | % | n/a | 0-3 | |
| Bilirubin, direct | µmol/L | 1.9 | <5 | |
| Bilirubin, total | µmol/L | 1.9 | <17 | |
| Calcium | mmol/L | 1.4 | 2.20-2.60 | |
| Chloride | mmol/L | 0.8 | 97-107 | |
| Creatinine | µmol/L | 2.0 | Male: 50-110 | Female:50-90 |
| C-reactive protein (CRP) | mg/L | 3.0 | <5 | |
| γ-glutamyl transferase (γ-GT) | U/L | 1.9 | Male: <55 | Female: <38 |
| Glucose | mmol/L | 1.5 | 4.0-5.5 (fastening) | |
| Hemoglobin (Hb) | mmol/L | 1.3 | Male:8.7-10.6 | Female: 7.5-9.9 |
| Lactate | mmol/L | 1.5 | 0.5-2.2 | |
| Lactate dehydrogenase (LDH) | U/L | 1.3 | Male: <248 | Female: <247 |
| Leukocytes | 109/L | 1.8 | 4-10 | |
| Potassium | mmol/L | 0.8 | 3.5-5.0 | |
| Sodium | mmol/L | 0.7 | 135-145 | |
| Thrombocytes | 109/L | 4.4 | 150-350 | |
| Urea | mmol/L | 2.5 | 2.5-7.5 | |
| Study specific additional biomarkers | | | | |
| Cortisol | nmol/L | 3.8 | 08:00: 200-800<br>16:00: 100-400<br>22:00: 50-200 | |
| D-dimer | ng/ml | 4.5 | <500 | |
| High-sensitivity troponin T (hs-Trop T) | ng/L | 5.0 | <14 | |
| N-terminal prohormone of brain natruretic peptide (NT pro-BNP) | ng/L | 2.2 | -75 year: <175 | >75 year: <450 |

CV, averaged inter- and intra-essay coefficient of variation during the study inclusion period.

informed consent. The blood in these vials was analyzed for four additional routinely available biomarkers, as shown in Table 1. These biomarkers were added for the following reasons: N-terminal prohormone of brain natruretic peptide (NT pro-BNP) as a marker for fluid overload, cortisol as a marker for stress response, D-dimer for coagulation status and marker of disseminated intra-vascular coagulation and troponin T as a marker of myocardial damage.

At $T_1$, new blood samples were collected and immediately analyzed for all biomarkers shown in Table 1. The patient's vital signs were also recorded at $T_1$ using the same procedures and equipment as at $T_0$. Furthermore, we recorded the amount of intravenous fluids given to the patient in the ED until $T_1$. In case a patient was transferred to the ICU or a ward before $T_1$, a researcher took the $T_1$ blood samples and vital signs there according to the study protocol.

The attending physician was asked for the suspected focus of sepsis at the moment the patient was transferred out of the ED and was allowed to select multiple options. Demographic data were collected from the patient's electronic medical records. All patients received treatment according to the routine sepsis protocol, including fluid resuscitation, antibiotics and supplemental oxygen. According to protocol, fluid resuscitation was performed by an initial fluid challenge of 500 mL saline solution (NaCl 0.9%) in 10 min, followed by 500 mL every 15 min until a mean arterial pressure (MAP) of >65 mm Hg was reached[6]. When the MAP was still <65 mm Hg after 2 L of saline, an intensivist was consulted to transfer the patient to the ICU and start inotropic medication. From previous studies in our department, we know that the median time to start fluid resuscitation was 21 min (sepsis 26, severe sepsis 15 and septic shock 4 min). Antibiotics were given in accordance with the guidelines provided by the Dutch Working Party on Antibiotic Policy (SWAB)[14]. The median time to intravenous antibiotics was 61 min (sepsis 75, severe sepsis 54 and septic shock 45 min) from ED entrance in previous sepsis studies in our department. Supplemental oxygen was given to maintain an SaO2 between 94% and 98%. The treatment protocol did not change during the inclusion period of the study.

## STATISTICAL METHODS

Continuous data are presented as mean with SD or median with IQR depending on their distribution. Normality was tested using the Shapiro-Wilk test for normality. Categorical data are presented as absolute numbers with percentages. The Wilcoxon-related samples signed rank test was used for comparison of biomarker levels and vital signs between $T_0$ and $T_1$. Effect sizes are presented as Cohen's d[15]. The variance between the sepsis severity groups and effect of medication or comorbidities on the response to treatment was tested using the non-parametric Jonckheere-Terpstra test. Missing data were excluded for analysis. All statistical analyses were performed using IBM SPSS Statistics for Windows V.22.0 (IBM Corp, Armonk, New York, USA). A p value of $<0.05$ was considered significant; all tests were two tailed.

