Prehospital antibiotics in the ambulance for sepsis: a multicentre, open label, randomised trial

*Nadia Alam, Erick Oskam, Patricia M Stassen, Pieternel van Exter, Peter M van de Ven, Harm R Haak, Frits Holleman, Arthur van Zanten, Hien van Leeuwen-Nguyen, Victor Bon, Bart A M Duineveld, Rishi S Nannan Panday, Mark H H Kramer, Prabath W B Nanayakkara, on behalf of the PHANTASi Trial Investigators and the ORCA (Onderzoeks Consortium Acute Geneeskunde) Research Consortium the Netherlands**

Lancet Respir Med 2018; 6: 40–50

Published Online November 28, 2017 http://dx.doi.org/10.1016/S2213-2600(17)30469-1

See Comment page 5

*Investigators are listed in the appendix

Section of Acute Medicine, Department of Internal Medicine, VU University Medical Center, and The Institute for Cardiovascular Research (ICAR-VU), Vrije Universiteit, Amsterdam, the Netherlands (N Alam MD, B A M Duineveld MD, R S Nannan Panday MD, Prof M H H Kramer FRCP, P W B Nanayakkara FRCP); Department of Epidemiology and Biostatistics, VU University Medical Center, Amsterdam, Netherlands (P M van de Ven PhD); Department of Emergency Medicine, Albert Schweitzer Hospital, Dordrecht, Netherlands (E Oskam MD); Section of Acute Medicine, Department of Internal Medicine, Maastricht University Medical Center, Maastricht, Netherlands (P M Stassen PhD); Ambulance Amsterdam, Amsterdam, Netherlands (P van Exter MD, V Bon MSc); Section of Acute Medicine, Department of Internal Medicine, Maasstad Hospital, Rotterdam, Netherlands (H van Leeuwen-Nguyen MD); Section of Acute Medicine, Department of Internal Medicine, Máxima Medical Center, Eindhoven, Netherlands and Department of Internal Medicine, Division of General Internal Medicine, Maastricht University Medical Center and CAPHRI School for Public Health and Primary Care, Ageing and Long-Term Care, Maastricht, Netherlands (Prof H R Haak PhD); Section of Acute Medicine, Department of Internal Medicine, Academic

Summary

Background Emergency medical services (EMS) personnel have already made substantial contributions to improving care for patients with time-dependent illnesses, such as trauma and myocardial infarction. Patients with sepsis could also benefit from timely prehospital care.

Methods After training EMS personnel in recognising sepsis, we did a randomised controlled open-label trial in ten large regional ambulance services serving 34 secondary and tertiary care hospitals in the Netherlands. We compared the effects of early administration of antibiotics in the ambulance with usual care. Eligible patients were randomly assigned (1:1) using block-randomisation with blocks of size 4 to the intervention (open-label intravenous ceftriaxone 2000 mg in addition to usual care) or usual care (fluid resuscitation and supplementary oxygen). Randomisation was stratified per region. The primary outcome was all-cause mortality at 28 days and analysis was by intention to treat. To assess the effect of training, we determined the average time to antibiotics (TTA) in the emergency department and recognition of sepsis by EMS personnel before and after training. The trial is registered at ClinicalTrials.gov, number NCT01988428.

Findings 2698 patients were enrolled between June 30, 2014, and June 26, 2016. 2672 patients were included in the intention-to-treat analysis: 1535 in the intervention group and 1137 in the usual care group. The intervention group received antibiotics a median of 26 min (IQR 19–34) before arriving at the emergency department. In the usual care group, median TTA after arriving at the emergency department was 70 min (IQR 36–128), compared with 93 min (IQR 39–140) before EMS personnel training (p=0·142). At day 28, 120 (8%) patients had died in the intervention group and 93 (8%) had died in the usual care group (relative risk 0·95, 95% CI 0·74–1·24). 102 (7%) patients in the intervention group and 119 (10%) in the usual care group were re-admitted to hospital within 28 days (p=0·0004). Seven mild allergic reactions occurred, none of which could be attributed to ceftriaxone.

Interpretation In patients with varying severity of sepsis, EMS personnel training improved early recognition and care in the whole acute care chain. However, giving antibiotics in the ambulance did not lead to improved survival, regardless of illness severity.

Funding The NutsOhra Foundation, Netherlands Society of Internal Medicine (NIV).

