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ORIGINAL

Effect of the 1-h bundle on mortality in patients with suspected sepsis in the emergency department: a stepped wedge cluster randomized clinical trial

Yonathan Freund[1,2*], Marta Cancella de Abreu[2], Soufiane Lebal[3], Alexandra Rousseau[3], Thomas Lafon[4], Youri Yordanov[1,5], Richard Macrez[6], Fabien Coisy[7], Pierrick Le Borgne[8], Florent Femy[9], Delphine Douillet[10,11], Neus Robert Boter[12], Xavier Eyer[13], Jean-Baptiste Bouillon-Minois[14], Carl Ogereau[15], Donia Bouzid[16], Hélène Goulet[17], Mélanie Roussel[18], Geoffroy Rousseau[19], Jeremy Guénézan[20], Celine Occelli[21], Tahar Chouihed[22], Gina Osorio Quispe[23], Marine Clea Renard[24], Judith Gorlicki[25], Ben Bloom[26], Tabassome Simon[1,3] and Camille Gerlier[27]

Abstract

Purpose: The efficacy of the 1-h bundle for emergency department (ED) patients with suspected sepsis, which includes lactate measurement, blood culture, broad-spectrum antibiotics administration, administration of 30 mL/kg crystalloid fluid for hypotension or lactate ≥ 4 mmol/L, remains controversial.

Methods: We carried out a pragmatic stepped-wedge cluster-randomized trial in 23 EDs in France and Spain. Adult patients with Sepsis-3 criteria or a quick sequential organ failure assessment (SOFA) score ≥ 2 or a lactate > 2 mmol/L were eligible. The intervention was the implementation of the 1-h sepsis bundle. The primary outcome was in-hospital mortality truncated at 28 days. Secondary outcomes included volume of fluid resuscitation at 24 h, acute heart failure at 24 h, SOFA score at 72 h, intensive care unit (ICU) length of stay, number of days on mechanical ventilation or renal replacement therapy, vasopressor free days, unnecessary antibiotic administration, and mortality at 28 days. 1148 patients were planned to be analysed; the study period ended after 873 patients were included.

Results: 872 patients (mean age 66, 42% female) were analyzed: 387 (44.4%) in the intervention group and 485 (55.6%) in the control group. Median SOFA score was 3 [1–5]. Median time to antibiotic administration was 40 min in the intervention group vs 113 min in the control group (difference − 73 [95% confidence interval (CI) − 93 to − 53]). There was a significantly higher rate, volume, and shorter time to fluid resuscitation within 3 h in the intervention group. There were 47 (12.1%) in-hospital deaths in the intervention group compared to 61 (12.6%) in the control group (difference in percentage − 0.4 [95% CI − 5.1 to 4.2], adjusted relative risk (aRR) 0.81 [95% CI 0.48 to 1.39]). There were no differences between groups for other secondary endpoints.

Conclusions: Among patients with suspected sepsis in the ED, the implementation of the 1-h sepsis bundle was not associated with significant difference in in-hospital mortality. However, this study may be underpowered to report a statistically significant difference between groups.

Keywords: Sepsis, Emergency department, Shock, Fluids resuscitation

*Correspondence: yonathan.freund@aphp.fr
[2] Emergency Department, Hôpital Pitié-Salpêtrière, Assistance Publique-Hôpitaux de Paris (AP-HP), Paris, France
Full author information is available at the end of the article

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Introduction

Sepsis and septic shock, characterized by a dysregulated host response to infection leading to organ dysfunction or shock, impacts nearly 50 million people globally, contributing to approximately 11 million deaths [1].

The early identification and management of sepsis, including source control, antimicrobial therapy and fluid resuscitation are reportedly associated with reduced mortality [2–4]. The Surviving Sepsis Campaign (SSC), composed of international experts, recommends a sepsis bundle incorporating early lactate measurement, microbiological culture, antibiotherapy, and for patients with hypotension or lactate ≥ 4 mmol/L, fluid resuscitation with 30 mL/kg of crystalloid. A large retrospective study suggested that early antibiotic administration within the first hour was associated with improved outcomes, but early fluid resuscitation was not [4]. The 2018 SSC's update of the 2016 guidelines recommended initiating this bundle within 1 h of triage [5, 6]. A major concern with the 1-h bundle is its application in routine practice in the emergency department (ED) to patients with suspected sepsis and no signs of shock. Treatment is expected to be initiated within 1 h of triage, despite inherent challenges in confirming sepsis diagnosis within such a constrained timeframe. Furthermore, the criteria to start the sepsis bundle are unclear, and not clearly established, because the presence of sepsis, according to the Sepsis-3 definitions, can be difficult to ascertain rapidly. Indeed, identifying all criteria to define sepsis may not happen before a few hours after the first assessment, especially considering the time to get results of biological exams. Although the 2021 SSC guidelines recommended against using the quick sequential organ failure assessment (qSOFA) as a single-screening tool for sepsis, a qSOFA ≥ 2 may be considered as a criterion to initiate the sepsis bundle [7]. Amidst ongoing debate around, and insufficient evidence for the 1 h bundle, the 2021 SSC recommended the use of the 3-h bundle [8–10].

