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Recognition of acute organ failure and associated fluid and oxygen resuscitation by emergency medical services of emergency department patients with a suspected infection

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ABSTRACT

Introduction: Recognition of acute organ failure is essential for recognition and resuscitation of sepsis by emergency medical services (EMS). We assessed how many EMS patients with suspected infection had clinical signs of acute organ failure (i.e. hypotension), received fluids and oxygen, and how many EMS patients without clinical signs of organ failure appeared to have organ failure in the emergency department (ED).
Methods: We interrogated an existing database in which consecutive ED patients hospitalized with suspected infection were prospectively collected. Outcomes were 1) number of patients *without* clinical signs of organ failure in the ambulance who developed clinical signs of organ failure or appeared to have biochemical signs of organ failure (i.e. hyperlactatemia) in the ED, and 2) number of patients who received fluids and oxygen in the ambulance.
Results: Of the 788 analyzed EMS patients, 529 (67.1%) had clinical signs of organ failure, of whom only 161 (30.4%) received fluids and 372 (70.3%) received oxygen. Clinical signs of organ failure were absent in 259 (32.9%) EMS patients, of which 165 patients (63.7%) developed organ failure in the ED.
Conclusions: In patients with suspected infection, acute organ failure is poorly recognized and treated by EMS, partly because of delayed development of organ failure.

1. Introduction

Sepsis is defined as a "life-threatening organ dysfunction caused by a dysregulated host response to infection [1], leading to substantial morbidity and mortality and health-care related costs [2]. Previous studies have shown that early detection and treatment of sepsis improve outcome [3–5]. Approximately half of the emergency department (ED) sepsis patients arrive by ambulance [6–11] suggesting that early detection and treatment could be initiated by emergency medical services (EMS), correspondent to their role in the management of acute myocardial infarction, stroke and trauma [12–14]. To achieve this, recognition of acute organ failure by EMS is crucial. However, previous studies, using older sepsis definitions, revealed poor sepsis recognition and resuscitation by EMS [9,15–20] in Europe and the United States of America (USA).

This poor recognition and treatment of sepsis by EMS could be explained as follows: First, ~23% of patients with a suspected infection without acute organ failure progress to infection with organ failure (sepsis), often with a delay [21,22]. It is obvious that these patients cannot be recognized by EMS. Secondly, patients with only biochemical signs of acute organ failure, i.e. with hyperlactatemia or impaired renal function, cannot be recognized in the ambulance as they have no means to measure this. Finally, current American and Dutch EMS guidelines only provide recommendations for unstable patients with shock [23,24], while optimal treatment of patients with a suspected infection with and without acute organ failure have been shown to improve outcome [25], and in older patients shock (especially hypotension) is often not recognized [26,27].

If many patients with a suspected infection without acute onset sepsis-induced organ failure in the ambulance develop acute organ failure in the ED, or appear to have biochemical signs of acute organ failure (which cannot be recognized in the ambulance), it would be beneficial to initiate fluid and oxygen therapy in all patients with a suspected infection transported to the ED by EMS. EMS guidelines may then need adjustments. Although, the administration of pre-hospital antibiotics, regardless of illness severity, did not improve outcome [18],

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the initiation of fluid resuscitation by EMS might as Leisman et al. have shown that initiation of fluid resuscitation within 30 min improves outcome [4].

2. Study aim

In the present study, we therefore determined how many patients without clinical signs of acute organ failure in the ambulance developed clinical signs of acute organ failure in the ED or appeared to have biochemical signs of organ failure (i.e. hyperlactatemia) in the ED. In addition, we assessed the number of patients with a suspected infection with and without clinical signs of acute organ failure (i.e. hypotension) in the ambulance and in which of these patients fluid resuscitation and oxygen administration were initiated.

