Study protocol for a Multi-centre, Investigator-initiated, Randomized Controlled Trial to Compare the Effects of Prehospital Antibiotic Treatment for Sepsis Patients with Usual Care after Training Emergency Medical Services (EMS) Personnel in Early Recognition (– The Prehospital ANTibiotics Against Sepsis (PHANTASi) trial

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ABSTRACT

Introduction: *Sepsis is one of the most frequent reasons for referral to emergency departments (EDs) worldwide. Sepsis becomes more serious when left untreated with a high mortality rate, exceeding even those of myocardial infarction and stroke. Therefore, much effort has been put in to start with appropriate therapy as early as possible. Emergency medical services (EMS) personnel have already made a significant difference in improving care for patients with acute coronary syndrome, multiple trauma and stroke. Patients with severe sepsis or septic shock could also benefit from timely pre-hospital care. Earlier recognition and initiation of treatment by EMS personnel may improve survival of these critically ill patients.*

Methods and analysis: *The Prehospital Antibiotics against Sepsis (PHANTASi) trial is an investigator- initiated, multicentre, randomized controlled open-label clinical trial nested within a step wedge design. This study compares the effects of usual care to that of training EMS personnel in recognizing and initiating treatment in the prehospital setting together with early administration of antibiotics for patients suspected of (severe) sepsis and septic shock. Primary outcome is 28 day mortality. Secondary outcomes include, length of hospital stay and admission to intensive care units.*

Ethics and dissemination: *This study has been approved by the research ethics committee of VU University Medical Centre, Amsterdam, The Netherlands (Protocol 2013.458/ NL 42001.029.13). The results of the study will be disseminated at several research conferences and international peer reviewed journals. The study will be implemented and reported in line with the CONSORT statement.*

Keywords

randomized controlled trial, sepsis, antibiotics, statistical analysis plan, prehospital.

Strengths and limitations of this study

- This study is the first prospective, randomized controlled, open-label, multicenter trial l investigating the effects of training EMS personnel in early recognition and initiating treatment together with early prehospital antibiotic administration in sepsis patients compared to usual care
- Results of this trial may help to develop new guidelines for the treatment of sepsis in the prehospital/hospital setting and thereby strengthen the whole acute care chain
- Through this trial awareness of sepsis will likely increase and usual care may improve, which will make it difficult to differentiate between the positive effects of intervention.

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Introduction

Sepsis presents a major public health problem with a rising incidence and high mortality which increases dramatically with the severity of the disease ranging from 10% for sepsis to 80 % for septic shock.[1-3]

In 2002, The "Surviving Sepsis Campaign" (SSC) was launched,[4] with the aim of creating awareness for better recognition and treatment of sepsis. Through this campaign a directive was set up, which amongst other recommendations, stated that broad-spectrum antibiotics should be administered as soon as possible, preferably within one hour after arrival at the emergency room. According to several retrospective studies rapid antibiotic administration could lead to better chance of survival as well as to a reduction in the chance of developing lasting physical problems. Moreover, rapid intervention may shorten hospital stay and even prevent the need for ICU admission.[5-10] However, in daily practice, implementation of the SSC directives is not always easy, and the start of antibiotic treatment is often delayed in patients with suspected sepsis.[11-13] The so-called 'onset to needle time' can be as high as several hours. A retrospective study conducted by Kumar and colleagues showed that only 32.5% of the patients received the first gift within the first 3 hours.[5] According to this study any delay in the administration of antibiotics, may cause an increase in mortality with almost 8% per hour. Sepsis is thus an urgent and time-dependent illness which requires prompt recognition and immediate medical attention. Emergency Medical Service (EMS) personnel are often the initial healthcare providers for septic patients.

In recent years, EMS personnel have made significant contributions in improving care for patients with other critical, time-dependent illnesses such as acute coronary syndrome, multiple trauma and stroke.[14;15] In parallel, patients with severe sepsis or septic shock could also benefit greatly from timely pre-hospital care.[16] Indeed, in retrospective studies, providing prehospital care for sepsis patients by EMS personnel accelerated and improve care in the hospital setting,[17;18] however an important point to note is that all the studies which state that early antibiotic administration is associated with improved survival, were retrospective and uncontrolled studies, where selection bias may have influenced the results. One of the reasons why physicians may not be very keen on initiating the antibiotics early (before a definitive diagnosis is made) may be the fact that they consider current evidence insufficient and incomplete.