The 1BED trial was a multicenter trial designed to evaluate whether the 1-h bundle, compared with usual care, would lower 28-day in-hospital mortality for patients with suspected sepsis in the emergency department.

Methods

Study design and oversight

This study was a pragmatic, open, stepped-wedge cluster-randomized controlled trial that was conducted in 20 emergency departments in France and 3 in Spain. The institution review board "IDF VII, Le Kremlin Bicêtre, France" approved the study in France and "Comité de ética de la Investigación con medicamentos del Hospital Clínico, Barcelona, Spain" in Spain. The protocol and statistical analysis plan are available in the appendix. The study was funded by a grant from Programme Hospitalier de Recherche Clinique—PHRC 2020 (French Ministry of Health) and the sponsor was Assistance Publique—Hôpitaux de Paris. Patients were included between June 13th 2022 and September 13th 2023, and follow-up ended on December 15th 2023. In France, if the patient was alert and had capacity to understand trial-specific information, oral consent was sought before inclusion. If not, consent was sought from a family member or close relative. In the absence of appropriate relatives, a procedure for inclusion in emergency situation was authorized. Delayed oral informed consent was obtained as soon as the patient's clinical state allowed. In Spain, written informed consent was mandatory. The trial was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines, registered at ClinicalTrials.gov (NCT05273034) before initiation, and was overseen by an independent data and safety monitoring board. The trial protocol and statistical analysis plan are available in the supplement. Data collected on sites were monitored by clinical research personnel who were independent of the clinical team. The reporting of this trial followed the Consolidated Standards of Reporting Trials (CONSORT) statement extended to stepped-wedge cluster randomized trials [11, 12].

Take-home message

In this stepped wedge, cluster randomized trail in France and Spain, the implementation of the 1 h sepsis bundle was not associated with a significant change in in-hospital mortality. However, this trial may be underpowered to detect a clinically significant difference.

Study population

Thirty Emergency Departments with previous experience in pragmatic clinical trials or affiliated with the IMProving Emergency Care research federation (FHU IMPEC) were contacted to participate in the study. Among the 26 centers who initially agreed to participate, two withdrew participation before randomization for period switch was performed, and one after but before inclusion of patients, leaving 23 recruiting EDs (20 in France and 3 in Spain).

Patients 18 years or older who met eligibility criteria within 6 h of triage were screened for inclusion. Inclusion criteria included suspicion of infection and at least one of the following severity criteria: serum lactate > 2 mmol/L, qSOFA ≥ 2, hypotension with systolic

blood pressure < 90 mmHg or evidence of organ dysfunction with a SOFA score ≥ 2.

Patients with clinical suspicion of acute heart failure were not eligible. We also excluded patients that were living in assisted-living residential homes or palliative centers, had an estimated life expectancy of less than 3 months, patients under legal protection or prisoners, patients with no social security, and pregnant or breastfeeding patients.

Randomization and intervention

Initially, all centers began in the control phase for 4 weeks. Subsequently, after every 4-week interval (step), two centers were randomly assigned to switch to the intervention phase, i.e., implementation of the 1-h sepsis bundle. After the last center had switched to the intervention period, a final step of 16 weeks concluded the intervention phase in all centers (supplemental Fig. 1). Because of the stepped wedge design, and to avoid imbalance between group and period effect, it was not possible to extend the recruitment period beyond the last 16 weeks, where all centers were in the intervention group.

Prior to study commencement, EDs were classified according to their size based on their annual census. Randomization was stratified by cluster size (annual census higher or lower than the overall median). Each step included 1 small and 1 large site. Randomization was computer generated by an independent biostatistician from Unité de Recherche Clinique de l'Est Parisien, independent of the study and before the study started.

Before the study started, the 2021 SSC guidelines advocating the 3-h sepsis bundle were presented to the participating center to guide routine practice.

The intervention consisted of the implementation of the 1-h sepsis bundle, which includes microbiological cultures (including blood, urine, catheter, or other targeted cultures), lactate measurement (either venous or arterial) and broad-spectrum antibiotic administration, and for patients with systolic blood pressure < 90 mmHg or a lactate > 4 mmol/L rapid initiation of 30 mL/kg crystalloid intravenous fluid resuscitation [5]. The sepsis bundle should be initiated within 1 h of presentation of the inclusion criteria as per the 2018 SSC recommendation [5]. Time zero was defined as the moment when inclusion criteria (hypotension, qSOFA ≥ 2 or lactate ≥ 2 mmol/L) were first met, either at nurse triage or physician evaluation.

In the control phase, patients received care as per the treating emergency physician's routine practice.

Study outcomes

The primary outcome of the study was the rate of in-hospital mortality due to any cause truncated at 28 days. Secondary outcomes included the total volume of fluid administered at 24 h, the presence of acute heart failure at 24 h, SOFA score at 72 h, intensive care unit (ICU) length of stay at 28 days, number of days on mechanical ventilation at 28 days, number of days on renal replacement therapy at 28 days, vasopressor free days at 28 days, unnecessary antibiotic administration at 28 days, and all-cause mortality at 28 days in or out of hospital.

