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Impact of early haemodynamic assessment by echocardiography on organ dysfunction and outcome of patients admitted to the emergency department with sepsis or septic shock: protocol of a multicentre randomised controlled trial (GENESIS)

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ABSTRACT

Introduction Acute circulatory failure plays a major role in the development of sepsis-related organ dysfunction. Current 'bundles' of the *Surviving Sepsis Campaign* (SSC) include the administration of a fluid loading of 30 mL/kg in the presence of hypotension within the first hour of sepsis identification. The impact of haemodynamic assessment using echocardiography at the early phase of management of septic patients in the Emergency Department (ED) on patient-centred outcomes is unknown.

Methods and analysis This is a two-parallel arm randomised trial with blinded assessment comparing early haemodynamic assessment using transthoracic echocardiography aimed at guiding therapeutic management to standard of care according to current SSC recommendations in septic patients during initial management in 13 French EDs. Patients with suspected or documented infection and a qualifying quick Sequential Organ Failure Assessment (qSOFA) score (haemodynamic criterion required: systolic blood pressure≤100 mm Hg) will be 1:1 randomised after 500 mL of fluid loading initiation. In the intervention group, echocardiography will allow identifying the haemodynamic profile at the origin of sepsis-induced circulatory failure and monitoring the efficacy and tolerance of fluid resuscitation, or of any other therapeutic intervention according to a predefined therapeutic algorithm. The control group will receive conventional 30 mL/kg fluid resuscitation (unless pulmonary venous congestion) according to SSC recommendations. Primary outcome will be the course of organ dysfunction assessed by the crude change in the modified SOFA score between baseline and 24 hours after randomisation. Secondary outcomes will be the nature of therapeutic interventions resulting from echocardiography (fluid loading, early initiation of vasopressor support or inotrope), the prevalence of the different haemodynamic profiles, the evolution of lactatemia, the safety of the initial therapeutic, the proportion of patients who develop secondarily septic shock, the orientation of patients after ED discharge and both day 7 and in-hospital mortality. We plan to randomise 312 patients.

Ethics and dissemination Approved by the Ethics Committee *CPP Ouest V* on 18 January 2021 (ref: 20/075-2-20.10.16.57638). The dissemination plan includes presentations at scientific conferences and publication of results in a peer-reviewed journal.

Trial registration number NCT04580888.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ GENESIS is a two-parallel arm multicentre randomised trial with blinded assessment conducted in 13 academic and non-academic Emergency Departments in France.
⇒ Participants are randomly assigned to either the control or intervention arm with a 1:1 ratio allocation as per a computer-generated randomisation schedule, stratified by centres using permuted blocks of random sizes.
⇒ In the intervention arm, an initial echocardiography is performed after the administration of the first 500 mL of crystalloids by a trained operator with a level II echocardiography in Emergency Medicine, to identify the haemodynamic profile at the origin of the sepsis-induced circulatory failure.
⇒ Echocardiographic evaluation is coupled with a predefined therapeutic algorithm, which guides management according to the haemodynamic profile.
⇒ Primary outcome is the evolution of modified Sequential Organ Failure Assessment score between inclusion and 24 hours after randomisation.

INTRODUCTION

Sepsis is a life-threatening dysregulated systemic response to infection leading to tissue damage, organ failure and death,[1] with

around 48.9 million new cases of sepsis in 2017,[2] and in-hospital mortality as high as 20%.[3] The WHO adopted a resolution to improve its prevention, diagnosis and management.[4] Early and aggressive treatment of sepsis, based on '*Bundles*' in a given time-frame, is crucial to improve prognosis, reduce organ dysfunction and potentially mortality.[5 6] Cardiovascular failure is the main cause of organ dysfunction, especially at the initial phase of the disease,[7–9] and early and accurate identification of the leading mechanisms resulting in cardiovascular compromise is critical to improve prognosis. Sepsis combines various and intricate alterations of vascular, systolic and diastolic functions of both ventricles and of the microcirculation.[10] Five distinct cardiovascular phenotypes have been described during the initial course of septic shock: left ventricular (LV) systolic dysfunction (symptomatic septic cardiomyopathy), hyperkinetic state (sustained vasoplegia), fluid responsiveness (persistent hypovolaemia), right ventricular (RV) failure (frequently associated with primary acute respiratory distress syndrome) and 'normalised' haemodynamic profiles (ie, none of the preceding abnormalities).[11] Recently, sepsis-induced LV systolic dysfunction was shown to be independently associated with early mortality.[11] Dugar *et al*[12] described that both severe LV systolic dysfunction and hyperdynamic LV denoting associated profound vasoplegia, which is frequently associated with hypovolaemia,[13] were associated independently with in-hospital mortality.