Introduction

Sepsis is a complex syndrome associated with high morbidity and mortality. Although there has been a decline in mortality in the past two decades, the total number of deaths from sepsis is still rising due to increasing incidence.[1–6] However, this rise in incidence and decline in mortality can partly be attributed to the coding artifact, wherein milder cases are also recognised and coded as sepsis.[7] Hospitalisations[8,9] for this condition are accounted as the most expensive of all conditions.[10] Wang and colleagues[11] reported that more than half of patients with severe sepsis in the USA are initially seen in the emergency department. Additionally, over half of the patients with sepsis presenting at the emergency department arrive by ambulance.[12–14]

Early recognition and initiation of therapy is crucial in the management of sepsis. One of the cornerstones of therapy is the timely administration of antibiotics, preferably within 1 h after arrival at the emergency department. This approach was endorsed by the Surviving Sepsis Campaign (SSC) guidelines[15] after retrospective studies[16–18] showed that prompt antimicrobial therapy was associated with improved survival, and that any delay in administration of antibiotics after development of septic shock was associated with an increase in mortality of almost 7·6% per hour.[16] However, all studies which concluded that early antibiotic administration was associated with improved survival were retrospective and uncontrolled and thus selection bias might have affected the results. Whereas prospective observational studies have failed to show any association between early antibiotics and mortality benefit,[19–21] the mainstream doctrine of early antibiotic administration within an hour of sepsis recognition is still upheld.[22] To date, no prospective randomised controlled trial has been done to investigate the effects of early antibiotic administration in patients with suspected sepsis.

Next to general practitioners, emergency medical services (EMS) personnel are the first health-care providers

Research in context

Evidence before this study

Sepsis is a common, life-threatening illness that affects millions of people globally. Prognosis of patients with sepsis can be improved by early recognition and early intervention. One of the cornerstones of therapy is the timely administration of antibiotics, preferably within an hour of sepsis recognition. Emergency medical services (EMS) personnel have already made substantial contributions to improving care for patients with time-dependent illnesses, such as trauma and myocardial infarction; patients with sepsis might also benefit from timely prehospital care. However, knowledge and awareness about sepsis among EMS personnel is low leading to poor recognition of sepsis in ambulances. We searched PubMed for studies investigating the association between the timing of antibiotic administration and mortality from inception to Aug 21, 2017, with the terms "sepsis AND (antibiotics or antimicrobial therapy) AND clinical trial AND adults" without language restrictions. We found no randomised controlled trials investigating the effect of early antibiotic therapy in patients with sepsis. Sterling and colleagues did a systematic review with a meta-analysis. They found no significant improvement in survival when antibiotic administration occurred within 3 h of emergency department triage or within 1 h of severe sepsis and septic shock recognition. Our search identified several other retrospective and prospective studies, although with conflicting results.

Added value of this study

The PHANTASi trial is the first randomised controlled trial investigating the effects of early antibiotic treatment after training EMS personnel in recognising sepsis. In patients with varying severity of sepsis, training EMS personnel significantly improved recognition of sepsis as well as reducing time to antibiotics (TTA). However, the intervention did not lead to a significant difference in mortality in our patient population with varying severity of sepsis.

Implications of all the available evidence

Currently, we do not advise antibiotic administration in the ambulance in patients with suspected sepsis. However, training EMS personnel improves early recognition of sepsis and processes of care in the emergency department.

University Medical Center, Amsterdam, Netherlands (F Holleman PhD); **and Department of Intensive Care Medicine, Gelderse Vallei Hospital, Ede, Netherlands** (A van Zanten PhD)

Correspondence to:
Dr Prabath W B Nanayakkara, Section of Acute Medicine, Department of Internal Medicine, VU University Medical Center, De Boelelaan 1118, 1081 HZ, Amsterdam, Netherlands
p.nanayakkara@vumc.nl

See Online for appendix

that patients will encounter. In the past, EMS personnel have made substantial contributions to improving care for patients with other serious time-dependent conditions, such as acute coronary syndrome, poly-trauma, and stroke.[23–25] Patients with (severe) sepsis and septic shock might also benefit from timely prehospital care by EMS personnel. Studies have shown that recognising sepsis and providing these patients with prehospital care by EMS personnel accelerated and improved care in emergency departments.[26,27] However, knowledge and awareness about sepsis among EMS personnel is low[28] leading to poor recognition of sepsis in ambulances,[13,29,30] which suggests that there is room for improvement.

Therefore, we designed the first prospective randomised controlled multicentre Prehospital Antibiotics against Sepsis (PHANTASi) trial to test the hypothesis that increasing the awareness of sepsis through training of EMS personnel in recognising and initiating treatment with early prehospital administration of antibiotics leads to increased survival of patients with sepsis, severe sepsis, or septic shock compared with those patients receiving usual care.