3. Methods

3.1. Study design and setting

This is an observational cohort study using an existing database in which consecutive ED patients who were hospitalized with a suspected infection and intravenous antibiotics were prospectively enrolled. The database contains 1800 ED patients included between June 2011 and January 2016 at the Leiden University Medical Center (LUMC) and has been described in detail previously [25]. The Regional Ambulance Service Hollands Midden (RAVHM) is responsible for most of the ambulance transports in the EMS district "Hollands Midden". This district covers 875 km^2 with 760.000 citizens and is accountable for ~60,000 transports per year. Moreover, in 95% of the rides the RAVHM arrive at the scene within 15 min of the dispatch call. In the Netherlands specific training is required for the EMS team, which consists of a trained EMT driver and an expert registered nurse, to ensure that EMS personnel are experienced and proficient.

The study was approved by the medical ethics committee of the LUMC.

3.2. Selection of participants

All ED patients aged 17 years or older with a suspected infection and Manchester triage category yellow, orange or red (constituting those with urgent medical needs) who received intravenous (i.v.) antibiotics and were subsequently hospitalized were included as described previously [25].

3.3. Data collection

3.3.1. Data already in existing database

As described in detail previously [25,28], the collected data consist of patients' demographic characteristics and comorbidities, laboratory values, triage categories and vital signs, initiation of oxygen and fluid therapy in the ED, treatment administered in the ED (amount of oxygen, fluids and time to antibiotics), and disposition from ED. The presence of acute-onset organ failure was determined as described by Dellinger et al. [29]. In addition, disease severity was calculated using the patient's initial Predisposition, Infection, Response and Organ failure (PIRO) score [30]. The PIRO score was used because it differentiates between the non-modifiable Predisposition and Infection (PI) aspects and the potentially reversible Response and Organ (RO) failure aspects. Furthermore, charts were reviewed to determine whether patients had a "Do Not Resuscitate (DNR)"status.

3.3.2. Newly collected data from ambulance forms

The EMS forms for all the included patients were transferred from the original EMS forms to the data collection file (SPSS) by a medical student (AA). These data consisted of vital signs, fluid and/or oxygen administration and documentation of sepsis.

3.3.3. Definition of the variables

Clinical signs of acute onset sepsis-induced organ failure were defined as follows:

- Circulatory failure: A systolic blood pressure (BP) < 90 mmHg, and/or documented signs op peripheral hypoperfusion, i.e. capillary refill time > 3 s or pale skin and sweating.
- Respiratory failure: Respiratory rate of > 20/min, and/or oxygen saturation of < 92%, and/or documented increased respiratory effort.
- Altered mental status as documented in the ambulance as Glasgow Coma Scale (GCS) < 15 and/or clear disorientation in time place or person.

Patients were considered to have clinical signs of acute onset sepsis-induced organ failure if one or more of the aforementioned signs were present. For the initiation of fluid and oxygen therapy any amount of fluid or oxygen administered in the ambulance was deemed sufficient. Furthermore, the presence of biochemical signs of acute organ failure in the ED were determined as described by Dellinger [29], i.e. sepsis induced lactate > 4 mmol/L, creatinine > 178 μmol/L, INR > 1.5 or APTT > 60 s (if no anticoagulant use), platelets < 100 10^9/L, bilirubin > 38 μmol/L.

3.4. Outcome measures

Our primary outcome was the number of patients without clinical signs of acute onset sepsis-induced organ failure in the ambulance that developed clinical signs of acute onset sepsis-induced organ failure in the ED or appeared to have biochemical signs of acute onset sepsis-induced organ failure in the ED. Our secondary outcome was the number of patients that received fluid and oxygen therapy.

3.5. Data analysis

Patient characteristics were described as follows: normally distributed data were presented as mean (SD) and skewed data as median (IQR). Categorical data were presented as number (N, % of total). Patient characteristics were compared using unpaired t-tests or Mann-Whitney U tests for continuous data and Pearson x^2 tests for categorical data, as appropriate.

For all analyses an α of 0.05 was used to assess statistically significant differences. The analyses were performed in SPSS version 23.0 (IBM, New York, USA).