Fluid resuscitation is a key component of the initial management of septic patients in the Emergency Department (ED) to correct the underlying absolute and relative hypovolaemia.[14] Current *Surviving Sepsis Campaign* (SSC) bundles include the administration of 30 mL/kg of fluids in hypotensive patients with sepsis within the first hours of identification.[15] A retrospective analysis of adults presenting to the ED with sepsis or septic shock showed that failure to receive 30 mL/kg of crystalloid fluid therapy within 3 hour of sepsis onset was associated with increased odds of in-hospital mortality, delayed resolution of hypotension and increased intensive care unit (ICU) length of stay, irrespective of comorbidities.[16] Although this is a strong recommendation, it is based on low quality evidence, where the 30 mL/kg dose is derived from a statistical association between mortality and volume of fluid administered. Several trials[17–19] reported an average volume of fluid administered before randomisation around 30 mL/kg, which may have contributed to the fact that this volume of fluid resuscitation has been adopted in routine clinical practice.[20] The 1 hour bundle and the potential benefit of a uniform fluid loading of 30 mL/kg[6 21–24] has recently been challenged,[25] especially because aggressive fluid loading may be harmful in certain patients.[26] Analysis of large databases suggested that there may be a U-shaped response curve, where limited volumes as well as excessive volumes of fluid resuscitation are associated with worse outcome, the best response being observed within a range of 15–45 mL/kg.[27] We previously showed that septic patients early assessed in the ED using echocardiography exhibited LV or RV systolic dysfunction in approximately 30% of cases.[28] Current SSC recommends a personalised approach to fluid therapy and recognises this issue as one of the priority areas of research.[29 30]

Echocardiography provides unparalleled information on central haemodynamics and helps the diagnostic work-up in identifying the leading mechanism of circulatory failure in patients with undifferentiated shock.[31] Guidelines and consensus statements recommend echocardiography as best medical practice in the initial assessment of haemodynamically unstable patients.[32–34] Although authors have recently reported various haemodynamic profiles using echocardiography in patients admitted to the ED for sepsis, the impact of this information on early management and prognosis is unknown.[35–38] Recent studies based on the MIMIC-III and IV (Medical Information Mart for Intensive Care) databases reported discrepant results regarding the association between early echocardiographic assessment and mortality in patients with sepsis.[39 40] When performed in the ED, echocardiography directly alters therapeutic management in 27%–53% of septic patients.[28 41] In a before–after study, guiding the initial management of patients admitted to the ED with undifferentiated shock allowed a significant reduction in mortality at 28 days (56% vs 66%: p=0.04).[42] However, a prospective randomised study carried out in 270 patients with shock in the ED (52% related to sepsis) did not show a significant difference in hospital mortality or 30-day mortality between patients who underwent an ultrasound assessment and those who did not.[43] There are several hypotheses that may explain this result. First, authors explain that point-of-care ultrasonography is not a therapeutic intervention, unlike the present trial where transthoracic echocardiography is coupled with a predefined therapeutic algorithm. Second, the heterogeneity of the population since they studied patients with undifferentiated hypotension (septic or not) and potentially different haemodynamic profiles and prognosis according to the underlying condition. Third, the choice of 30-day mortality as a primary outcome is presumably too robust to be attributed to the sole haemodynamic assessment at the early phase of management. Accordingly, this study was prematurely stopped for futility.[43]

Overall, the impact on organ failure and prognosis of early haemodynamic evaluation of patients admitted to the ED with sepsis using echocardiography remains to be determined by randomised controlled trials.