Methods

Study design and participants

We did this nationwide randomised controlled open-label trial in ten large regional ambulance services serving 34 secondary and tertiary care hospitals in the Netherlands, where 25 regional ambulance services provide prehospital service to 94 emergency departments.[31]

Patients were recruited by EMS personnel. Eligible patients were at least 18 years of age, had a diagnosed or suspected infection, a temperature higher than 38°C or less than 36°C, and at least one other criterion of the systemic inflammatory response syndrome (heart rate >90 beats per min or respiratory rate >20 per min, or both). An abnormal white-blood-cell count was not taken into account as a criterion due to lack of diagnostic tests in the ambulance. An abnormal temperature was used as an obligatory inclusion criterion to minimise the chance of incorrectly including patients with other diagnoses (eg, heart failure). Sepsis severity was categorised into three groups according to the 2001 SSCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference guidelines:[32] uncomplicated (non-severe) sepsis, severe sepsis, and septic shock. The sepsis classification was done by the investigators after inclusion of the patients and was done by means of admission letters, discharge letters, vital parameters, and laboratory values, which all could be found in the electronic patient record. Patients with sepsis and organ dysfunction were classified as having severe sepsis. Organ dysfunction was defined as one or more of the following: arterial hypoxaemia, acute oliguria, increase in creatinine level, coagulation abnormalities, ileus, thrombocytopenia, hyperbilirubinaemia, hyperlactataemia, and altered mental status[32] (for a detailed description of the criteria see the appendix pp 5, 6). Patients with known allergy to ceftriaxone or to other beta-lactam antibiotics, with known pregnancy, or suspected prosthetic joint infections were excluded from the study (see the appendix p 5 and study protocol).

The study was done according to the principles of the Declaration of Helsinki. The study protocol was approved by the medical ethical committee of the VU

University Medical Centre, the coordinating centre, and all ethical bodies of each participating hospital. The trial was overseen by an independent monitoring board which monitored the study data according to the Good Clinical Practice guidelines[33] and also did source control and data verification by visiting the participating centres. Furthermore, the monitoring board also verified whether all the serious adverse events and suspected unexpected serious adverse reactions were appropriately reported.

Due to the complexity of the study, the ethics committees granted approval to obtain deferred consent when necessary. Informed consent before study enrolment or deferred consent was obtained from all patients or their legal representatives or surrogates. All effort was made by EMS personnel to obtain informed consent before study inclusion provided the acuity of the situation allowed it. More details can be found in the study protocol.[34]

Randomisation and masking

Eligible patients were randomly assigned (1:1) to the intervention group or usual care group using block-randomisation with blocks of size 4. Randomisation was stratified per region. Lists with random sequences were centrally generated and consecutively numbered indistinguishable envelopes containing a note with the group assignment (intervention or usual care) were put in all participating ambulances by the local research team. After obtaining one sample for blood culture analysis, the patients in the intervention group received open-label ceftriaxone 2000 mg intravenously in the ambulance in addition to usual care (fluid resuscitation and supplementary oxygen). Patients in the usual care group received usual care only. Although EMS protocols for critical illnesses, such as trauma or acute coronary syndrome, are very extensive, existing national EMS guidelines for sepsis were very brief. Therefore, we modified the local EMS guidelines in the participating ambulance regions by adding a separate comprehensive sepsis protocol with the aim of prompt recognition and treatment of sepsis in the prehospital setting. Existing treatment policies (eg, choice of antibiotics, number of blood cultures to obtain) for patients with sepsis in the participating hospitals remained unaltered.

Procedures

EMS transport in the Netherlands is divided into three categories, with category A1 as the highest urgency (life-threatening situation), category A2 as urgent (not immediately life-threatening), and category B as non-urgent[35] (appendix p 18). The emergency medical dispatch centre assesses the urgency of EMS transport; if necessary the urgency category can change during the journey to hospital. The triage system used to determine the clinical severity and urgency is called the Advanced Medical Priority Systems (AMPDS), of which the automated version (ProQA) is used in the Netherlands.[36]

Before initiation of the study, EMS nurses in the Netherlands received no specific training in recognising and treating sepsis and no educational materials about sepsis were available. Before the start of the trial, all participating EMS personnel were trained to recognise all forms of sepsis promptly and effectively. The research team organised team training for the EMS personnel in collaboration with the training coordinators from the local ambulance regions. The curriculum was written and training was given by the members of the research team and was implemented sequentially in the participating regions (appendix p 3). For some regions, the train-the-trainer method was used: members of the research team trained site investigators so that they could train other site members in turn. More than 750 EMS personnel of the participating ambulance regions were trained in recognising and treating sepsis in the prehospital setting.