Acute heart failure was defined by the presence clinical signs of acute heart failure associated with either elevated brain natriuretic peptide or signs of pulmonary edema on chest imaging. Unnecessary antibiotic administration was defined as antibiotic administration on patients in whom infection was ultimately ruled out.

Statistical analysis

Sample size calculation

Assuming an anticipated 28-day in-hospital mortality of 25% in the control group, and a relative risk reduction of 38% (15.5% 28-day in-hospital mortality) in the intervention group, a power of 80% using a two-sided test at the 5% level of significance, we needed to include 560 patients [13]. The choice of the anticipated relative risk reduction represented a compromise between a clinically relevant effect and potential of recruitment in the participating centers, predicted to be 2 patients per week.

Based on the study plan of a stepped wedge cluster trial with 24 clusters, 2 clusters per sequence, an intracluster correlation coefficient (ICC) of 0.018 and design effect estimated at 2.05, 1148 patients were required for analysis [14]. To take into account a predicted proportion of 10% non-evaluable patients, 1263 patients were needed, corresponding to about 4 per clusters for each period.

The assumptions for this sample size calculation are detailed in the statistical analysis plan.

Data analysis

Cluster level and patient level were both considered for baseline patient characteristics. At center level, characteristics at the beginning of the study were described. Baseline characteristics of patients were summarized by group (intervention and control). Qualitative data are summarized as frequencies and percentages, and quantitative data are summarized as mean, standard deviation or as median, interquartile interval, according to the distribution. Hypotheses concerning the

distribution of quantitative variables were verified graphically using histograms and density curves.

The primary outcome, 28-day in-hospital mortality (truncated at 28 days from the date of inclusion) was compared between groups. The unadjusted difference in proportions between groups and its 95% confidence interval was provided (Wald method with continuity correction). For the primary outcome, the in-hospital mortality truncated at 28 days was compared between groups by taking account of adjustment factors using generalized linear regression mixed model (GLMM) with Bernoulli distribution. Intervention (control as reference), time period (period 16 as reference), and cluster size (small cluster size as reference) were considered as fixed effects, and cluster (hospital) as a random effect. Results are expressed as adjusted relative risk (RR) (log link function) and two-sided 95% confidence interval (CI).

For the secondary outcomes, the unadjusted difference in proportions between groups (intervention minus control) and its 95% CI were provided by Wald method with continuity correction for qualitative outcomes. To account for adjustment factors, a generalized linear regression mixed model (GLMM) with Bernoulli distribution (or Poisson distribution for the proportion of overall fluid resuscitation in the first 24 h) was performed. Intervention (control as reference), time period (period 16 as reference), and cluster size (small cluster size as reference) were considered as fixed effects, and cluster (hospital) as a random effect. Results are expressed as adjusted relative risk (RR) (log link function) and 2-sided 95% CI. Details on analysis of the endpoints are reported in the statistical analysis plan.

All analyses were conducted according to the intention-to-treat (ITT) analysis principle. Results are reported among the ITT population set defined as all included patients according to the period assigned by the randomization to the center, regardless of the strategy effectively received by the patient.

Sensitivity analysis

Two sensitivity analyses were performed for the primary outcome. First in the ITT set, using the same model as the main analysis, adding country (France as reference) as fixed effect. Then, performing the primary analysis on the per-protocol population set, defined as all included patient treated without major protocol violations/deviations defined as eligibility criteria not fulfilled, non-respect of the cluster randomized strategy allocation (i.e., non-respect of administration of broad-spectrum antibiotics and fluid resuscitation within the first 70 min following inclusion in the intervention group) and missing data for the primary outcome.

Post-hoc analysis

Subgroup analyses were performed to assess the effect of 1-h sepsis bundle on the primary outcome among patients with hypotension or lactate > 4 mmol/L and those without hypotension and having lactate ≤ 4 mmol/L, using the same model as the main analysis.

Statistical analyses were performed using SAS software version 9.4 (SAS Institute Inc. Cary, NC, USA) and R Studio version 4.2.1 (R: A Language and Environment for Statistical Computing, R Core Team, R Foundation for Statistical Computing, Vienna, Austria, https://www.R-project.org). All tests were two-sided, statistical significance were considered when p value < 0.05 indicated statistical significance. No adjustment was made for multiplicity. Full details of the statistical analysis plan are provided in the Supplementary Appendix.

Results

Clusters and patients

Details of the 23 participating centers are reported in the appendix (eTable 1). During the study period (between June 13th 2022 and September 13th 2023), 873 patients were included and 872 were analyzed (1 patient wrongly included was excluded shortly after screening without collection of data because he did not present with inclusion criteria), 387 (44.4%) in the intervention group and 485 (55.6%) in the control group (Fig. 1). The median number of patients included was 30 (interquartile range [IQR] 19–43) per center and 54 (IQR 36–67) per step (eFigure 1).