A definitive answer to the question what the optimal timing of antibiotic administration is, can only be obtained by a prospective randomized controlled trial that avoids selection bias. However, it may be unethical to randomize patients and delay initiation of antibiotic therapy at the ED. An alternative, and perhaps better, option is to perform a prospective randomized trial in the pre-hospital setting, i.e. in the ambulances. In current practice, initiation of antibiotic therapy starts at the emergency department (ED) and not in the ambulances. Pre-hospital antibiotic administration on the one hand may be a solution to avoid delays in treatment at the ED and on the other hand a way to finally perform a prospective randomised trial to examine the effect of onset to needle time on clinical endpoints such as improved survival, shorter hospital stay and better quality of life. Therefore, we designed this study with the aim of investigating whether prehospital administration of antibiotics after training EMS personnel to recognize suspected (severe) sepsis or septic shock leads to improvement in patient outcomes such as a reduction in 28 day mortality compared to usual care.

The Prehospital Antibiotics against Sepsis (PHANTASi) trial is an investigator-initiated, randomized controlled, multicentre, open-label trial to compare the effects of early prehospital antibiotic treatment for sepsis patients with usual care nested within a step wedge design to evaluate the effect of the training of EMS personnel.

Our hypothesis is that increasing awareness of sepsis through training EMS personnel together with pre-hospital administration of antibiotics in patients with suspected (severe) sepsis or septic shock, will improve the care in patients with sepsis in the acute care chain and cause an improvement in patient outcomes.

Approval from the medical ethical committee was obtained and the trial is registered with Clinical Trials.gov **(NCT01988428).** The PHANTASi trial is funded by Stichting Fonds Nuts Ohra (FNO) and the Dutch Association of Internists (NIV). The funders do not have any role in the study design; this includes collection, management, analysis, interpretation of data, writing of the manuscript and the decision to submit results

Methods/Design

Setting

Pre-hospital (i.e. ambulance), ED and inpatients of all participating centres.

Study population

All patients above the age of 18 years, with suspected (severe) sepsis or septic shock and transferred to the ED by the EMS, are eligible for study inclusion.

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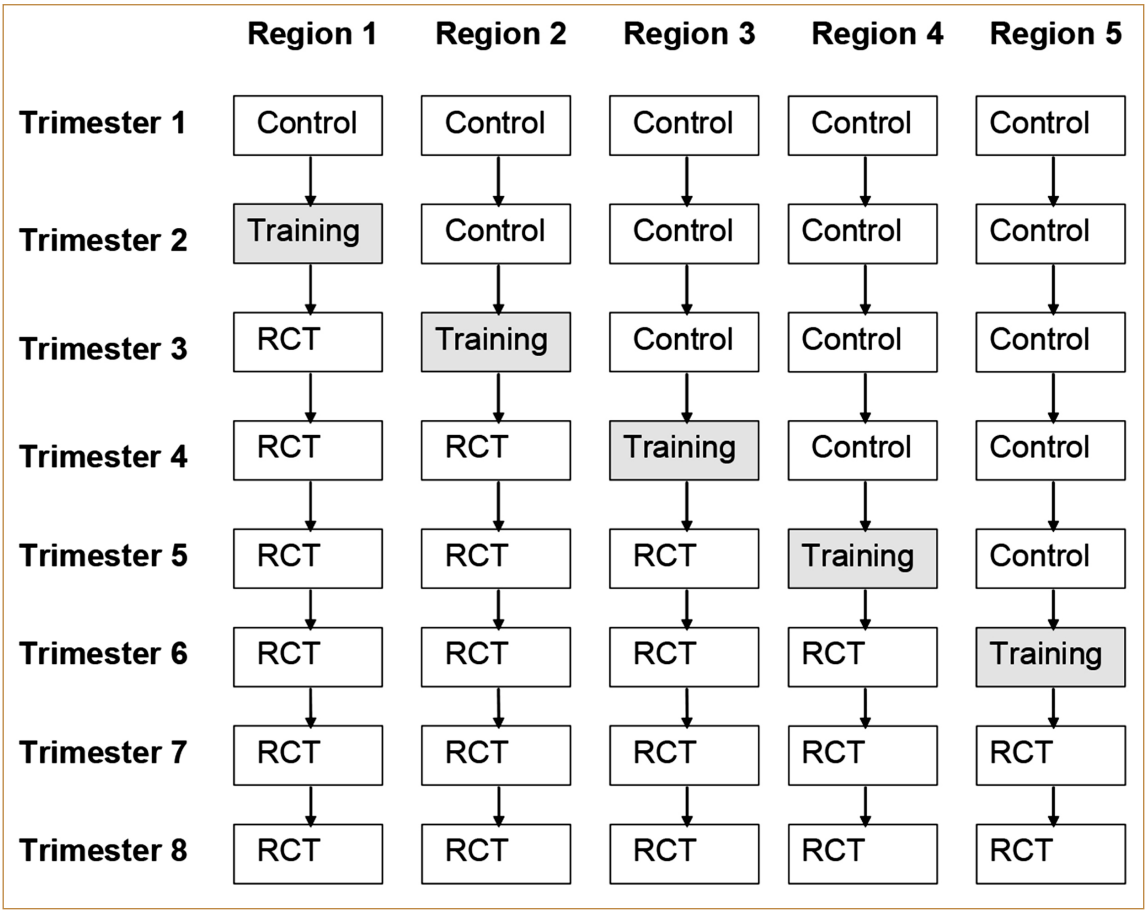