## RESULTS

In total, 101 patients were included. Two patients were excluded since informed consent could not be obtained from one patient before $T_1$ and was withdrawn by another patient. The remaining 99 patients were included in the final analysis. Of these patients, 63 presented with sepsis, 30 with severe sepsis and 6 with septic shock at ED admission. Patient characteristics, including comorbidities and medication use prior to ED presentation, are shown in Table 2. Patients with severe sepsis more frequently had a history of mild liver disease (p=0.02). Patients with sepsis used diuretics more often (p=0.02). The presumed focus of infection, vital signs and treatment parameters are shown in Table 3. The most frequent foci were pulmonic and urogenital. The frequency of these foci did not differ between severity groups. Patients in the septic shock group received more intravenous fluids (3.5 L; IQR 2.9–5.0 L) compared with those with severe sepsis and those with sepsis (p=0.009).

**TABLE 2. Patient characteristics, comorbidity, medication at presentation in the emergency department**

| | N | Overall | Sepsis | Severe sepsis | Septic Shock | P |
|---|---|---|---|---|---|---|
| Number of patients | 99 | 99 (100.0%) | 63 (63.6%) | 30 (30.3%) | 6 (6.1%) | - |
| Demographics | | | | | | |
| Age [median (IQR)] | 99 | 59 (47-70) | 60 (49-70) | 56 (44.5-73.3) | 56.5 (47-68.8) | 0.50 |
| Gender [n (%)] | | | | | | |
| Male | 99 | 57 (57.6%) | 29 (46.0%) | 23 (76.7%) | 5 (83.3%) | 1.00 |
| Female | 99 | 42 (42.4%) | 34 (54.0%) | 7 (23.3%) | 1 (16.7%) | 1.00 |
| Comorbidity [n (%)] | | | | | | |
| Myocardial infarction | 99 | 13 (13.1%) | 11 (17.5%) | 2 (6.7%) | 0 (0%) | 0.08 |
| Congestive heart failure | 99 | 6 (6.1%) | 5 (7.9%) | 1 (3.3%) | 0 (0%) | 0.29 |
| Peripheral vascular disease | 99 | 6 (6.1%) | 4 (6.3%) | 2 (6.7%) | 0 (0%) | 0.80 |
| Cerebrovascular disease | 98 | 12 (12.1%) | 9 (14.3%) | 2 (6.7%) | 1 (16.7%) | 0.44 |
| Dementia | 99 | 3 (3.0%) | 2 (3.2%) | 1 (3.3%) | 0 (0%) | 0.86 |
| Chronic pulmonary disease | 99 | 23 (23.2%) | 17 (27.0%) | 14 (13.3%) | 2 (33.3%) | 0.33 |
| Connective tissue disease | 99 | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 1.00 |
| Ulcer disease | 99 | 2 (2.0%) | 1 (1.6%) | 1 (3.3%) | 0 (0%) | 0.76 |
| Mild liver disease | 99 | 11 (11.1%) | 3 (4.8%) | 8 (26.7%) | 0 (0%) | 0.02* |
| Diabetes | 99 | 16 (16.2%) | 12 (19.0%) | 4 (13.3%) | 0 (0%) | 0.25 |
| Hemiplegia | 99 | 2 (2.0%) | 1 (1.6%) | 1 (3.3%) | 0 (0%) | 0.76 |
| Moderate or severe renal disease | 99 | 23 (23.2%) | 11 (17.5%) | 10 (33.3%) | 2 (33.3% | 0.08 |
| Diabetes with end-organ damage | 99 | 3 (3.0%) | 2 (3.2%) | 1 (3.3%) | 0 (0%) | 0.86 |
| Any tumor | 99 | 30 (30.3%) | 20 (31.7%) | 9 (30.0%) | 1 (16.7%) | 0.60 |
| Leukemia | 99 | 5 (5.1%) | 3 (4.8%) | 2 (6.7%) | 1 (16.7%) | 0.92 |
| Lymphoma | 99 | 7 (7.1%) | 6 (9.5%) | 1 (3.3%) | 0 (0%) | 0.20 |
| Moderate or severe liver disease | 99 | 4 (4.0%) | 1 (1.6%) | 3 (10.0%) | 0 (0%) | 0.16 |
| Metastatic solid tumor | 99 | 8 (8.1%) | 6 (9.5%) | 2 (6.7%) | 0 (0%) | 0.44 |
| AIDS | 99 | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 1.00 |
| Charlson index [median (IQR)] | 99 | 2 (1-4) | 2 (1-4) | 2 (2-4) | 1 (1-2) | 0.80 |
| Medication at emergency department presentation [n (%)] | | | | | | |
| RAS inhibitor | 99 | 25 (25.3%) | 16 (25.4%) | 5 (16.7%) | 4 (66.7%) | 0.70 |
| β-blocker | 99 | 34 (34.3%) | 21 (33.3%) | 10 (33.3%) | 3 (50.0%) | 0.69 |
| Calcium-channel blocker | 99 | 15 (15.2%) | 12 (19.0%) | 2 (6.7%) | 1 (16.7%) | 0.19 |
| Antibiotic | 99 | 30 (30.3%) | 19 (30.2%) | 10 (33.3%) | 1 (16.7%) | 0.93 |
| Immunosuppressive medication | 99 | 33 (33.3%) | 19 (30.2%) | 13 (43.3%) | 1 (16.7%) | 0.51 |
| Diuretic | 99 | 24 (24.2%) | 20 (31.7%) | 4 (13.3%) | 0 (0%) | 0.02* |
| Non-steroid anti-inflammatory drug | 99 | 32 (32.3%) | 23 (36.5%) | 9 (30.0%) | 0 (0%) | 0.16 |
| Paracetamol | 99 | 18 (18.2%) | 11 (17.5%) | 7 (23.3%) | 0 (0%) | 0.99 |
| Anti-diabetic medication | 99 | 17 (17.2%) | 13 (20.6%) | 4 (13.3%) | 0 (0%) | 0.19 |