3.6. Sensitivity analyses

Several sensitivity analyses were performed to investigate the impact of the incomplete and missing EMS forms on the main results. First, we performed a sensitivity analysis in which we assumed that all patients from the incomplete and missing EMS forms had clinical signs of acute organ failure and received fluid resuscitation. Secondly, we performed a sensitivity analysis in which we assumed that the diagnosis sepsis and the initiation of fluid resuscitation was documented in all patients from the incomplete and missing EMS forms.

4. Results

4.1. Patient inclusion and characteristics

Fig. 1 provides an overview of patient flow through the study. Of the 1800 ED patients, 25 had unknown means of transportation and were excluded. Of the 1775 included patients, 857 (48.3%) patients were transported to the ED by EMS of which 788 (44.4%) were included in the analyses. An overview of patient characteristics is shown in Table 1. ED patients who were transported by EMS were older, more often male

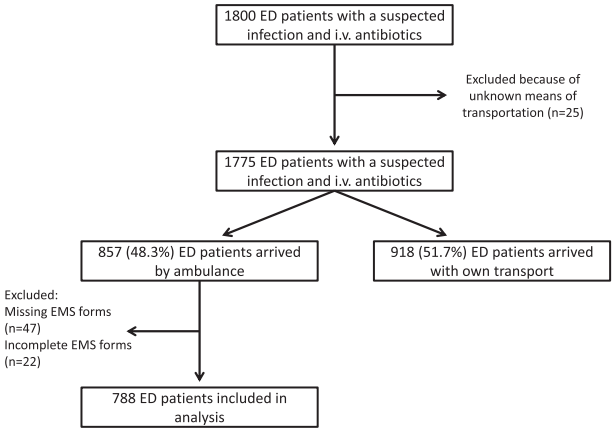

Fig. 1. Patients included in study. Abbreviation: ED: Emergency department.

and had more comorbidities.

Table 2 provides an overview of disease severity and outcomes of ED patients who arrived by ambulance versus by own transport. ED patients transported by EMS were more likely to be allocated to a higher triage category and more often had acute organ failure. The non-modifiable PI score and the modifiable RO score were also higher in patients who were transported by EMS. Similarly, patients transported by EMS had a longer hospital length of stay, higher ICU admission rates and considerably higher in-hospital mortality.

4.2. Recognition of clinical signs of organ failure by EMS and development of organ failure in the ED

In the sepsis 3.0 definition, sepsis has been defined as life threatening organ dysfunction caused by a dysregulated host response to infection [1]. Thus, to recognize sepsis, it is crucial to recognize organ failure. Therefore, we looked at clinical signs of acute organ failure as a measure for sepsis recognition in the ambulance.

Of the 788 included patients transported to the ED by EMS, 529 (67.1%) had clinical signs of acute organ failure in the ambulance. Of these, 220 (41.6%) appeared to have biochemical signs of organ failure in the ED as well. Although 259 (32.9%) patients did not have clinical signs of acute organ failure in the ambulance, 131 (50.6%) patients developed clinical signs of acute organ failure in the ED and 69 (26.6%) patients appeared to have biochemical signs of acute organ failure in the ED, as is shown in Fig. 2, with an overlap of 13.5% of patients who appeared to have both in the ED. Thus, 165 (63.7%) of the 259 ambulance patients without clinical signs of acute organ failure either had clinical or biochemical signs of organ failure in the ED.

Furthermore, the diagnosis sepsis was documented by EMS in only 179 (22.7%) patients.

4.3. Treatment by EMS

As shown in Table 2, patients transported to the ED by EMS were more severely ill and had worse outcome. Consequently, they should have received more often oxygen and/or fluid resuscitation than patients who arrived with own transport. To investigate whether this was indeed the case we looked at the documentation of the initiation of fluid and oxygen therapy by EMS.