Figure 1. Schematic of the study design

Inclusion criteria

All patients must be:

- ≥ 18 years of age
- have a suspected infection
- have an abnormal temperature (>38 °Celsius or < 36 °Celsius)

and meet at least one of the following two SIRS criteria:

- abnormal pulse (> 90 beats per minute)

and/or

- abnormal respiratory rate (> 20 per minutes);

Exclusion criteria

Patients with the following criteria are excluded:

- known with severe allergy to ceftriaxone or to other beta lactam antibiotics
- known pregnancy
- patients with suspected prosthetic joint infections

Objectives and hypotheses

Primary Objectives

To evaluate whether early recognition and pre-hospital administration of antibiotics reduces 28-day mortality in patients referred to the ED with suspected (severe) sepsis or septic shock.

Secondary Objective(s)

1. To evaluate whether early recognition and pre-hospital administration of antibiotics reduces the length of hospital stay and the proportion of patients admitted to intensive or medium care units as compared to usual care.
2. To evaluate whether implementation of the training programme to increase the early recognition and treatment of sepsis reduces 28-day mortality, length of hospital stay in patients referred to the ED with suspected (severe) sepsis or septic shock.
3. To document any adverse events in the group of patients who receive pre-hospital antibiotics and compare the incidence of adverse events to the incidence under usual care.
4. To evaluate whether early recognition and pre-hospital administration of antibiotics has a beneficial effect on the quality of life after discharge from hospital. This will be measured one month after discharge using validated questionnaires (SF 36).

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Main study outcomes

We will assess in hospital mortality, all-cause 28-day mortality, hospital length of stay, admission to intensive or medium care unit (ICU/MCU), including duration of stay at ICU/MCU. We will assess quality of life (QoL) after one month of discharge using SF 36 questionnaires.

Study design

The design is a multicentre, open-label randomized controlled trial for assessing the effect of pre-hospital administration of antibiotics nested within a stepped-wedge design to assess effect of training on initiation of treatment.

Training EMS personnel

Prior to the start of this trial, EMS personnel will be trained in order to recognize all forms of sepsis (SIRS to septic shock) promptly and effectively. This training will be given by the members of the research team. After training, EMS personnel will screen patients and include them if they fulfil the inclusion criteria.

The training of EMS personnel will be implemented sequentially in different regions (i.e. phased implementation). The training is first implemented in the region of Amsterdam because of logistical reasons. The order in which training occurs in the other regions is randomized. Every 3 months a new region is trained. A schematic of the study design is given in *Figure 1.*

Randomisation, blinding and treatment allocation

Once the training of EMS personnel in a region is completed, eligible patients transferred to ED by ambulance in that region will be randomized. Randomisation will occur non-blinded (1:1 allocation) using a block-randomisation with blocks of size 4. Randomisation is stratified by region. Lists with random sequences will be centrally generated and notes with group assignments (intervention or control) will be put in consecutively numbered envelopes by the research team. Envelopes will be distributed over all participating ambulances. The envelope contents are not distinguishable when sealed.

Control group- treatment

Patients in the control group will receive usual care.