RAS, renin angiotensin system.
*Significant result.

## VITAL SIGNS

Blood pressure at $T_0$ and $T_1$ was inversely related to sepsis severity as blood pressure decreased with increasing severity of sepsis. The results of all vital sign measurements are shown in Table 3 and Table 4. Table 2 shows the vital signs for $T_0$ and $T_1$ separated by the sepsis severity groups. Table 4 includes the δ's between $T_0$ and $T_1$ for each vital sign; these are also graphically represented in Figure 1. We found significant differences for all measured vital signs. As becomes apparent from Figure 1, all vital signs decreased during the measurement time frame, except for peripheral oxygen saturation which increased by 1.1%. The heart rate and respiratory rate dropped by >10% during resuscitation ($p<0.001$). At the same time, the systolic blood pressure decreased by 5% and diastolic blood pressure decreased by >9% ($p<0.001$).

## BIOMARKERS

The results for the biomarker levels are shown in Table 4, including δ's between $T_0$ and $T_1$ for each biomarker. These δ's are also shown in Figure 2. Almost all routine biomarkers levels decreased during resuscitation in the ED, except for C reactive protein (CRP), bands, potassium and direct bilirubin which remained stable. Levels of sodium and chloride increased slightly by 0.8% and 2.1% ($p<0.001$), respectively. The levels of NT pro-BNP increased by 3.0% ($p=0.039$) during resuscitation. Cortisol and D-dimer levels decreased by 20.1% ($p<0.001$) and 3.7% ($p=0.039$), respectively. The high-sensitivity troponin T (hs-Trop T) levels did not show a significant trend.

Biomarker levels were below the laboratory's lower detection limit in several instances. In these instances, their value was set to half the lower detection limit. Direct bilirubin levels were below the detection limit (1.0 μmol/L) in five cases at $T_0$ and three cases at $T_1$, D-dimer levels (detection limit: 150 ng/mL) in five cases at $T_0$ and seven cases at $T_1$, hs-Trop T levels (detection limit: 3.0 ng/L) in three cases at $T_0$ and five cases at $T_1$. During the calculation of the δ's, the $T_0$ values of the biomarkers were zero in a few cases. To avoid division by zero problems during the calculation of the percentual difference, these values were handled as missing data. Band levels were zero in five instances at $T_0$ and in one instance the thrombocyte level was zero at $T_0$, these six instances have been excluded from analysis.