Of the 529 patients transported to the ED by EMS with clinical signs of acute organ failure in the ambulance 220 (41.6%) also had biochemical signs of organ failure in the ED. In these 220 patients the initiation of fluid resuscitation was documented by EMS in only 88 (40%) and oxygen therapy was documented in 151 (68.6%). Of the remaining 309 (58.4%) patients without biochemical signs of organ failure in the ED, the initiation fluid resuscitation was documented by EMS in 73 (23.6%) and oxygen therapy was documented in 221 (71.5%) patients.

Of the 259 (32.9%) patients without clinical signs of organ failure 69 (26.6%) patients appeared to have biochemical signs of organ failure in the ED, in whom the initiation of fluid resuscitation was documented

Table 1
Patient characteristics of ED patients who arrived by ambulance or by own transport.

	Total Cohort	Arrived by ambulance	Own transport	P-value
Demographics				
N (%) (1775)	1775 (100)	857 (48.3)	918 (51.7)	
Age, mean (SD) (1759)	59.5 (16.8)	66.2 (14.8)	53.3 (16.1)	< 0.001
Gender (male), N (%) (1759)	1017 (57.3)	536 (62.5)	481 (52.4)	< 0.001
Comorbidities, N (%)				
COPD (1757)	228 (12.9)	152 (17.8)	76 (8.3)	< 0.001
Heart failure (1758)	274 (15.4)	198 (23.1)	76 (8.3)	< 0.001
Liver disease (1759)	100 (5.6)	31 (3.6)	69 (7.5)	< 0.001
Renal disease (1759)	352 (19.8)	141 (16.5)	211 (23)	< 0.001
Nursing home resident (1758)	95 (5.4)	86 (10)	9 (1)	< 0.001
Immunocompromised (1758)	831 (46.8)	308 (35.9)	523 (57)	< 0.001
Malignancy (no metastases) (1759)	190 (10.7)	82 (9.6)	108 (11.8)	0.135
Malignancy (with metastases) (1759)	285 (16)	113 (13.2)	172 (18.7)	< 0.001
DNR status, N (%) (1756)	308 (17.3)	215 (25.1)	93 (10.2)	< 0.001
Vital signs at ED presentation				
Systolic blood pressure, mean (SD) (1529)	131 (24.9)	130 (27)	131 (23)	0.462
Heart rate, mean (SD) (1715)	108 (21)	106 (21)	109 (20)	0.021
Respiratory rate, mean (SD) (1274)	23 (6.7)	24.2 (7.1)	21.4 (5.9)	< 0.001
Oxygen saturation (%),mean (SD) (1695)	95.6 (4.7)	95 (5)	96 (4)	< 0.001
Temperature (°C), mean (SD) (1694)	38.7 (1.1)	38.7 (1.2)	38.7 (1.0)	0.914
Laboratory analysis at ED presentation				
Lactate (mmol/L), median (IQR) (1550)	1.9 (1.5–2.7)	2 (1.6–3.1)	1.8 (1.4–2.4)	< 0.001
Platelets ($\times 10^9$/L), median (IQR) (1724)	204 (145–276)	207 (149–278)	202 (142–272)	0.269
Creatinine (μg/L), median (IQR) (1751)	87 (67–120)	89 (67–127)	86 (66–114)	0.047
Urea (mmol/L), median (IQR) (1749)	6.9 (5.1–10.2)	7.8 (5.7–11.3)	6.3 (4.7–9.1)	< 0.001
Bilirubin (μmol/L), median (IQR) (1614)	12 (8–19)	12 (8–19.8)	12 (9–18)	0.489

The number between brackets reflects the number of patients on which the analyses were performed.
Abbreviations: ED: Emergency Department. COPD: Chronic Obstructive Pulmonary Disease. IQR: Inter Quartile Range. SD: Standard Deviation. N: Number.

Table 2
Disease severity and outcomes in ED patients with a suspected infection arrived by ambulance or by own transport.