Objective of the study

Primary objective

The main objective of the trial is to determine the impact of early haemodynamic assessment using echocardiography coupled with a predefined therapeutic algorithm on the course of organ dysfunction in patients admitted to the ED with sepsis, when compared with standard of care based on current SSC guidelines.[15]

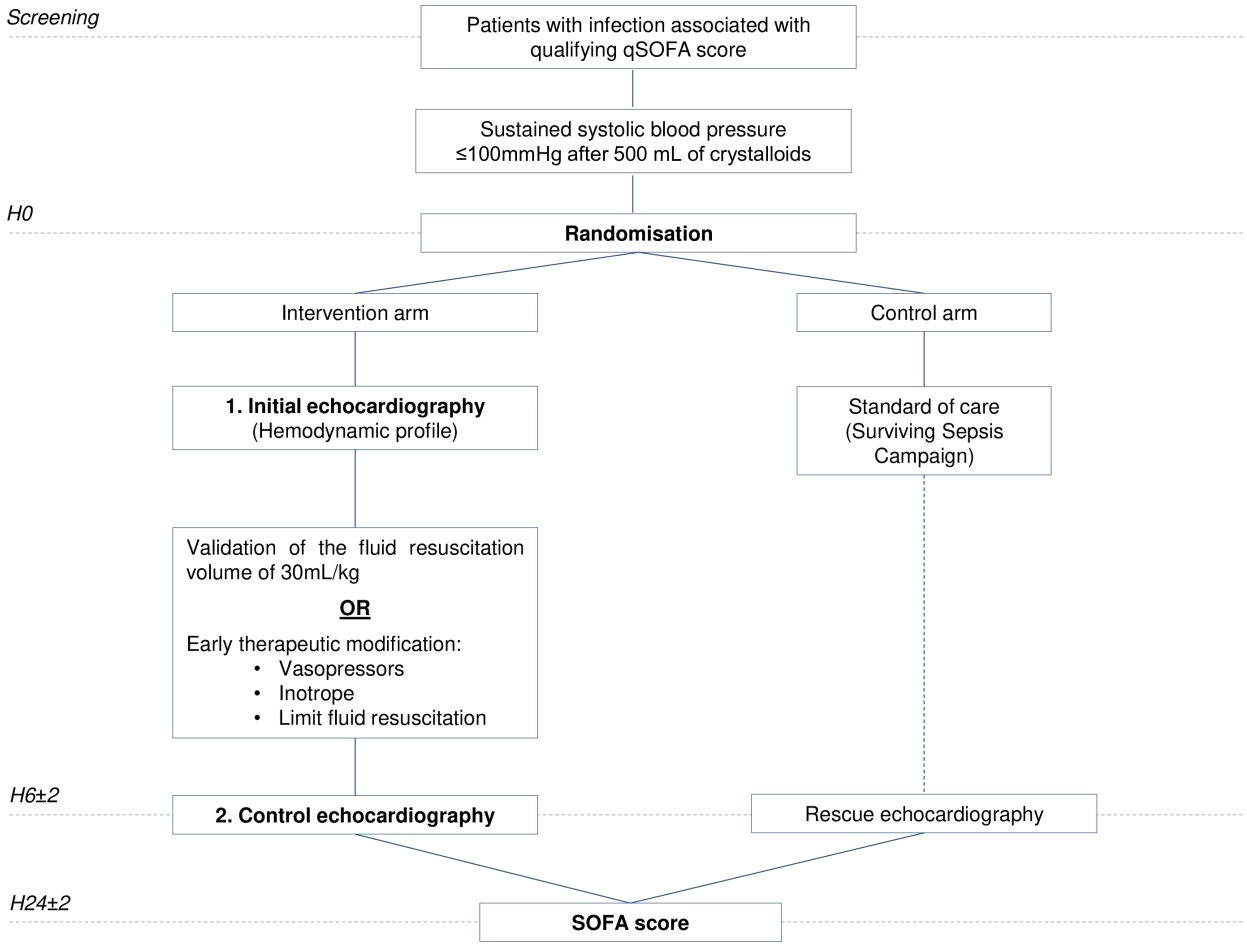

Figure 1 Study flow chart. qSOFA, quick Sequential Organ Failure Assessment; SOFA, Sequential Organ Failure Assessment.