Data for the primary endpoint were obtained for all patients. The mean age was 66 years (standard deviation [SD] 16) and 362 (41.5%) were female. The median lactate value and SOFA score were 2.4 mmol/L (IQR 1.5–3.9) and 3 points (IQR 1–5) in the intervention group and 2.5 mmol/L (IQR 1.6–3.6) and 3 points (IQR 1–4) in the control group. Baseline characteristics are reported in Table 1 and in detail in the appendix (supplemental Table 2). A total of 49 (5.7%) patients died at 72 h and 114 (13.1%) at 28 days, which included 108 (12.4%) in-hospital deaths at 28 days.

Treatment received in the ED

Compared to the control group, there was a higher proportion of patients that received antibiotics and fluid resuscitation in the ED in the intervention group: 371 (96.1%) vs 432 (89.1%) (difference in percentage 7.0; 95% CI 3.4–10.7) and 346 (90.3%) vs 407 (84.1%) (difference in percentage 6.2; 95% CI 1.6–10.9), respectively. There was

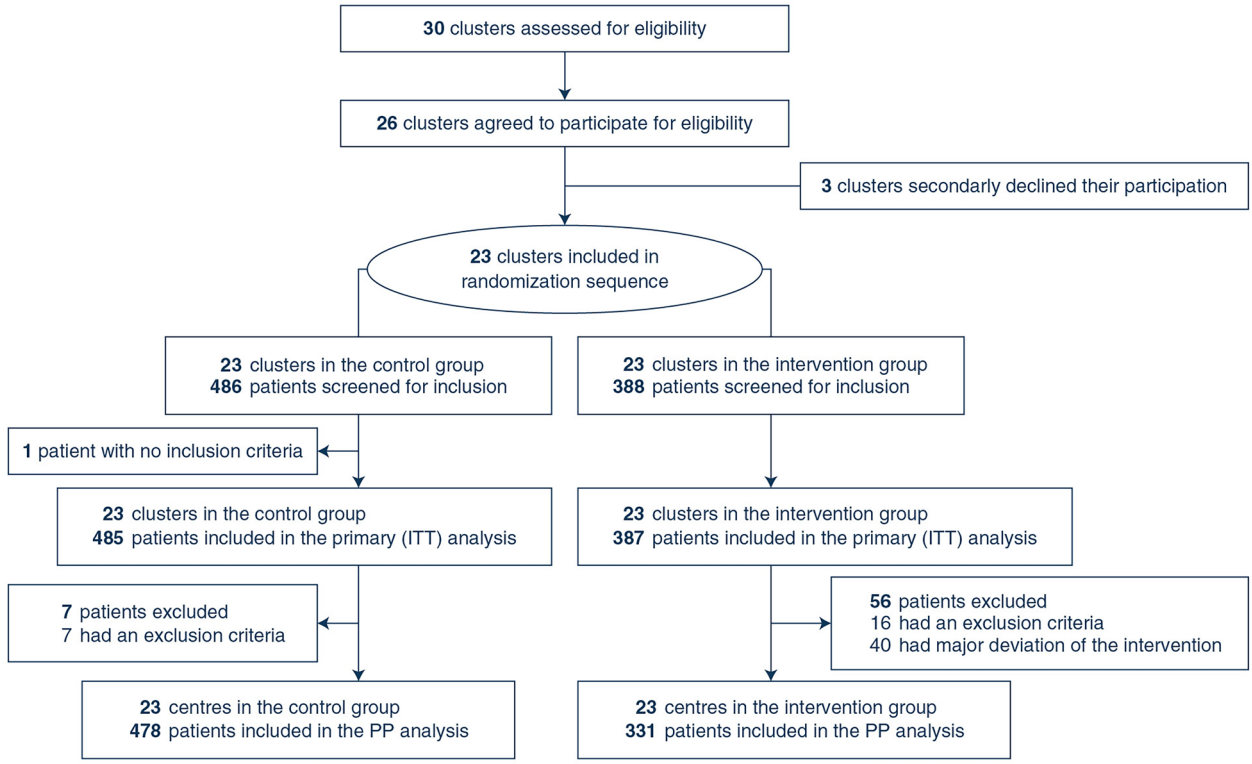

Fig. 1 Flow chart of clusters and patients. *ITT* intention to treat. *PP* per protocol

also a shorter median time to antibiotic administration and fluid resuscitation in the intervention group: 40 min (IQR 10–77) vs 113 (26–241) (difference −73 min; 95% CI −92 to −53) and 16 min (IQR 3–44) vs 30 (IQR 4–97) (difference −14; 95% CI −23 to −6). Details of the treatments received in the ED are reported in Table 2.

Endpoints

The primary outcome of in-hospital death within 28 days occurred in 47 (12.1%) patients in the intervention group and 61 (12.6%) in the control group (difference in percentage −0.4 [95% CI −5.1 to 4.2], adjusted RR 0.81 [95% CI 0.48–1.39, $p=0.41$]) (Table 3; Fig. 2).

Between the intervention group and the control group, there was no difference in the secondary clinical outcomes of total volume of fluids resuscitation at 24 h, presence of acute heart failure within 24 h, SOFA score at 72 h, ICU length of stay, number of days on mechanical ventilation, number of days on renal replacement therapy, vasopressor free days at days 28, unnecessary antibiotic administration and 28-day all-cause mortality (Table 2).