	Total Cohort	Arrived by ambulance	Own transport	P-value
N (%) (1775)	1775 (100)	857 (48.3)	918 (51.7)	
Disease severity in the ED				
Triage category (1766)				< 0.001
Yellow	759	463	296	
Orange	970	445	525	
Red	37	6	31	
Total PI score, median (IQR) (1775)	4 (2–6)	5 (3–7)	3 (2–5)	< 0.001
Total RO score, median (IQR) (1775)	4 (2–8)	6 (2–8)	2 (2–7)	< 0.001
Total PIRO score, median (IQR) (1775)	9 (4–13)	11 (7–15)	6 (4–11)	< 0.001
Acute-onset organ failure*, N (%) (1759)	475 (26.8)	313 (36.5)	162 (17.6)	< 0.001
Number of failing organs, median (IQR) (1759)	0 (0–1)	0 (0–1)	0 (0–0)	< 0.001
Outcomes				
Hospital LOS (days), median (IQR) (1775)	4 (2–8)	5 (3–10)	4 (2–8)	< 0.001
Admission to ICU and/or MCU, N (%) (1775)	171 (9.6)	133 (15.5)	38 (4.1)	< 0.001
In-hospital mortality, N (%) (1747)	105 (5.9)	71 (8.4)	34 (3.7)	< 0.001

The number between brackets reflects the number of patients on which the analyses were performed.
Abbreviations: PIRO: Predisposition, Infection Response and Organ failure [28]. ED: Emergency Department. IQR: Inter Quartile Range. LOS: Length of Stay. ICU: Intensive Care Unit. MCU: Medium Care Unit. N: Number.
* Acute-onset organ failure as defined by Dellinger [26].

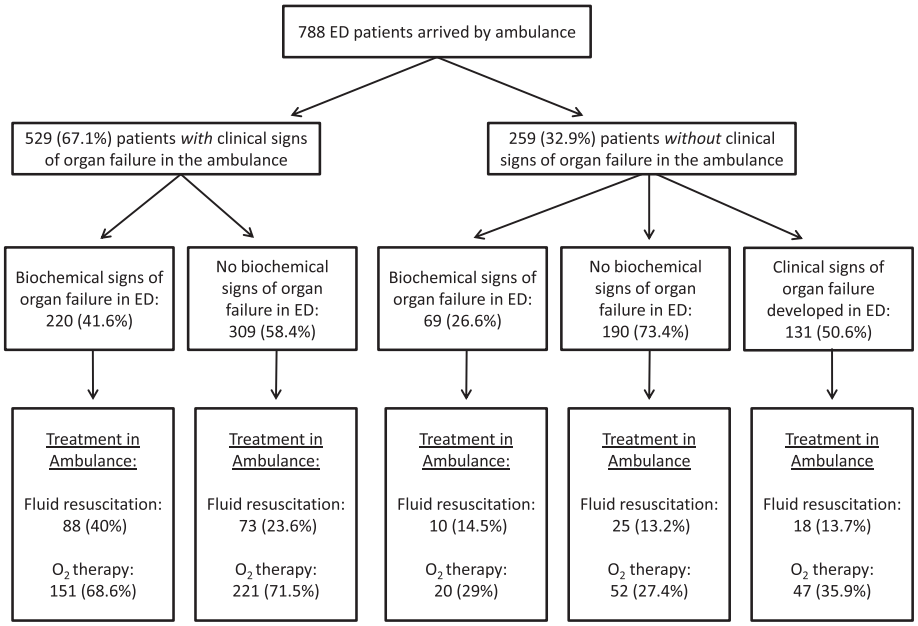

Fig. 2. Analyzed patient flow through study. Abbreviation: ED: Emergency department.

by EMS in only 10 (14.5%) and oxygen therapy was documented in 20 (29%). Of the remaining 190 (73.4%) patients without biochemical signs of organ failure in the ED, the initiation of fluid resuscitation was documented by EMS in 25 (13.2%) and oxygen therapy was documented in 52 (27.4%).