Secondary objectives

The secondary objectives will be:

- To determine the nature of therapeutic interventions resulting directly from early echocardiography assessment.
- To determine the prevalence of the different haemodynamic profiles identified in the intervention arm.
- The evolution of the initial tissue hypoperfusion (lactatemia).
- The safety of the initial therapeutic.
- The proportion of patients who develop secondarily septic shock.
- The orientation of patients after ED discharge
- Day-7 mortality
- In-hospital mortality.

METHODS AND ANALYSIS

Design and participants

GENESIS is a two-parallel arm multicentre randomised trial with blinded assessment (figure 1). The study started in July 2021 and will be completed around April 2025.

Patients will be recruited in 13 academic and non-academic EDs in France, which are listed in the online supplemental table 1.

Inclusion criteria

Adult patients (≥18 years old) admitted to the ED will be eligible if they fulfil all the following criteria:

- Sepsis defined as a clinically suspected or documented acute infection associated with a quick Sequential Organ Failure Assessment (qSOFA) score ≥2 points, including a systolic blood pressure ≤100 mm Hg requiring a fluid challenge.
- Persistent systolic blood pressure ≤100 mm Hg despite an initial fluid challenge of 500 mL of crystalloids administered within 30 min maximum.

Exclusion criteria

- Decision to limit or withdraw care.
- Moribund status or patient deemed not eligible to transfer to the ICU by the investigator.
- Pregnancy or breastfeeding.
- Persons under juridical protection.

Intervention

In the intervention arm, the initial echocardiography will be performed as soon as possible after the administration of the first 500 mL of crystalloids by a trained operator (two to three per participating centre) with a level II echocardiography in Emergency Medicine,[44] to identify