## MEDICATION AND COMORBIDITY

To explore confounding factors that might have affected the response to treatment, we analyzed associations between medication use at ED presentation, comorbidity and the measured vital signs and biomarker levels. The use of anti-hypertensive medication did not have a significant effect on the changes in vital signs, although trends in NT pro-BNP levels showed higher ascending trends in patients using renin angiotensin system (RAS) inhibitors (median 8.7%, IQR 3.1–37.2%) compared with patients who did not use RAS inhibitors (median 0.2%; IQR –10.5% to 14.1%; $p=0.024$). NT pro-BNP levels also showed higher ascending trends in patients with congestive heart disease (median 23.1%, IQR 5.2–37.1%) compared with patients without (median 1.0%, IQR –10.2% to 13.0%; $p=0.006$). Patients using diuretics also had higher ascending trends in NT pro-BNP levels (median 14.8%, IQR 1.7–41.2%) compared with patients without diuretics (median 0.2%, IQR –11.3% to 10.9%; $p=0.004$). However, patients using diuretics (median 1.0 L, IQR 0.5–1.0 L) received less fluid

**TABLE 3. Presumed focus, vital signs and treatment parameters in the emergency department**

| | N | Overall | Sepsis | Severe sepsis | Septic Shock | P |
|---|---|---|---|---|---|---|
| Number of patients | 99 | 99 (100.0%) | 63 (63.6%) | 30 (30.3%) | 6 (6.1%) | - |
| Presumed focus [n (%)] | | | | | | |
| Respiratory | 99 | 49 (49.5%) | 31 (49.2%) | 13 (43.3%) | 5 (83.3%) | 0.71 |
| Urogenital | 99 | 31 (31.3%) | 21 (33.3%) | 8 (26.7%) | 2 (33.3%) | 0.61 |
| Skin/soft-tissue/wound | 99 | 6 (6.1%) | 4 (6.3%) | 2 (6.7%) | 0 (0.0%) | 0.80 |
| Intra-abdominal | 99 | 21 (21.2%) | 13 (20.6%) | 6 (20.0%) | 2 (33.3%) | 0.76 |
| Catheter/tube/implant | 99 | 3 (3.0%) | 2 (3.2%) | 1 (3.3%) | 0 (0.0%) | 0.86 |
| Meningitis | 99 | 1 (1.0%) | 1 (1.6%) | 0 (0.0%) | 0 (0.0%) | 0.46 |
| Other or unknown focus | 99 | 15 (15.2%) | 10 (15.9%) | 4 (13.3%) | 1 (16.7%) | 0.82 |
| Vital signs [median (IQR)] | | | | | | |
| $T_0$: Heart rate (bpm) | 99 | 110 (100-120) | 110 (100-120) | 112.5 (104.5-120.8) | 113.5 (93.5-136.8) | 0.66 |
| $T_1$: Heart rate (bpm) | 93 | 98 (90-108.5) | 98 (89-110) | 100 (94.3-105) | 100 (88.8-138) | 0.71 |
| $T_0$: Syst. blood pressure (mm Hg) [mean ± SD] | 99 | 124.1 ± 21.87 | 128.9 ± 18.96 | 123.3 ± 17.63 | 78.2 ± 17.00 | 0.002* |
| $T_1$: Syst. blood pressure (mm Hg) [mean ± SD] | 91 | 115.4 ± 19.09 | 119.7 ± 17.84 | 112.3 ± 17.41 | 89.8 ± 17.66 | 0.002* |
| $T_0$: Diast. blood pressure (mm Hg) [mean ± SD] | 99 | 71.5 ± 15.58 | 73.4 ± 14.48 | 71.7 ± 15.63 | 50.2 ± 12.22 | 0.03* |
| $T_1$: Diast. blood pressure (mm Hg) [mean ± SD] | 91 | 64.6 ± 13.32 | 65.3 ± 12.50 | 64.9 ± 15.46 | 55.5 ± 7.01 | 0.27 |
| $T_0$: MAP (mm Hg) [mean ± SD] | 99 | 89.2 ± 15.98 | 91.9 ± 14.01 | 89.4 ± 14.71 | 59.67 ± 13.32 | 0.02* |
| $T_1$: MAP (mm Hg) [mean ± SD] | 91 | 81.5 ± 14.12 | 83.5 ± 13.05 | 80.3 ± 15.38 | 67.2 ± 10.23 | 0.02* |
| $T_0$: Respiration rate (rpm) | 93 | 23 (18-28) | 23 (18-27.3) | 23 (18-27.5) | 29 (21-34.8) | 0.31 |
| $T_1$: Respiration rate (rpm) | 86 | 20 (17.8-24) | 20 (18-27) | 20 (18.8-24) | 24 (14.3-34.3) | 0.27 |
| $T_0$: Oxygen saturation (%) | 98 | 96 (93-98) | 95 (93-98) | 96 (92.8-98) | 94 (86.5-98) | 0.88 |
| $T_1$: Oxygen saturation (%) | 89 | 97 (95-98.5) | 97 (96-98) | 97 (95.3-99) | 96 (93.5-97.3) | 0.72 |
| $T_0$: Temperature (°C) | 99 | 38.4 (37.5-38.9) | 38.4 (37.7-38.9) | 38.6 (37.8-39.0) | 36.9 (34.5-38.8) | 0.58 |
| $T_1$: Temperature (°C) | 91 | 37.7 (36.8-38.6) | 37.7 (37.1-38.5) | 37.7 (36.6-38. 8) | 36.6 (36.6-39.2) | 0.60 |
| Treatment parameters [median (IQR)] | | | | | | |
| Intravenous fluids (L) | 98 | 1.0 (0.5-2.0) | 1.0 (0.5-1.5) | 1.0 (0.9-2.0) | 3.5 (2.9-5.0) | 0.009* |
| $T_0$: Supplemental oxygen (L) | 99 | 0.0 (0.0-2.0) | 0.0(0.0-2.0) | 0.0(0.0-2.0) | 2.0(0.0-15.0) | 0.74 |
| $T_1$: Supplemental oxygen (L) | 87 | 2.0 (0.0-3.0) | 2.0(0.0-3.0) | 0.0(0.0-2.5) | 13.5(1.5-15.0) | 0.25 |