Sensitivity analyses showed similar results (eTable 3).

Discussion

In this multicenter, stepped-wedge cluster-randomized controlled trial conducted across 23 emergency departments in France and Spain, the implementation of a 1-h sepsis bundle did not result in a statistically significant reduction in 28-day in-hospital mortality rates for patients with suspected sepsis compared to usual care with a difference in mortality rate of −0.4 (95% CI −5.1 to 4.2) and an adjusted risk ratio of 0.81 (95% CI 0.48–1.39) when compared to the control group. Notably, due to a lower than anticipated rate of inclusion, the trial was concluded with achieving approximately 75% of the target patient enrollment. Due to the stepped-wedge design, it was impossible to extend the inclusion period beyond the last step, where all centers had already switched to the intervention.

This may have implications for the interpretation and generalizability of the findings.

The controversy surrounding the 1-h sepsis bundle was mainly due to its lack of evaluation in clinical trials, along with questions regarding feasibility of implementation [9, 10, 15, 16]. Regarding the latter issue, our trial confirms that the 1-h bundle may be difficult to implement, because even in an interventional trial (though pragmatic), only 63.5% of patients received antibiotics (AB)

Table 1 Baseline characteristics

Variable	1 h sepsis bundle		Control group	
	n = 387		*n* = 485	
	n		*n*	
Sex, n. (%)	387		485	
Male		233 (60.2)		277 (57.1)
Female		154 (39.8)		208 (42.9)
Age, mean (SD)	387	66.6 (15.6)	485	66 (16)
Comorbidities, n. (%)	383		484	
Hypertension		176 (46)		227 (46.9)
Chronic respiratory failure		43 (11.2)		42 (8.7)
Active cancer		90 (23.5)		118 (24.4)
Chronic kidney failure		50 (13.1)		56 (11.6)
Chronic heart failure		40 (10.4)		45 (9.3)
Immunodepression		42 (11)		41 (8.5)
Diabetes mellitus		93 (24.3)		120 (24.8)
Vital signs				
Systolic blood pressure (mmHg), mean (SD)	383	102.9 (27.3)	485	102.6 (28.4)
Diastolic blood pressure (mmHg), mean (SD)	383	61.7 (16.8)	485	61.3 (16.9)
Mean blood pressure (mmHg), mean (SD)	383	75.4 (19.1)	485	75.1 (19.4)
Heart rate (bpm), mean (SD)	382	104.6 (24.3)	485	103.4 (24.2)
O_2 saturation (%) in room air, Median, [IQR]	364	95 [91; 97]	473	95 [92; 98]
Temperature, mean (SD)	383	37.7 (1.3)	481	37.6 (1.3)
Respiratory rate (breaths per minute), mean (SD)	356	25.5 (7.4)	425	25.2 (7.4)
GCS, median [IQR]	378	15 [15; 15]	483	15 [15; 15]
Biological value				
Lactate (mmol/L), median [IQR]	371	2.4 [1.5; 3.9]	420	2.5 [1.6; 3.6]
Creatinin (µmol/L), median [IQR]	361	109 [76; 167]	481	113 [78; 179]
CRP (mg/L), median [IQR]	347	121 [37.3; 239.8]	450	129 [46.5; 254]
SOFA score at day 0, median [IQR]	383	3 [1; 5]	485	3 [1; 4]

BPM beat per minute; *CRP* C-reactive protein; *GCS* Glasgow Coma Scale; *IQR* interquartile range; *SD* standard deviation; *SOFA* sequential organ failure assessment

Table 2 Treatment received in the emergency department

Variable	Intervention		Control		Unadjusted difference	*p* value
	n = 387		*n* = 485			
Broad-spectrum antibiotics	*n*		*n*			
Broad-spectrum antibiotics, no (%)	386	371 (96.1)	485	432 (89.1)	7 (3.4 to 10.7)	0.0001
Broad-spectrum antibiotics within 1 h, no (%)	384	244 (63.5)	475	151 (31.8)	31.8 (25.1 to 38.4)	< 0.0001
Time between inclusion and broad-spectrum antibiotics initiation (minutes), median [IQR]	369	40 (10; 77)	422	113 (26; 241)	− 73 (− 92.6 to − 53.4)	< 0.0001
Fluid resuscitation						
Fluid resuscitation, no (%)	383	346 (90.3)	484	407 (84.1)	6.2 (1.6 to 10.9)	0.007
Fluid resuscitation within 1 h[a], no (%)	201	148 (73.6)	254	117 (46.1)	27.6 (18.5 to 36.7)	< 0.0001
Time between inclusion and fluid resuscitation (minutes), median [IQR]	305	16 (3; 44)	305	30 (4; 97)	− 14 (− 22.5 to − 5.5)	
Perfused volume in the first 3 h (mL), median [IQR]	379	1000 (500; 2000)	472	750 (250; 1500)	250 (− 100 to 600)	< 0.0001
Lactate						
Lactate performed, no (%)	383	371 (96.9)	485	421 (86.8)	10.1 (6.3 to 13.8)	< 0.0001
Lactate performed within 1 h, no (%)	382	221 (57.9)	479	212 (44.3)	13.6 (6.7 to 20.5)	< 0.0001