When comparing the number of patients with and without clinical signs of acute organ failure in which fluid and oxygen resuscitation were initiated, patients with clinical signs of acute organ failure in the ambulance received significantly more fluid and oxygen therapy than patients without clinical signs of organ failure ($p < 0.001$).

Table 3 provides an overview of EMS treatment for the different clinical signs of acute organ failure in the ambulance. As shown, 51 (7.2%) of the 788 patients had a systolic blood pressure (SBP) < 90 mmHg. However, the initiation of fluid resuscitation was documented by EMS in only 34 (66.7%) and oxygen therapy was documented in 31 (62%). Furthermore, the initiation of fluid resuscitation increased with decreasing SBP. Of the 396 (53.6%) patients with a respiratory rate > 20 and/or hypoxemia, the initiation of fluid resuscitation was documented by EMS in 117 (30%) and oxygen therapy was documented in 332 (84.5%). Of the 167 (23.8%) patients with a GCS < 15, the initiation of fluid resuscitation was documented in 61 (36.5%) and oxygen therapy was documented in 99 (59.6%). Furthermore, of the 179 (22.7%) patients with documented sepsis the initiation of fluid resuscitation was documented in 85 (48%) and oxygen therapy was documented in 115 (64.2%). In addition the initiation of fluid resuscitation increased with an increasing amount of clinical signs of organ failure present.

Finally, studies have suggested that arriving by EMS and initiation of treatment by EMS improve quality of care in the ED [11,31,32]. Therefore, we assessed treatment in the ED for patients with and without clinical signs of acute organ failure in the ambulance, as is shown in Table 4. Patients with clinical signs of acute organ failure in the ambulance had a shorter time to antibiotics and received a larger amount of fluids and oxygen.

Table 3
Treatment in ambulance in patients with clinical signs of acute organ failure.

	N (%)	Fluid resuscitation initiated (%)	Amount of fluids (L), median (IQR)	O_2 therapy initiated (%)	Amount of O_2 (L/min), median (IQR)
Total cohort	788 (100)	196 (25.8)	0 (0–0.25)	444 (58.2)	2 (0–6)
Clinical signs of organ failure in the ambulance					
Respiratory rate (> 20/min) (576)	235 (40.8)	82 (35.3)	0 (0–0.5)	194 (82.6)	5 (2–10.75)
Hypoxemia (SpO_2 < 92%) (698)	289 (41.4)	82 (28.7)	0 (0–0.5)	261 (91.3)	6 (3–10.25)
Respiratory rate (> 20/min) and/or hypoxemia (SaO_2 < 92%) (739)	396 (53.6)	117 (30)	0 (0–0.5)	332 (84.5)	4 (2.25–9)
Hypotension (systolic RR mmHg) (704)					
< 80	25 (3.6)	17 (68)	0,5 (0–0.5)	15 (60)	3 (0–6)
< 90	51 (7.2)	34 (66.7)	0,5 (0–0.5)	31 (62)	4 (0–6)
< 100	96 (13.6)	53 (57)	0,5 (0–0.5)	59 (63.4)	3 (0–6)
< 110	176 (25)	79 (45.7)	0 (0–0.5)	109 (63)	3 (0–6)
< 120	273 (38.8)	105 (39)	0 (0–0.5)	161 (59.9)	3 (0–6)
< 130	369 (52.4)	125 (34.5)	0 (0–0.5)	217 (59.9)	3 (0–6)
< 140	467 (66.3)	146 (32.2)	0 (0–0.5)	276 (60.7)	3 (0–6)
Heart rate (> 100/min) (740)	477 (64.5)	131 (28.2)	0 (0–0.5)	303 (64.7)	3 (0–6)
GCS < 15 (702)	167 (23.8)	61 (36.5)	0 (0–0.5)	99 (59.6)	3 (0–6)
Total clinical signs of organ failure in the ambulance					
Circulatory failure (737)	235 (31.9)	96 (41.2)	0 (0–0.5)	167 (71.4)	4 (0–10)
Respiratory failure (756)	397 (52.5)	117 (29.9)	0 (0–0.5)	332 (84.3)	4 (2–9)
Altered mental status (702)	167 (23.8)	61 (36.5)	0 (0–0.5)	99 (59.6)	3 (0–6)
Number of clinical signs of organ failure present					
1	309 (39.2)	74 (24.3)	0 (0–0.1)	191 (62.4)	3 (0–5)
2	170 (21.6)	61 (36.3)	0 (0–0.5)	136 (80.5)	4 (2–10.5)
All	50 (6.3)	26 (52)	0.4 (0–0.5)	45 (90)	6 (4–15)
Clinical signs of organ failure present (788)	529 (67.1)	161 (30.8)	0 (0–0.5)	372 (70.9)	4 (0–6)
Sepsis documented on EMS form (788)	179 (22.7)	85 (48)	0 (0–0.5)	115 (64.2)	3 (0–6)