bpm, beats per minute; MAP, mean arterial pressure; rpm, respirations per minute; syst, systolic; diast, diastolic
*, significant result

resuscitation (median 1.5 L, IQR 1.0–2.1 L; p=0.004). The change in body temperature was not affected by the anti-pyretic effect of NSAIDs. However, in patients using paracetamol, an ascending trend in body temperature (median 0.8%, IQR −1.8% to 1.8%) was observed, while patients without paracetamol showed a descending trend in body temperature (median −1.4%, IQR −2.8% to 0.3%; p=0.021).

The use of antibiotics prior to ED presentation did not affect the response to treatment of the infection parameters (leukocytes, CRP); neither was the leucocyte response associated with the use of immunosuppressive medication. However, users of immunosuppressive medication (median 3.7%, IQR −4.8% to 43.0%) showed a tendency of ascending CRP levels (median −1.4%, IQR −40.1% to −5.8%; p=0.017). An effect of immunosuppressive or other medication on cortisol levels was not found.

Patients with congestive heart failure showed less decrease in heart rate (median 1.4%, IQR −3.8% to 7.8%; vs median −10.3%, IQR −16.5% to −4.2%; p=0.006) and had an increasing requirement for supplemental oxygen (median 2.0 L, IQR 2.0–3.0 L; vs median 0.0 L, IQR 0.0–2.0 L; p=0.011). We did not find an association between chronic obstructive pulmonary disease (COPD) and the response in oxygen saturation or need for supplemental oxygen. Patients with metastasized tumors tended to have increasing D-dimer levels (median 4.4%, IQR −1.7% to 19.4%; vs median −4.7%, IQR −16.2% to 3.0%; p=0.023).