Intervention group -treatment

Broad spectrum antibiotics: ceftriaxone 2000 mg will be given intravenously after obtaining blood cultures. Ceftriaxone is registered for the indication sepsis and incorporated in institutional and national guidelines as a drug of choice for the treatment of sepsis of unknown origin.

Escape medication

Ceftriaxone very rarely (≥1/10,000 to <1/1,000) causes allergic reactions (i.e. severe acute hypersensitivity reactions and anaphylactic shock;. EMS personnel are trained how to recognize and treat such allergic reactions.

If a patients starts showing signs of allergic reaction, ceftriaxone therapy will be discontinued and appropriate emergency measures will be taken. If needed, the national ambulance-protocol "Anaphylactic reaction' will be followed; epinephrine, clemastine, salbutamol can be given if needed.

Study procedures

Apart from the timing of blood culture and ceftriaxone administration, there is no difference in treatment of the intervention group and the control group. In order to assess the defined study parameters we will use patients' records.

If informed consent cannot be obtained beforehand, permission will be asked for further follow-up when the patient's condition is stabilized (deferred consent). Informed consent (or deferred consent if applicable) will be obtained from all eventual participants.

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The treating physician can decide to withdraw a subject from the study for any sort of medical reason.

Baseline measurements

A retrospective data sample of patients, with severe sepsis and who were brought in with by the EMS, will be collected in all participating hospitals, in order to have baseline measurements (prior to the start of the PHANTASi trial) which will serve as comparison data set to investigate, together with the step wedge design, the effects the trial has on usual care. Data will be collected at the same period for 20-30 patients per hospital. Baseline measurements will include time to antibiotics at the ED, and documentation of vital parameters by EMS personnel and ED nurses.

Collection of blood samples to analyse biomarkers

With the consent of the patient and together with the standard blood samples collected at the ED, a pair of extra blood samples will be obtained and processed in the clinical chemistry laboratory of VUmc. The blood samples will be collected at three different time points: at entry ED (day 1), day 3 of admission and day 7 of admission (if applicable). These will be processed and stored in a freezer of -80 degrees Celsius, for the purpose of future investigation of the course of different biomarkers. The body material will be stored for up to 15 years, permission

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for storage will be obtained beforehand. The extra blood sample collection will only take place in the following participating hospitals: Academic Medical Centre Amsterdam (AMC), Amstelland Ziekenhuis, BovenIJ Ziekenhuis, Onze Lieve Vrouwe Gasthuis (OLVG) location East and West, , Maastricht Medical Centre and the VU Medical Centre (VUmc).

Power and sample size

The number of patients that need to be included in the randomized clinical trial part of the study is based on the effect of pre-hospital administration of antibiotics on 28-day mortality by trained EMS personnel. After training, we anticipate to see an absolute reduction in 28-day mortality as a result of this pre-hospital administration of antibiotics of at least 6%. If after training the 28-day mortality under standard care is 40% and mortality is reduced to 34% by pre-hospital administration of antibiotics, then the maximum required sample size to achieve 80% power (in case two-sided testing and incorporating three formal interim analyses for efficacy) is 2144 (1072 per group).

Data collection and follow up

Main and secondary study parameters will be derived from patient's records and will be retrieved for all the patients transported. The effect of the pre-hospital administration of antibiotics will be assessed using data from all patients included after the training in each region is completed and evaluation will be on an intention-to-treat basis. To assess the effect of training on primary and secondary outcomes measures, we will retrieve patient records for all the patients transported in the study period who meet the inclusion criteria. Because of the step-wedge design, the patients with suspected sepsis transported before the training of EMS personnel started will be used as controls. These controls will be compared regarding the before mentioned study outcomes with those transported after training and who were randomized to receive usual care (control group).