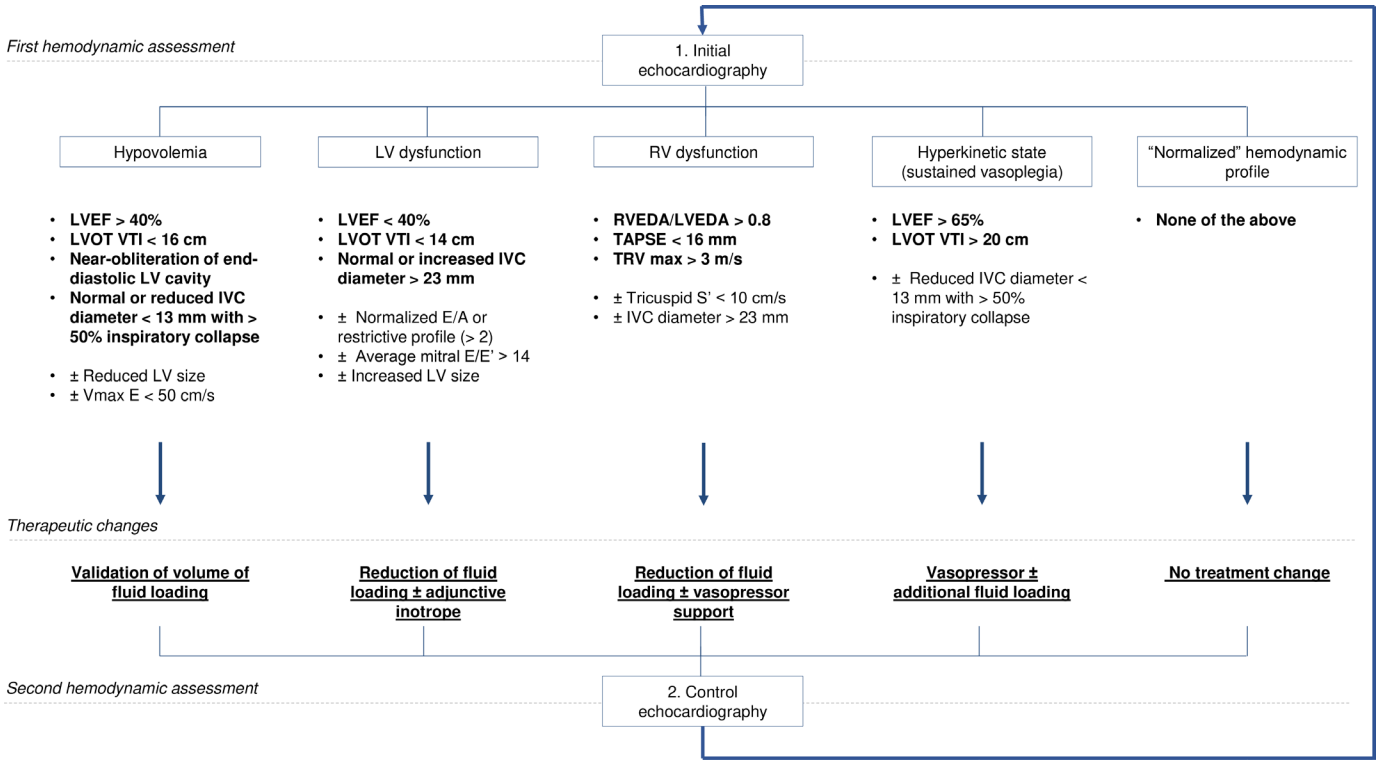

Figure 2 Standardised therapeutic algorithm. IVC, inferior vena cava; LVEF, LV ejection fraction; LVOT VTI, LV outflow tract velocity-time integral; TAPSE, tricuspid annular plane systolic excursion; TRV, tricuspid regurgitation velocity; RVEDA/LVEDA, Right ventricular end-diastolic area/left ventricular end-diastolic area

the haemodynamic profile at the origin of sepsis-induced circulatory failure. Each patient will be screened systematically for the long-axis and short-axis parasternal views, the apical four-chamber view and the subcostal four-chamber view including the examination of the inferior vena cava (IVC) in its longitudinal view. Ratio of RV and LV end-diastolic diameter (four-chamber view), tricuspid annular plane systolic excursion (TAPSE), tricuspid S′ velocity, tricuspid regurgitation velocity (TRV), mitral E/A and averaged E/E′ ratio, LV ejection fraction (LVEF), LV outflow tract velocity-time integral (LVOT VTI) and IVC diameter (with inspiratory collapse) will be measured (figure 2). The echocardiographic examination requires less than 10 min to be completed. The operator interprets online echocardiography results at the bedside and provides the attending physician with concluding remarks and a therapeutic proposal, according to the predefined algorithm.

We distinguished five cardiovascular phenotypes based on predefined echocardiographic criteria:[11]

- Hypovolaemia:
  - LVEF>40%.
  - LVOT VTI<16 cm.
  - Near-obliteration of end-diastolic LV cavity.
  - Normal or reduced IVC diameter<13 mm with >50% inspiratory collapse.
  - ± Reduced LV size.
  - ± Vmax E<50 cm/s.
- LV dysfunction:
  - LVEF<40 %.
  - LVOT VTI<14 cm
  - Normal or increased IVC diameter>23 mm.
  - ±Normalised E/A or restrictive profile (>2).
  - ± Average mitral E/E′>14.
  - ± Increased LV size.
- RV dysfunction
  - RVEDA/LVEDA>0.8.
  - TAPSE<16 mm.
  - TRV max>3 m/s.
  - ±Tricuspid S′<10 cm/s.
  - ±IVC diameter>23 mm.
- Hyperkinetic state (sustained vasoplegia)
  - LVEF >65%.
  - LVOT VTI>20 cm.
  - ± Reduced IVC diameter <13 mm with >50% inspiratory collapse.
- 'Normalised' haemodynamic profile.

According to a predefined therapeutic algorithm, this first haemodynamic assessment will lead to the following:

- Complete the 30 mL/kg initial fluid loading.
- Early initiate vasopressor support in the presence of marked vasoplegia and administer additional fluids in the presence of persisting hypovolaemia.
- Reduce the volume of initial fluid loading (<30 mL/kg) in the presence of LV and/or RV systolic dysfunction when associated with indirect signs of venous congestion.
- Suggest early administration of inotrope in the presence of severe LV systolic dysfunction with low flow state.

The second echocardiography assessment (control echocardiography) will assess both the efficacy and tolerance of fluid resuscitation, or of any other therapeutic intervention (eg, inotrope) resulting from the initial haemodynamic evaluation, within a 6±2 hour time frame after randomisation or shortly after the introduction of a new drug (left at the discretion of the attending physician). This second examination will be systematically performed by the same operator to adjust subsequent therapeutic management: interruption of fluid administration or not, initiation of vasopressor or inotrope support according to both the haemodynamic profile and clinical picture (figure 2).