**TABLE 4. The δ in vital signs and biomarker levels between $T_0$ and $T_1$**

| | N | $T_0$ | N | $T_1$ | δ ($T_1$-$T_0$) | P | d |
|---|---|---|---|---|---|---|---|
| Vital signs [median (IQR)] | | | | | | | |
| Heart rate (bpm) | 99 | 110 (100-120) | 93 | 98 (90-108.5) | -10 (-17.5;-4.0) | <0.001* | -0.75 |
| Syst. blood pressure (mm Hg) [mean ± SD] | 99 | 124.1 ± 21.87 | 91 | 115.4 ± 19.09 | -7.5 ± 19.02 | <0.001* | -0.38 |
| Diast. blood pressure (mm Hg) [mean ± SD] | 99 | 71.5 ± 15.58 | 91 | 64.6 ± 13.32 | -6.4 ± 13.37 | <0.001* | -0.44 |
| MAP (mm Hg) [mean ± SD] | 99 | 89.2 ± 15.98 | 91 | 81.5 ± 14.12 | 7.0 ± 13.86 | <0.001* | -0.46 |
| Respiration rate (rpm) | 93 | 23 (18-28) | 86 | 20 (17.8-24) | -2 (-6;-2) | 0.003* | -0.32 |
| Oxygen saturation (%) | 98 | 96 (93-98) | 89 | 97 (95-98.5) | 1.0 (-1.0;5.0) | 0.001* | -0.35 |
| Supplemental oxygen (L) | 99 | 0.0 (0.0-2.0) | 87 | 0.0 (0.0-3.0) | 0.0 (0.0;2.0) | <0.001* | -0.40 |
| Temperature (°C) | 99 | 38.4 (37.5-38.9) | 91 | 37.7 (36.8-38.6) | -0.4(-1.0;0.3) | <0.001* | -0.41 |
| Routine biomarkers [median (IQR)] | | | | | | | |
| Albumin (g/L) | 93 | 37 (35-40.5) | 98 | 34 (31.8-37) | -3.0 (-5.0;-1.0) | <0.001* | -0.78 |
| ALP (U/L) | 97 | 83 (55-136) | 98 | 71.5 (48.8-115.5) | -9.0 (-14.8;-3.0) | <0.001* | -0.77 |
| AST (U/L) | 98 | 26 (20-38.3) | 98 | 24 (18-36.3) | -2.0 (-4.5;-0.0) | <0.001* | -0.56 |
| Bands (%) | 82 | 0.0 (0.0-2.3) | 97 | 0.0 (0.0-3.5) | 0.0 (0.0;0.0) | 0.72 | -0.04 |
| Bilirubin, direct (μmol/L) | 97 | 4 (3-8) | 98 | 4 (3-9) | 0.0 (-1.0;1.0) | 0.36 | -0.09 |
| Bilirubin, total (μmol/L) | 97 | 12 (8-18) | 98 | 11 (8-16) | -1.0 (-2.0;0.0) | <0.001* | -0.41 |
| Calcium (mmol/L) | 92 | 2.23 (2.14-2.30) | 98 | 2.09 (1.98-2.20) | -0.1 (-0.2;-0.08) | <0.001* | -0.78 |
| Chloride (mmol/L) | 92 | 100 (96-102) | 98 | 102 (99-106) | 2.0 (1.0;4.0) | <0.001* | -0.78 |
| Creatinine (μmol/L) | 99 | 85 (64-123) | 98 | 83.5 (63.5-128.3) | -1.5 (-8.0;4.0) | 0.02* | -0.24 |
| CRP (mg/L) | 99 | 93 (36-201) | 98 | 99.5 (45.8-184.3) | 0.0 (-12.3;8.5) | 0.45 | -0.08 |
| γ-glutamyl transferase (U/L) | 96 | 46 (26.5-106.5) | 98 | 39.5 (24.8-92.8) | -4.0 (-12.0;-1.0) | <0.001* | -0.70 |
| Glucose (mmol/L) | 99 | 7.1 (6.1-8.6) | 97 | 6.7 (5.9-7.7) | -0.5 (-1.2;0.3) | 0.001* | -0.34 |
| Hemoglobin (mmol/L) | 99 | 7.9 (6.9-8.7) | 99 | 7.3 (6.5-8.2) | -0.6 (-0.8;-0.2) | <0.001* | -0.79 |
| Lactate (mmol/L) | 86 | 1.6 (1.08-2.1) | 96 | 1.2 (0.9-1.7) | -0.2 (-0.8;0.1) | <0.001* | -0.39 |
| LDH (U/L) | 98 | 212 (163-257.5) | 98 | 177 (142.5-232.8) | -21.0 (-41.0;-8.0) | <0.001* | -0.69 |
| Leukocytes (10E9/L) | 99 | 12.1 (8.4-20.4) | 99 | 11.9 (7.9-17.0) | -0.6 (-1.6;0.4) | 0.005* | -0.28 |
| Potassium (mmol/L) | 98 | 3.9 (3.5-4.3) | 97 | 3.8 (3.5-4.3) | 0.0 (-0.3;0.2) | 0.28 | -0.11 |
| Sodium (mmol/L) | 98 | 137 (133-139) | 98 | 138 (134-140.3) | 1.0 (0.0;3.0) | <0.001* | -0.59 |
| Thrombocytes (10E9/L) | 99 | 208 (163-284) | 99 | 188 (143-259) | -15.0 (-29.0;-3.0) | <0.001* | -0.63 |
| Urea (mmol/L) | 99 | 7.2 (4.8-12.2) | 98 | 6.8 (4.1-12.1) | -0.4 (-0.8;-0.1) | <0.001* | -0.64 |
| Study specific additional biomarkers [median (IQR)] | | | | | | | |
| Cortisol (nmol/L) | 91 | 860 (505-1245) | 90 | 765 (366.3-1150) | -127.5 (-352.5;-20.0) | <0.001* | -0.43 |
| D-dimer (ng/ml) | 92 | 735 (354-2274) | 90 | 779 (357-2403) | -44 (-171;23) | 0.003* | -0.32 |
| hs-Trop T (ng/L) | 92 | 20 (8.3-39) | 92 | 23 (8.3-40.8) | -0.5 (-3.0;3.0) | 0.68 | -0.04 |
| NT pro-BNP (ng/L) | 93 | 409 (143-2036) | 91 | 483 (155-2788) | 10.0 (-21.0;169.0) | 0.04* | -0.22 |