Randomisation (prehospital)

Patient's records of (electronic) EMS case report forms will be used to determine

- Demographic details
- Eligibility criteria
- Exclusion criteria (if excluded)
- Urgency of ambulance ride
- Vital signs (temperature, heart rate, blood pressure, respiratory rate, oxygen saturation, Glasgow Coma Scale,[19] total IV fluids administered, vasopressor administration)
- National Early Warning Score (NEWS)[20]
- Time to antibiotics (if in intervention group)
- Interventions (total IV fluids administered, vasoactive administration, antibiotic administration)
- Description of adverse events and serious adverse events (complications related directly to intervention), severity of adverse events and relation to treatment
- Severity of sepsis (sepsis, severe sepsis, septic shock)

Measurements (at the ED)

Patients' records of hospital admission will be used to determine

- Demographics details
- Comorbidities (Charlson comorbidity index score)
- National Early Warning Score (NEWS)
- Administration of prior antibiotics (till seven days before)
- Vital signs (temperature, heart rate, blood pressure, respiratory rate, oxygen saturation
- Glasgow Coma Scale, arterial blood gas, lactate, biochemistry, haematological and coagulation measurements)
- Interventions (total IV fluids administered, vasoactive administration, antibiotic administration)
- Time to antibiotics (door to needle time)

Hospital follow up data

- Time and duration of antimicrobial therapy given
- Severity of sepsis (sepsis, severe sepsis, septic shock)
- Microbiology (positive cultures, resistance patterns, source of infection)
- Description of adverse events and serious adverse events (complications related directly to intervention), severity of adverse events and relation to treatment)
- Length of stay at ICU/MCU and at hospital
- In hospital mortality
- 28 day mortality (if a patient is no longer hospitalized, his/her general practitioner will be contacted in order to retrieve mortality within 28 days)
- Long term mortality (90 days)
- QoL (one month post discharge)

Interim analysis

The interim analyses are planned as soon as the primary outcome for the first 25, 50 and 75 percent of patients has been observed. The O'Brien-Fleming stopping criteria will be used to control the overall (two-sided) type I error probability at the 5% level. This means that interim analyses will be performed

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when data of the first 536, 1072 and 1608 patients are available. At the planned interim analyses, we will test for a difference in the 28-days mortality at two-sided significance levels of 0.005%, 0.42% and 1.94%, respectively. The final analysis will be performed at a significance level of 4.29%. When the 28-mortality probabilities are 34% and 40% in intervention and control group, respectively, the cumulative probability of stopping and rejecting the null hypothesis at each of the three interim analyses equals 4.3%, 19.6% and 55%. Overall power is 80%. If mortality under standard care is less than 40% the power to detect an absolute decrease of 6% as a result of pre-hospital administration of antibiotics will be even higher.

The effect of training on 28-day mortality will be estimated using data from patients suspected of sepsis and randomized to receive standard care and patients transported after start of the randomized trial in their region matching the inclusion criteria but not participating in the trial (the standard care after-training group) and those suspected with sepsis (matching the inclusion criteria) and transported before the personnel was trained (the standard care before-training group). As training could not be randomized the estimate will need to be corrected for relevant parameters (such as ambulance region and trimester of transportation). No formal power analysis is performed for assessing the effects of training.

Premature termination of the study

A formal interim analysis will be performed after 28-day mortality has been observed for the first 536, 1072 and 1608 patients included, respectively. If a statistically significant difference is apparent at one of these interim analyses, the trial will be stopped and pre-hospital administration of antibiotics will be concluded effective if the observed 28-day mortality is lower in the intervention group. If at one of these interim analyses a significant difference is found in favour of standard care, the trial will also be stopped and we will conclude that pre-hospital administration has an adverse effect.

Safety

All adverse events (AE) and serious adverse events (SAE) observed will be recorded and study data will be monitored according to Good Clinical Practice (GCP) guidelines by an independent monitor (quality officer).

All serious adverse events (SAEs) will be reported to the ethics committee. A study suspension and formal ethics committee consultation will ensue if the incidence of SAE's in the intervention group exceeds 10% of included patients. It is predominantly an allergic reaction to antibiotics, which is anticipated to be the least unlikely SAE.

Ethical Considerations

Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki (59th WMA General Assembly, Seoul, 2008) and in accordance with the Medical Research Involving Human Subjects Act (WMO). The Medical Ethical Committee of the VU Medical Centre (reference number: 2013.458; NL42001.029.13) and all ethical bodies of each participating site approved the study (see Appendix C) .

Recruitment and consent

The ethical implications of the study design are complex. This is a therapeutic study, which often concerns incapacitated adults in an emergency situation. Relatives or other legal representatives are often either not present, or in a state of acute emotional shock. Hence, it is possible that there is no possibility to ask patients or relatives for informed consent. Patients suspected of sepsis must be treated with antibiotics at the emergency department. Thus, the intervention used in this trial is actually usual medical care but given at an earlier stage. All effort will be made by EMS personnel to ask for informed consent if the acuity of the situation allows this. If this is not the case, then, as the intervention is a medical necessary one, the antibiotics will be given after ensuring there is no contra-indication. All patients, who have not given prior informed consent, will be asked deferred consent: they will be informed of the study afterwards, and are then free to decline further participation. All their data will then be removed from the trial.