In the control arm, patients will be treated according to standard of care based on current SSC recommendations, including a fluid resuscitation of 30 mL/kg within the first 3 hours of resuscitation initially and the subsequent use of vasopressors in patients with persisting hypotension.[15]

Depending on the clinical context and in particular patients vulnerable to volume intolerance (eg, severe heart failure, anuric patients), investigators have the possibility of performing a 'rescue' echocardiography to validate ongoing management.

The use of alternative haemodynamic monitoring systems will not be allowed in both study arms. In contrast, there will be no restriction on drug use.

Recruitment

The study will be conducted in the ED, which is the place of the first medical contact in the hospital, irrespective of the reason for admission. Academic and non-academic centres were selected to reflect current epidemiology of sepsis and based on their experience in conducting emergency trials within the *Société Française de Médecine d'Urgence*. Participating centres were selected based on the routine use of echocardiography on clinical grounds with trained ED physicians and their expertise in conducting clinical trials. All operators who will perform echocardiography were trained to standardise measurements and therapeutic interventions. Each participating centre used local processes to confirm credentialing, qualifications and skill level.

In each centre, an identification process will be adapted to the local organisation ('Sepsis Alert') to facilitate patients screening using the qSOFA score. A check-up list (source documentation) will facilitate the screening of patients by investigators and bedside recording of information required for randomisation. This facilitated procedure aims at detecting and including patients as soon as possible after ED admission, to obtain a homogeneous cohort with minimal therapeutic interventions performed at the time of randomisation. In patients fulfilling inclusion criteria secondarily in the ED, enrolment into the trial will be possible because of the absence of the required time window.

Randomisation

Participants will be randomly assigned to either the control or intervention arm with a 1:1 ratio allocation as per a computer-generated randomisation schedule, stratified by centres using permuted blocks of random sizes.

Participants will be randomised using Ennov Clinical, an online central randomisation procedure. The randomisation procedure will not be possible until the participant has been recruited into the trial. Notably, all selection criteria must be collected and met. The allocation sequence will be generated by a statistician who is not involved in the recruitment or follow-up of the participants.

Blinding

The nature of the intervention precludes blinding of the healthcare staff and patients to group assignment. Nevertheless, the primary endpoint will be assessed by an independent assessor blinded to trial arm.[45]

Criteria for discontinuing or modifying allocated intervention

In the control arm, investigators will have the possibility to perform a 'rescue' echocardiography in case of persistent hypotension with shock despite completed treatment, or in case of diagnostic uncertainty (eg, rule out infective endocarditis, tamponade). Echocardiography results will be used by the attending physician if clinically relevant and recorded into the electronic case report form (eCRF).

Strategies to improve adherence to intervention

To optimise the implementation of the intervention and haemodynamic monitoring using echocardiography, we will use parameters recommended by the French Society of Emergency Medicine (*Société Française de Médecine d'Urgence,* SFMU). Given that sepsis patients must be reassessed regularly, especially in the early phase, a 6 hour interval was decided between the two echocardiographic examinations corresponding to the biological control and allowing the calculation of the SOFA score. The objective of this strategy was to guarantee feasibility in the context of permanent flow in ED and the availability of operators.

Primary outcome

The primary outcome will be the crude variation of modified Sequential Organ Failure Assessment (mSOFA) score between baseline (inclusion) and 24 hours after randomisation. Since the evaluation of the Glasgow score to determine the severity of the neurological function is subjective and not reproducible for intermediate values, the initial value obtained before randomisation will be kept at follow-up to avoid any undue variation of the SOFA score secondary to heterogeneous neurological assessment. Accordingly, the mSOFA score will purposely exclude the neurologic component of the SOFA score[46] and will be evaluated by an independent assessor blinded to trial arm.[45]

Secondary outcomes

The secondary outcomes will be as follows:

1. The number and proportion of patients in whom early echocardiography performed in the ED (intervention arm) modified ongoing therapy based on SSC recommendations (standard of care) according to the haemodynamic profile:
   - Interruption of fluid resuscitation before 30 mL/kg
   - Administration of fluids beyond 30 mL/kg
   - Early initiation of vasopressor support
   - Early initiation of inotropes
   - Any other therapeutic modification directly related to echocardiographic examination.
2. Number and proportion of patients presenting at the time of early echocardiographic assessment (intervention arm) with the following cardiovascular profile:
   - Persisting hypovolaemia.
   - Vasoplegia with LV hyperkinesia
   - LV systolic dysfunction
   - RV failure
   - Unremarkable haemodynamic profile (none of the above-mentioned abnormalities) due to adequate management of acute circulatory failure (avoid any potentially deleterious therapeutic change).
3. Number of adverse effects potentially related to initial therapeutic management, especially:
   - Hydrostatic pulmonary oedema (ie, cardiogenic origin, volume overload)
   - Supraventricular arrhythmias (ventricular rate >140 bpm), ventricular arrhythmias.
   - Acute coronary syndrome.
4. Lactate clearance (lactate level 6 hours after randomisation compared with baseline).
5. Number and proportion of patients who develop septic shock within 24 hours after randomisation.
6. Patient course after ED discharge: hospitalisation in regular ward (medicine, surgery), stepdown unit or intensive care unit.
7. Mortality (all-cause and sepsis-related) at day 7 and at hospital discharge.

Research timeline and data collection

Since the treatment of sepsis should be undertaken as a medical emergency, preinclusion visits to confirm the patient's eligibility for enrolment in the trial and inclusion visit will typically occur on the same day. Parameters collected and successive visits during the study period are summarised in table 1.

All the information required by the protocol will be recorded in the eCRF. Investigators will be uniformly trained to guarantee consistent data recordings and will be responsible for accurate data collection. Data will be entered in investigating centres through a secure website in a timely manner, under the responsibility of the investigator who will check for accuracy and completion. Data monitoring and queries will be edited by a data manager who will be in charge of checking missing or inconsistent data. After a blind review and resolution of all queries, the database will be locked for statistical analysis.

To obtain the SOFA score at H0 and H24, automatic e-mails will be sent to investigators to recall the different clinical and biological required information and their time points. Sepsis patients are hospitalised to the ICU or to 'intermediate units' which in France allow a continuous monitoring of vital parameters and regular biology testing, as opposed to regular wards. Accordingly, we will be able to appropriately collect

Table 1 Description of different steps from screening to study end

	Inclusion	H0	H6	H24	Day 7	Hospital discharge
Inclusion criteria	✓					
Consent	✓					
Clinical examination and score	✓	✓	✓	✓		
qSOFA score	✓	✓				
Biological samples		✓	✓	✓		
Score SOFA		✓	✓	✓		
First fluid bolus of 500 mL	✓					
Randomisation		✓				
Treatment		✓	✓	✓		
Echocardiography*		✓	✓	(✓)		
Adverse events			✓	✓		
Orientation after ED discharge				✓		
Vital status					✓	✓

*In the intervention group.
ED, Emergency Department; qSOFA, quick Sequential Organ Failure Assessment; SOFA, Sequential Organ Failure Assessment.

the primary criterion at 24 hours. The choice of early mortality at D7 and later during hospital stay was chosen to limit loss to follow-up.

Sample size

We hypothesised that the impact of early haemodynamic assessment will alter the therapeutic management in 30%–40% of patients,[28] and that echocardiography-guided therapy will result in a two-point reduction of the SOFA score at 24 hours when compared with standard of care. Considering an SD of initial SOFA score of 2.9 points,[28] 416 patients should be included to reach a power of 80%. Assuming that the correlation between the measurement of the SOFA score at baseline and at 24 hours will be 0.5, the required number of patients is then 312 patients.[47]

Statistical analysis of the primary outcome

The comparison of the crude variation of the mSOFA score 24 hours after randomisation between the intervention arm and the control arm will be carried out using a covariance analysis.