[a] Fluids resuscitation among patients with systolic blood pressure < 90 mmHg or a lactate > 4 mmol/L

IQR interquartile range

Table 3 Outcomes

Variable	Intervention *n* = 387		Control *n* = 485		Unadjusted difference	Adjusted relative risk	*p* value
	n		*n*				
Primary endpoint							
In-hospital death at day 28, no (%)	387	47 (12.1)	485	61 (12.6)	− 0.4 (− 5.1 to 4.2)	0.81 (0.48 to 1.39)	0.41
Secondary endpoints							
Fluid resuscitation in the first 24 h (mL), mean (SD)	326	2000 (1000; 3000)	394	1600 (1000; 3000)	426 (165; 687)	1.13 (0.95 to 1.35)	0.16
Acute heart failure within 24 h, no (%)	380	9 (2.4)	481	17 (3.5)	− 1.2 (− 3.7 to 1.3)	0.85 (0.23 to 3.11)	0.84
SOFA Score at 72 h, median (IQR)	383	2 (0; 4)	485	1 (0; 4)	1 (0.3 to 1.7)	1.19 (0.83 to 1.71)	0.34
Intensive care unit (days), median (IQR)	381	0 (0; 4)	485	1 (0; 6)	− 1 (− 2.1 to − 0.1)	0.75 (0.47 to 1.20)	0.23
Mechanical ventilation (days), median (IQR)	384	0 (0; 0)	481	0 (0; 0)	NC	0.74 (0.25 to 2.17)	0.58
Renal replacement therapy (days), median (IQR)	383	0 (0; 0)	480	0 (0; 0)	NC	1.18 (0.05 to 30.43)	0.92
Days alive free of vasopressor, median (IQR)	379	28 (21; 28)	476	28 (26; 28)	NC	0.92 (0.77 to 1.08)	0.31
Undue antibiotic administration, no (%)	385	67 (17.4)	482	94 (19.5)	− 2.1 (− 7.5 to 3.3)	0.58 (0.32 to 1.05)	0.10
All cause 28-day mortality, median (IQR)	386	48 (12.4)	484	66 (13.6)	− 1.2 (− 5.9 to 3.5)	0.82 (0.49 to 1.37)	0.42
Other clinical endpoints							
Mechanical ventilation, no (%)	385	54 (14)	482	62 (12.9)	1.2 (− 3.6 to 6)	0.81 (0.48 to 1.38)	0.41
Renal replacement therapy, no (%)	383	13 (3.4)	480	17 (3.5)	− 0.1 (− 2.8 to 2.5)	1.15(0.37 to 3.63)	0.81
Vasopressor treatment, no (%)	382	83 (21.7)	481	85 (17.7)	4.1 (− 1.5 to 9.7)	1.27 (0.81 to 1.98)	0.19
Delta SOFA (day 3 minus day 0), median (IQR)	383	− 1 (− 2; 0)	485	− 1 (− 2; 0)	0 (− 0.5 to 0.5)	1.04 (0.54 to 2.00)	0.91

Relative risks adjusted on time period and cluster size as fixed effects, and cluster as a random effect

IQR interquartile range; *NC* not calculated; *SD* standard deviation, *SOFA* sequential organ failure assessment

within 1 h and only 73.6% received fluid resuscitation when indicated within 1 h in the intervention groups.

Previous researches indicated that early administration of antibiotics and lactate measurement within 1 h may be associated with improved clinical outcomes. However, this remains controversial, particularly outside the specific situation of septic shock [4, 17, 18]. Conversely, no study has suggested that initiation of fluid resuscitation within 1 h is associated with clinical benefits. This lack of association was confirmed in the pivot study by Seymour et al. [4]. Of note, the SSC has issued several recommendations with differing time targets over the past two decades, and no trial has shown that one specific target improves clinical outcomes more than any other time target. Therefore, the very concept of a time frame for initiation or completion of a bundle is debated, although an observational study has reported improved outcome with compliance of the 3-h and the 6-h bundle [19–21].

These findings showed increased antibiotic prescription in the intervention group, which suggests an increased exposure to antibiotics with the implementation of the 1-h decision window. This observation raises questions regarding the potential for early clinical decisions made in the absence of complete clinical information leading to unnecessary treatments. Conversely, the anticipated risk of acute heart failure associated with rapid fluid administration in the 1-h bundle was not realized in this study, which reported a very low incidence in the intervention group.