Permanent discontinuation

Patients who initially consent but later withdraw consent will be asked to agree to allow current data to be used for analysis. If they agree for their existing data to be used, they will be included and analysed on an intention-to-treat basis.

Handling and storage of data and documents

All data will be stored in a central database. Data will not be directly traceable to individual patients, as all patients are coded. The key to the code will only be available to the primary investigators and research nurses.

Monitoring

Study data will be monitored according to Good Clinical Practice (GCP) guidelines by an independent monitor (quality officer). Monitoring visits will take place to ascertain that all relevant documents are in place and the trial is conducted according to the study protocol and Standard Operating Procedures.

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For a selected number of subjects, the Informed Consents will be checked. During onsite monitoring, Source Data Verification will be performed (control whether data in the Case Report forms (research forms/questionnaires) match source data such as patient records, laboratory results etc.). The intensity of this verification is related to the risk of the study. Data, that will be checked in any case are the inclusion and exclusion criteria and the primary outcomes of the study, the monitor will also check whether all (S) AE' s and SUSARs are appropriately reported within the timelines as required by laws and regulations.

Statistical analysis

Trial profile

We plan a Consolidated Standards of Reporting Trials (CONSORT) diagram to detail the movement of patients through the study. This diagram will include total patients screened, number who met inclusion and exclusion criteria, and number included in the study.

Descriptive statistics

Quantitative data will be recorded for the number of patients reaching the primary endpoints and the secondary endpoints survival and complications.

Univariate analyses

Regarding the effect of pre-hospital administration of antibiotics, 28-day mortality between the group receiving pre-hospital administration of antibiotics and those randomized to receive standard care (both after training of EMS personell) will be compared by means of chi-square tests at interim analyses and at the final analyses. Significance levels that will be used are given in section 1.4 (O'Brien-Fleming alpha-spending functions are used). Secondary outcome parameters will be compared between groups randomized to standard care and to receiving pre-hospital administration of antibiotics at the final analysis. Dichotomous outcomes (proportion of patients experiencing any adverse event, proportion of patients transferred to intensive or medium care and proportion of patients unnecessarily treated with antibiotics) will be compared using chi-square tests or Fisher's exact test when appropriate. Continuous outcomes (length of hospital stay, door-to-needle time and response time) will be compared with independent samples t-test or the non-parametric Mann-Whitney U-test in case of skewed distribution. All analyses will be performed according to intention-to-treat principle. Quality of life scores will be compared within the subgroup still four weeks after discharge from the hospital using independent samples t-test or Mann-Whitney U-test.

Multivariate analyses

Longitudinal data-analysis techniques will be used to evaluate the effect of training on primary and secondary outcome parameters. Generalized Estimating Equations (GEEs) will be used, which correct for observations made within the same ambulance region being more alike. The 28-day mortality and proportion of patients suspected with sepsis before and after training will be compared using GEE analysis for binary outcome data, an exchangeable correlation structure and robust standard errors. Continuous outcome data will also be compared using GEE analyses. Time since start of the (stepped-wedge) study and time since training (region specific) will be included in the models to distinguish temporal fluctuations in outcomes unrelated to training from those related to the training. In case the number of ambulance regions is small a fixed effect for ambulance region will be used and analysis will be done using generalized linear models (for dichotomous outcome parameters) and linear regression (for continuous outcome parameters).

Missing data

Analyses will be done on an intention to treat basis. We will strive to obtain the primary outcome (28-day mortality) for patients included in the trial by following up patients after discharge and contact the family doctor if needed. An electronic CRF is used to ensure completeness of baseline data. Quality of life is considered a secondary outcome and missings are likely to occur as a result of non-response. Missing quality of life scores will not be imputed. Characteristics of the responders will be summarized and compared with the complete subgroup of patients who are still alive at 28-days and the non-responders.