ALP, alkaline phosphatase; AST, aspartate transaminase; CRP, C reactive protein; hs-Trop T, high-sensitivity troponin T; LDH, lactate dehydrogenase; MAP, mean arterial pressure; NT pro-BNP, N-terminal prohormone of brain natruretic peptide.
*Significant result.

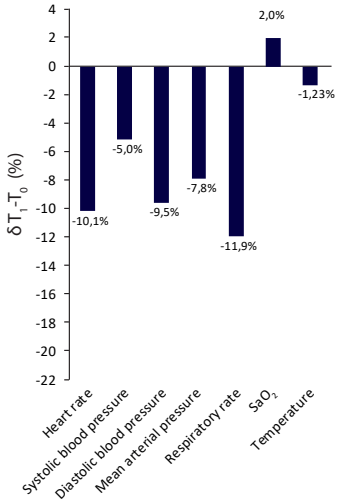


**FIGURE 1. The δ in vital signs between $T_0$ and $T_1$.** $SaO_2$, peripheral oxygen saturation.

## DISCUSSION

We performed a pilot study aimed at detecting trends in vital signs and biomarker levels during the early resuscitation of patients with sepsis in the ED. To the best of our knowledge, no other studies have analyzed trends in vital signs and routine biomarker levels during resuscitation in the ED. Nowak *et al* recently reported the registration of vital sign data in the first 4 h in the ED, but these data were neither analyzed nor reported[16].

We found a generally descending trend in most of the vital signs and biomarker levels during the patient's resuscitation in the ED. We specifically noticed descending trends in blood

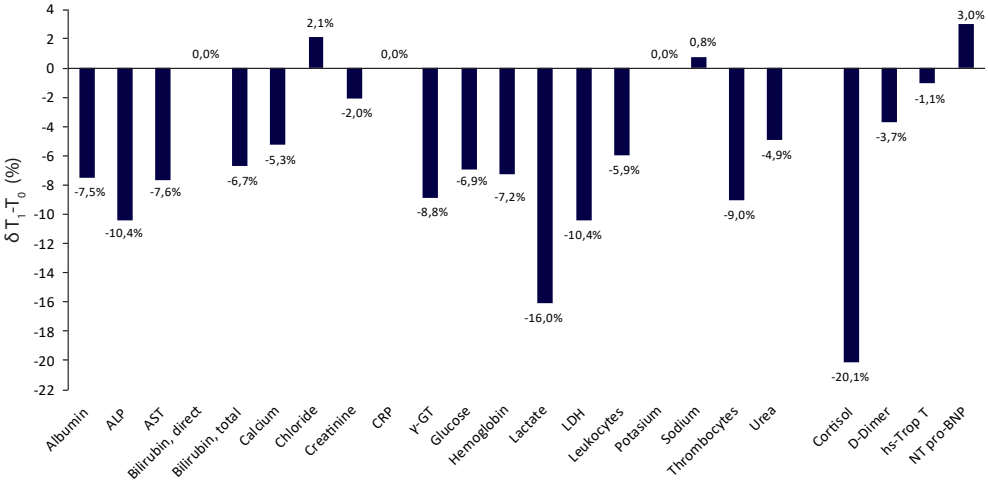


**FIGURE 2. The δ in biomarker levels between $T_0$ and $T_1$.** γ-GT, γ-glutamyl transferase; ALP, alkaline phosphatase; AST, aspartate transaminase; CRP, C reactive protein; hs-Trop T, high-sensitivity troponin T; LDH, lactate dehydrogenase; NT pro-BNP, N-terminal prohormone of brain natruretic peptide.