The number between brackets reflects the number of patients on which the analyses were performed. The numbers in the rows do not always add up because there was overlap between the patients who received fluids and oxygen.
Abbreviations: IQR: Inter Quartile Range. SpO_2:oxygen saturation. RR: blood pressure. GCS: Glasgow Coma Scale. EMS: emergency medical services.

4.4. Sensitivity analysis

The first analysis in which we assumed that all patients had clinical signs of acute organ failure and received fluid resuscitation yielded results similar to the original outcome. The percentage of patients in which clinical signs of acute organ failure were present went from 67.1% to 69.8% and the percentage of patients in which the initiation of fluid resuscitation was documented went from 30.8% to 38.5%. The second analysis in which we assumed that sepsis and the initiation of fluid resuscitation were documented on all the missing and incomplete EMS forms yielded similar percentages as well. The percentage of patients in which sepsis was document went from 22.7% to 28.9% and the percentage of patients in which the initiation of fluid resuscitation was documented went from 48% to 62.1%. Therefore, the incomplete and missing EMS forms did not influence the original results.

5. Discussion

The present study has two main conclusions. First, more than half of the patients without clinical signs of acute organ failure in the ambulance develop clinical signs of acute organ failure in the ED or appear to have biochemical signs of acute organ failure in the ED. Second, we found that EMS treatment is initiated in only a minority of the patients with a suspected infection.

5.1. Recognition of organ failure in patients with suspected infection

In the present study we looked specifically at documentation of clinical signs of organ failure, necessary to recognize sepsis according to the sepsis 3.0 definition.

Approximately ~50% of the patients with a suspected infection were transported to the ED by EMS, correspondent to previous studies [6–11]. These patients were more severely ill and had a higher mortality. In addition, documentation of acute organ failure or sepsis, as a proxy for recognition, was poor [9,15–20].

A new finding in the present study is that 63.7% of the patients with a suspected infection without clinical signs of acute organ failure in the ambulance developed clinical signs of organ failure in the ED, or

Table 4
Treatment in the ED for patients with and without clinical signs of acute organ failure in the ambulance.

	Total Cohort	With clinical signs of acute organ failure	Without clinical signs of acute organ failure	P-value
Treatment in the ED	N = 788	N = 529	N = 259	
Time to antibiotics (min), median (IQR) (788)	93 (54–154)	85 (49.5–136)	111 (68–179)	< 0.001
Appropriate antibiotics given, n (%) (767)	637 (83.1)	434 (83.9)	203 (81.2)	0.356
Amount of intravenous fluids administered (L), median (IQR) (788)	1 (0.5–1.6)	1 (0.5–2)	1 (0.5–1.5)	0.018
Amount of oxygen administered (L/min), median (IQR) (758)	4 (2–15)	5 (3–15)	3 (0–5)	< 0.001

The number between brackets reflects the number of patients on which the analyses were performed.
Similar results were found for patients with and without documented sepsis in the ambulance.
Abbreviations: ED: Emergency department. IQR: Inter Quartile Range.

appeared to have biochemical signs of organ failure in the ED. Delays in the development of organ failure has been described previously in a clinical setting [21,22]. As a consequence, many patients with sepsis will therefore not be recognized by EMS which may partially explain the low number of patients in whom oxygen and fluid resuscitation was started in the ambulance.