Statistical analysis of the secondary outcomes

1. The proportion of patients for whom targeted echocardiography performed in the ED (intervention arm) will modify the standard treatment will be reported as the point estimate with the 95% CI. The nature of the modification will be reported using descriptive statistics.
2. The proportion of patients progressing to septic shock 24 hours after randomisation between the two treatment arms will be compared using a χ^2 test or Fisher's exact test if necessary.
3. The frequency of the different mechanisms of haemodynamic dysfunction will be studied using descriptive statistics.
4. The comparison of lactate clearance between the two randomisation arms will be performed by a Student t-test or a Mann Whitney test.
5. The comparison of patient orientation at discharge from the ED between the two randomisation arms will be performed by a χ^2 test.
6. The comparison of all-cause and sepsis-related mortality at D7 between the two randomisation arms will be studied by a χ^2 test.
7. The comparison of mortality at discharge from hospital between the two randomisation arms will be studied using a competitive risk model.

Two-sided p values≤0.05 will be considered statistically significant.

Additional analyses

A subgroup analysis will be performed in patients with pre-existing heart failure (LVEF<40%), since this information will usually not be available at the time of screening and randomisation could then not be stratified. This analysis will be performed using a regression model including an interaction term.

Non-adherence and missing data handling

Analysis will be performed in all randomised patients according to the randomisation group, whatever it will occur.

For patients who died within the first 24 hours, the mSOFA calculated 6 hours after randomisation will be used as comparator with screening SOFA score, as a conservative approach.

In patients who expire within the first 6 hours following randomisation, the value of mSOFA will be imputed to the most pejorative observed among patients who died between 6 and 24 hours following randomisation.

Patient and public involvement

None.

In accordance with French regulation, participants will be informed of the overall results of the study at their request.

Ethics and dissemination

The study protocol was approved by the Ethics Committee CPP Ouest V on 18 January 2021 for all participating sites (ref: 20/075-2- 20.10.16.57638; online supplemental material 1). The investigator will collect written informed consent. Since patients with sepsis have frequently reduced consciousness, written informed consent of the legal representative will be obtained. If the legal representative is not available, an emergency procedure will be used and a written informed consent for continuation will be obtained as soon as possible from the patients' representative, and ultimately from the patients themselves (online supplemental material 2).

The publication policy will comply with international recommendations and the Consolidated Standards of Reporting Trials statement (http://www.consort-statement.org). Results will be presented in scientific congresses and published in a peer-reviewed journal.

DISCUSSION

This randomised trial will address a gap of knowledge regarding the potential impact of early guidance of therapeutic management of hypotensive patients with sepsis in the ED, according to their cardiovascular phenotype determined by echocardiography.[29 30] Indeed, no study has yet established a link between the personalisation of initial therapeutic management of sepsis-induced cardiocirculatory failure and the development of subsequent organ dysfunction and outcome.[48] This study will provide some solid data to design a new trial in ED. Currently, 302 out of 312 patients have been randomised.

The SSC strongly recommends the rapid administration of 30 mL/kg of crystalloids to patients with sepsis-induced hypotension or with a lactate level ≥4 mmol/L, with a low quality of evidence.[15] 'Optimal' fluid resuscitation would refer to the volume of fluids required to restore end-organ perfusion, while avoiding tissue oedema and venous congestion, which may participate in cellular

dysoxia and poor outcome.[22 49–51] Our primary hypothesis is that early haemodynamic assessment by echocardiography in the ED will primarily guide early fluid resuscitation, thus limiting deleterious positive fluid balance which is prognostic in septic patients.

The evolution of the SOFA score was purposely chosen as the primary outcome rather than mortality, which is influenced by numerous factors other than cardiovascular failure. The evolution in the first 24 hours of the SOFA score (ie, the minimum delay proposed between two SOFA determinations) is a relevant primary criterion to evaluate the impact of an intervention implemented on admission to the ED. SOFA score is an objective outcome which is reproducible and widely used worldwide, with high external validity.[46 52] The SOFA score is associated with early mortality,[53] and the initial variations between admission to the ED and admission to ICU are associated with prognosis.[54] To facilitate the screening and potential recruitment, we chose to identify patients using a qSOFA score with persistent hypotension, which represents approximately 15%–20% of infected patients in the ED.[55] In this subgroup of patients, in-hospital mortality reaches 24%,[56] and qSOFA score accurately predicts organ dysfunction.[57]

Overall, this clinical trial promises to optimise therapeutic management of septic patients in the ED using early echocardiography assessment, and ultimately to significantly reduce organ dysfunction at the initial phase of sepsis and associated short-term mortality, when compared with current standard of care.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research.

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