pressure, despite volume therapy. We observed this trend also in other (yet unpublished) studies in our ED. Paradoxically, the patients seem to improve despite this descending trend. This is supported by the relatively low in-hospital and 28-day mortality in our study of 5.1% and 3.0%, respectively. (Two patients died after >28 days in the hospital.) We can only speculate on the mechanism behind this seemingly paradoxical trend in blood pressure. During further analysis, we found that the use of anti-hypertensive or diuretic medication prior to ED admittance, as well as a history of congestive heart failure or myocardial infarction, did not explain the decrease in blood pressure. While patients with congestive heart failure did show less decrease in heart rate, the use of β-blockers did not affect the change in heart rate. The use of paracetamol prior to ED presentation led to an increasing trend in body temperature, perhaps while the anti-pyretic effect of paracetamol has worn off during the patient's stay in the ED. The descending trend in cortisol levels could not be explained by comorbidities or medication use prior to ED presentation; therefore, it is likely that it is partly influenced by its circadian rhythm and partly by the reduction of bodily stress as a response to treatment.

We found only a few ascending trends; we speculate that these ascending trends might be a direct result of the treatment modalities. The only vital sign that showed an ascending trend was the peripheral oxygen saturation, which is most likely caused by supplementation of oxygen, reflected by higher amounts of supplemental oxygen at $T_1$. Patients with a history of congestive heart failure showed an increasing oxygen need, while a history of COPD did not explain the additional oxygen requirement. The biomarkers that showed an ascending trend were sodium, chloride and NT pro-BNP. The increase in sodium and chloride levels can easily be explained by the patients receiving intravenous saline solution (NaCl 0.9%). This might also explain the increase in NT pro-BNP caused by the increased ventricular volume expansion of the heart. On the other hand, there might also be a direct association between NT pro-BNP and the systemic inflammatory response[17]. Furthermore, we found ascending trends in NT pro-BNP levels in patients using RAS inhibitors or diuretics, although patients using diuretics received less fluid resuscitation, which might suggest that they had earlier volume expansion of the heart.

## LIMITATIONS

The main limitation of our pilot study is that it was not designed to detect the cause of the trends, trends might or might not have evolved as a result of the treatment provided. Detected trends could be influenced by several factors such as comorbidity, medication use prior to ED presentation, treatment parameters, dilution effects (by intravenous fluids), variation in laboratory analyses or circadian rhythms. We performed post hoc tests to explore influences of comorbidities and medication use prior to ED presentation in our pilot population, as described above. Dilution might play a role, but we would expect a more even distribution over the different biomarkers when the effects were mainly caused by dilution. Of the measured biomarkers, only cortisol has a well-known circadian rhythm. The variance in laboratory analyses is unlikely to entirely explain the trends, as reflected by the average coefficient of variance during the study's inclusion period shown in Table 1. All factors aforementioned need to be taken into account in further research. Once the clinical value of the trends has been analyzed, they can potentially serve as a guide for treatment or to measure disease activity.

## RECOMMENDATIONS

In our pilot study design, we chose an arbitrary interval for the vital sign measurements and repeated blood draw of 3 h. Although trends became apparent during this time frame, the interval might not be the optimal one. We recommend that follow-up studies should determine the optimal interval, with either shorter or longer intervals between repeated measurements. We are currently running a follow-up study in patients with sepsis to detect trends in vital signs measured in 5-min intervals during their stay in our ED. In this follow-up study, we explore the course of vital sign changes in more detail. Furthermore, we are in the process of designing a new study, using the results of this pilot study, in which we will continuously record the patient's vital signs beat-to-beat during the first 48 h in the hospital. The latter study should provide valuable insight into the trends and variability of vital signs in patients with sepsis and potentially provide an early warning of patient deterioration[12]. Vital signs could also potentially be used to titrate the amount of fluid resuscitation and supplemental oxygen.

The routine biomarkers measured in this pilot study did, in general, only show relatively minor changes during the measurement interval. This makes them less suitable as a response to treatment parameter. The measured study-specific biomarkers, except hs-Trop T, showed larger changes during the measurement interval. We recommend further research to explore their specific responses to treatment. We expect that NT pro-BNP could be a parameter to measure response to fluid resuscitation and might in the future be used to titrate the amount of fluids given. Furthermore, cortisol could be a parameter to measure the body's stress level in response to treatment. The levels of D-dimer could provide information about the status of the coagulation system and disease activity, especially in patients with metastasized tumors.

On the basis of our results, we recommend further exploration of the use of vital signs as a response to treatment parameter in sepsis. They relatively show the largest changes within the measurement interval and are furthermore easily, cheaply and non-invasively measurable.

We expect that trends with a decrease in heart rate, respiratory rate and temperature, as well as an increase in oxygen saturation and blood pressure, could be valued as a positive response to treatment in patients with sepsis, although this pilot study could not (yet) confirm this assumption.

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