Early initiation of fluid resuscitation, in contrast to the initiation of prehospital antibiotics, could improve outcome [4,11,18]. However, treatment by EMS was initiated in a minority of the patients, correspondent with previous studies [9,11]. It has been suggested that more education is needed for EMS personnel to improve the recognition and management of sepsis in the pre-hospital phase [6,15,16]. However, despite educational programs, sepsis recognition remained poor [15,18–20]. Therefore, a practical approach in which all patients with a suspected infection transported to the ED by EMS receive fluid and oxygen therapy in the ambulance could be beneficial and has several advantages. First, recognition of sepsis would no longer be necessary, since treatment would be initiated in all patients with a suspected infection. This is especially beneficial for older patients, in whom sepsis (especially hypotension) is often not recognized. Secondly, although education is expected to contribute to improved recognition to some degree, it may not always have the desired effect and new knowledge is not easy to implement in routine clinical practice [15,18–20], depending on the type and frequency of education. With this practical approach in which all patients with a suspected infection transported to the ED by EMS receive fluid and oxygen therapy in the ambulance, EMS would only have to learn to initiate treatment in patients with a suspected infection. Finally, in addition to patients *with* acute organ failure patients without acute organ failure would also be treated timely and adequately, which could contribute to a reduction of sepsis related mortality [25].

6. Strengths and limitations

The strengths of the present study include the large sample size and the prospectively collected patients. However, there are several limitations. First, part of the data had to be collected retrospectively increasing the probability of information bias because in 69 of the patients ambulance forms were missing or incomplete. However, in the sensitivity analyses it was shown that the main conclusion of our study did not change.

Although it is possible that sepsis was recognized but not documented by EMS, the fact that the initiation of fluid resuscitation increased with decreasing SBP and with an increasing amount of clinical signs of organ failure present suggests that there is a certain amount of recognition amongst EMS and that the very low number of patients in whom treatment was initiated in the ambulance is not just due to poor documentation, but that awareness amongst EMS that early treatment can improve outcome may be lacking.

Secondly, patients with a suspected infection who were assessed by EMS and referred to the GP to be treated at home were not included in this study.

Finally, there are various ways to define clinical signs of acute organ failure. Since the focus of our study was the EMS setting we chose vital parameters that could have been assessed in the ambulance. A SBP of 90 mmHg was chosen because this is the cutoff value used in the Dutch EMS guidelines. Moreover, current sepsis guidelines such as the qSOFA use similar cutoff values. However, we included various SBPs in table 3 to explore other cutoff values as well. The cutoff value for respiratory rate and saturation was chosen based on the definitions and scores used in our database, NEWS, MEWS and PIRO [30,33,34]. The GCS was used as a component of the qSOFA [1].

7. Conclusion

A substantial proportion of patients with a suspected infection without clinical signs of acute organ failure in the ambulance appear to have acute organ failure in the ED. In addition, in a minority of patients in the ambulance treatment was initiated, despite previous observations that early fluid resuscitation improves outcomes. This suggests that acute organ failure is difficult to recognize and that a practical approach in which all patients with a suspected infection who are transported to the ED by EMS receive fluid and oxygen therapy in the ambulance could be beneficial. Future studies are needed to investigate if early initiation of fluid and oxygen resuscitation as a standard treatment in EMS guidelines for patients with a suspected infection who are transported to the ED improve outcomes.

Conflict of interest

The authors report no conflict of interest. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethical statement

The study was approved by the medical ethics committee of the LUMC.

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