In the present study, the 28-day mortality rate was 13% while in the ARISE, PROCESS and PROMISE major trials, the 28-day mortality ranged from 15% to 25% [22–24]. This lower mortality is explained by differing eligibility criteria; in this trial patients were eligible if they had a qSOFA ≥ 2. Consequently, there was a substantial proportion of patients that were included with a diagnosis of sepsis that was ultimately ruled out. This reflects the pragmatic nature of our trial, and explains that the overall median ICU length of stay is 1, with a first quartile of 0. This was not the case for ARISE, PROCESS and PROMISE, which limited eligibility to patients with hypotension or elevated lactate. Patients with an

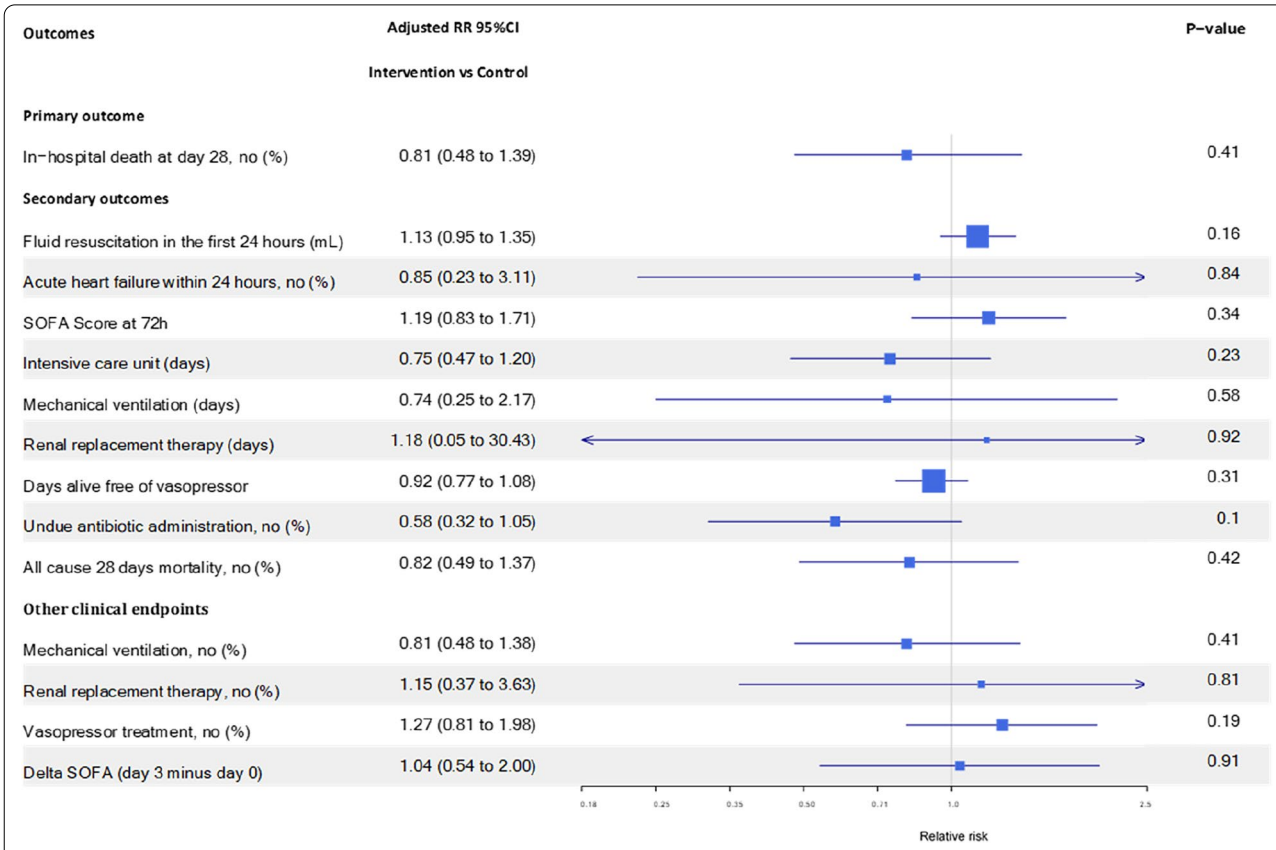

Fig. 2 Outcomes. Forest plot of relative risks adjusted on time period and cluster size as fixed effects, and cluster as a random effect. Blue square: relative risks, horizontal blue line: 95% confidence interval, vertical black line: line of null effect

isolated qSOFA ≥ 2 may not have any organ dysfunction, and may not be diagnosed ultimately with sepsis, but should be managed as if they were having sepsis. This is a pragmatic strategy because since not all sepsis criteria can be confirmed rapidly in the ED, obtaining all objective sepsis criteria may, therefore, delay the treatment initiation. Including patients with qSOFA ≥ 2 is, therefore, a strength of this study and suggests good external validity due to this pragmatic approach.

Limitations

This trial has some limitations.

First, the incomplete recruitment in our trial constrains our ability to conclusively determine the 1-h bundle's efficacy, leaving open the possibility of both potential benefits and harms. Similarly, there was no significant difference in all the secondary endpoints. This trial may have been underpowered to detect a significant difference. However, the absolute difference in mortality of this trial (−0.4 [95% CI −5.1 to 4.2]) was similar to the ones of the PROMISE and ARISE trials that concluded a lack of effect of the intervention, with a mortality difference of −0.3 (95% CI −5.4 to 4.7) and −0.3 (95% CI −4.1 to 3.6), respectively [22, 23].