Subgroup analyses

Subgroup analyses will be performed for all outcome variables and for subgroups (a.o age, comorbidities and NEWS) defined by severity of sepsis (sepsis, severe sepsis and septic shock). To perform subgroup analysis for the univariate statistical analyses that evaluate the effect of pre-hospital administration of antibiotics, standard logistic and linear regression techniques will be applied. Models will include main effects of the intervention variable and the severity of sepsis together with their interaction. If the interaction is significant, separate estimates of the intervention effect will be calculated by performing the corresponding univariate analysis separately in the strata defined by staging. For the longitudinal multivariate analyses that evaluate the effect of training, the main effect of the severity of sepsis and the interaction between time since start

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of treatment and stage of sepsis will be added to the GEE models. If the interaction is significant, separate estimates of the effect of training will be calculated by performing the original GEE analysis (as described under multivariate analyses) separate in each of the three subgroups defined by staging.

Discussion

Treatment of a critically ill patient requires teamwork and an optimally functioning acute care chain. This applies in particular to patients with severe sepsis, who preferably should be treated in a well-organized team of healthcare providers consisting of members from the prehospital as well as the hospital area. While in the past decades, modern medicine has become increasingly sophisticated, and the treatment of diseases, such as heart failure and cancer is greatly improved, establishing a clinical care pathway for sepsis throughout the whole acute care chain still remains a challenge.

Timely recognition and rapid initiation of treatment of sepsis appears crucial, but recognizing sepsis is not always easy: the symptoms are often non-specific and can simulate various other diseases as well.[21] Furthermore, recognition and documentation of sepsis by EMS personnel is poor (%),[22-25] as well as by physicians.[26;27] A large proportion of patients with severe sepsis and septic shock are missed in the prehospital setting[22] and are transported with a low urgency ride.[23] The information transfer is hereby often incomplete or not entirely accurate (from the general practitioner to the EMS personnel/hospital or from the EMS to the ED) causing substantial delays in initiating treatment. Moreover, delays in the administration of antibiotics are partly caused by extensive diagnostic work-up, while in one third of the patients, clinical history and physical examination are sufficient enough to choose the right antibiotics.[28] Therefore, much can be gained by training EMS personnel and getting them skilled enough in recognizing sepsis and initiating treatment in the prehospital setting. Indeed, out of hospital care has a positive impact on improving in hospital processes for septic patients.[17]

In order to minimize the chance of wrongly enrolling patients such as those with heart failure or trauma, abnormal temperature was made an obligatory inclusion criterion, as SIRS is common in the ED, with only a quarter of the patients presenting with SIRS having an infection.[29] We hope to include a sicker patient population than the self-referrals with sepsis presenting to the ED, since most of the severe sepsis patients are transferred to the hospital by EMS personnel.[18;23;24] Through this trial awareness of sepsis will likely increase and usual care may improve, which makes it difficult to differentiate between the positive effects of intervention. Hence, we decided to include baseline measurements prior to start of the trial.

In summary, the PHANTASi trial is the first prospective investigator-initiated randomized controlled trial to investigate the effects of early prehospital antibiotic treatment for sepsis patients together with the effect of training EMS personnel. With the PHANTASI trial, a national collaboration between emergency medical services and hospitals has been established and the collaboration of prehospital and hospital healthcare providers is promoted in order to let the entire acute care chain function as a whole. The goal of this project is to increase the awareness for sepsis and improve the integrated care for septic patients. Results of this trial may help to develop new guidelines for the treatment of sepsis in the prehospital and hospital setting.

Trial status

At the time of submission, the study is actively recruiting patients since June 2014, with a total of 35 participating centres. Currently, over 2000 participants have been enrolled in the study.

List of abbreviations used

- **CRF**: Case Report Form
- **ED** :Emergency Department
- **EGDT**: Early Goal Directed Therapy
- **EMS**: Emergency Medical Services
- **GEEs**: Generalized Estimating Equations
- **ICU**: Intensive Care Unit
- **ICMJE:** International Committee of Medical Journal Editor
- **MCU**: Medium Care Unit
- **NEWS**: National Early Warning Score
- **SIRS**: Systematic Inflammatory Response Syndrome
- **SAE**: Serious Adverse Events
- **SSC**: Surviving Sepsis Campaign
- **QoL**: Quality of Life

Competing interests

The authors declare that they have no competing interests.

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Collaboration

Dutch Association of Emergency Physicians (Nederlandse Vereniging voor SEH artsen - NVSHA)
Ambulancezorg Nederland

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