Second, the higher antibiotic exposure in the intervention group was not captured by the secondary endpoint of unnecessary antibiotic prescription. This is partly due to the inherent challenge of confirming the absence of infection retrospectively, especially in patients treated with antibiotics. This is confirmed by the higher reported rate of "confirmed infection" in the intervention group (81% vs 73%). The fact that a substantial proportion of included patients did not have a confirmed infection is also a reflection of the pragmatic approach of our trial, and indicates good external validity.

Third, we did not evaluate patient outcomes beyond 28 days. This decision was based on the premise that the intervention tested—a very early sepsis management strategy—would, if effective, show its impact within the acute phase of sepsis treatment, which unfolds within days rather than months. Given the immediacy of the interventions within the 1-h bundle, a 28-day follow-up is appropriate for assessing their short-term effectiveness without diluting the results with later, potentially unrelated events.

Fourth, we did not collect specific data on the type of crystalloid fluid or class of antibiotics that were prescribed.

Fifth, there was no formal training for the implementation of the intervention. There was no designated champion, and the local investigator was in charge of the dissemination. However, as reported in the results, and in Table 2, the intervention seemed to have been followed, with a clear difference in early care of included patients in the two periods.

Finally, this was not a trial randomized at the patient level. However, in this stepped-wedge randomized trial, patient's characteristics were similar between groups.

Conclusions

Among patients with suspected sepsis in the ED, the implementation of the 1-h sepsis bundle was not associated with significant difference in in-hospital mortality. However, this study may be underpowered, with subsequent large confidence intervals for the clinical endpoints.

Supplementary Information

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Author details

[1] Sorbonne Université, IMProving Emergency Care (IMPEC) FHU, Paris, France. [2] Emergency Department, Hôpital Pitié-Salpêtrière, Assistance Publique-Hôpitaux de Paris (AP-HP), Paris, France. [3] Department of Clinical Pharmacology and Clinical Research Platform Paris-East (URCEST-CRC-CRB), St Antoine Hospital, APHP. Sorbonne University, Paris, France. [4] Emergency Department, Hôpital Universitaire Dupuytren Limoges, Nancy, France. [5] Emergency Department, Hôpital Saint Antoine, APHP, Paris, France. [6] Emergency Department, University Hospital of Caen, UNICAEN, INSERM UMR-S U1237, GIP Cyceron, Institut Blood and Brain Normandie University, Caen, France. [7] Emergency Department, Hôpital Universitaire de Nîmes, Nîmes, France. [8] Emergency Department, Hôpitaux Universitaires de Strasbourg, Strasbourg, France. [9] Emergency Department, Hôpital Européen Georges Pompidou, Assistance Publique-Hôpitaux de Paris (AP-HP), Paris, France. [10] Emergency Department, University Hospital of Angers, Angers, France. [11] UNIV Angers, UMR MitoVasc CNRS 6215 INSERM 1083, Angers, France. [12] Emergency Department, Hospital Universitari Germans Trias i Pujol, Barcelona, Spain. [13] Emergency Department, CHU Lariboisière, APHP, Paris, France. [14] Emergency Department, CHU Gabriel Montpied, 63000 Clermont-Ferrand, France. [15] Emergency Department, Hôpital Saint-Louis, APHP, Paris, France. [16] Emergency Department, Bichat Claude Bernard University Hospital, Université Paris Cité, APHP, Paris, France. [17] Emergency Department, Hôpital Tenon, APHP, Paris, France. [18] Emergency Department, Univ Rouen Normandie, CHU Rouen, Rouen, France. [19] Emergency Medicine Department, University Hospital of Tours, Tours, France. [20] Emergency Medicine Department, University Hospital of Poitiers, Poitiers, France. [21] Emergency Department, University Hospital of Nice, Université Côte d'Azur, Nice, France. [22] Emergency Medicine Department, University of Lorraine, UMR_S1116, CHRU Nancy, Limoges, France. [23] Emergency Department, Hospital Clinic, Barcelona, Spain. [24] Emergency Department, Hospital Del Mar, Barcelona, Spain. [25] Emergency Department, Hôpital Avicenne, APHP, Bobigny, France. [26] Emergency Department, Royal London Hospital, Barts Health NHS Trust, London, UK. [27] Emergency Department, Paris Saint-Joseph Hospital Group, Paris, France.

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Author contributions

YF, SL and TS conceived the study, contributed to develop the study protocol, contributed to perform the data analysis and to interpret its results, and drafted the manuscript. YF, BB, TS and CG contributed to interpret the results of the data analysis and revised the manuscript for important intellectual content. SL performed the statistical analysis and revised the manuscript for important intellectual content. MC, TL, YY, RM, FC, PLB, FF, DD, NRB, XE, GR, JBBM, CO, DB, HG, MR, GR, JG, CO, TC, GOQ, MCR, JG, BB, and CG recruited patients. All authors read and approved the final version of the manuscript and approved its submission for publication. All authors agree to be accountable for all aspects of the study.

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Data access

YF and TS had full access to all the study data in the study and take full responsibility for the integrity of the data and the accuracy of the data analysis. All the study data can be provided upon reasonable request to the corresponding author.

Declarations

Conflicts of interest

None of the authors has any conflicts of interest to declare in relation with this study.

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