Besides training the EMS personnel to recognise sepsis and to integrate this in their daily work, we used social media and mass media channels to promote the study among EMS personnel and general practitioners with the aim of increasing awareness about sepsis and thereby improving recognition and management of these patients in the acute care chain. Additionally, multiple training sessions and briefings were held for all other stakeholders, including emergency department personnel (nurses and doctors) and physicians from different specialties before initiation of the trial. A handbook of the PHANTASi trial with standard operating procedures was made available to all team members and participating centres. Site visits were done regularly by members of the research team and an independent team of auditors to assess the management and proper follow-up of the study, and if necessary additional feedback and training were given. Monthly newsletters were distributed to the EMS and hospitals to keep everyone involved and updated.

The effect of training was assessed by comparing time to antibiotics (TTA) in the group randomly assigned to usual care with TTA in a prospective cohort of patients meeting the inclusion criteria for the trial but transported before ambulance personnel received training. Due to logistic and ethical reasons this comparison was restricted to the three largest ambulance regions (Amsterdam, Dordrecht, and Maastricht). Additionally, we measured the recognition and documentation of sepsis by EMS personnel in the largest ambulance region (Amsterdam) before and after the training.

Outcomes

The primary outcome was all-cause mortality at 28 days. Secondary outcomes were the number of misdiagnoses in patients enrolled in the study by EMS personnel, mortality during hospital stay and within 90 days, length of hospital stay, intensive care unit (ICU) admission, length of stay in the ICU, TTA in the emergency department for the usual

care group and TTA before hospital arrival for the intervention group, microbiological data, adverse events, and quality of life 1 month after discharge as measured with the SF-36 questionnaire.

Statistical analysis

Analyses were done according to a previously reported statistical analysis plan.[34] Briefly, the sample size calculation was based on the effect of training and prehospital administration of antibiotics on 28 day mortality by trained EMS personnel. After training and with the implementation of prehospital administration of antibiotics on top of usual care, we anticipated an absolute reduction in 28 day mortality of at least 6%. The maximum required sample size to achieve 80% power was 2144 patients (1072 per group; assuming two-sided testing at an overall 5% significance level while incorporating formal interim analyses for efficacy after observing outcomes of the first 25%, 50%, and 75% of patients and using the O'Brien-Fleming alpha-spending function). No formal power analysis was done for assessing the effects of training. We analysed all data according to the intention-to-treat principle.

Continuous variables are reported as means and SDs or medians and IQRs and categorical variables as proportions. Dichotomous outcomes were compared using χ^2 tests or Fisher's exact test when appropriate. Continuous outcomes were compared with independent samples using the *t* test or the non-parametric Mann-Whitney *U* test when variables were not normally distributed. We used the Kaplan-Meier method and log-rank test to compare survival curves from randomisation until 28 days. Both relative risks and risk differences were calculated as effect sizes together with their 95% CIs. Subgroup analyses were done for the primary outcome for the following variables: age (<65 or ≥65 years), National Early Warning Score (NEWS [<5 or ≥5]),[37] systolic blood pressure (≤100 or >100 mm Hg), and severity of sepsis (ie, non-severe sepsis, severe sepsis, or septic shock). In 2016, Sepsis-3 criteria[38] were introduced so we also did a subgroup analysis after retrospectively categorising our population according to quick Sepsis-related Organ Failure Assessment (qSOFA) criteria (<2 or ≥2). qSOFA is a bedside clinical score to promptly identify patients with possible sepsis who are at risk for a poor outcome.[38] This score consists of three clinical variables: respiratory rate of at least 22 per min, systolic blood pressure less than 100 mm Hg, and altered mental status. The results of these subgroup analyses are presented in a forest plot. TTA was compared using a generalised estimating equation analysis with the log of TTA as the dependent variable and an indicator for pre-training or post-training as the independent variable. An exchangeable correlation structure was used to take into account possible correlation of outcomes for patients transported within the same ambulance region. Pre-training and post-training comparisons for other outcomes were descriptive only. All analyses were done with IBM SPSS 20.0 and R 3.4. Windows 64 bit, with $p<0{\cdot}05$ considered statistically significant. The trial is registered at ClinicalTrials.gov, NCT01988428.

Role of the funding source

The sponsor had no role in study design, data collection, data analysis, data interpretation, or in the writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

2698 patients were enrolled between June 30, 2014, and June 26, 2016, of whom 1548 were assigned to the intervention and 1150 to the usual care group (figure 1). 18 were lost to follow-up, while eight withdrew consent, leaving 2672 for the intention-to-treat analysis (1535 in the intervention group and 1137 in the usual care group). Some patients who were eligible for the study were excluded for several reasons, for example patients with a language barrier, patients who were not able to give informed consent due to their mental state (eg, pre-existing

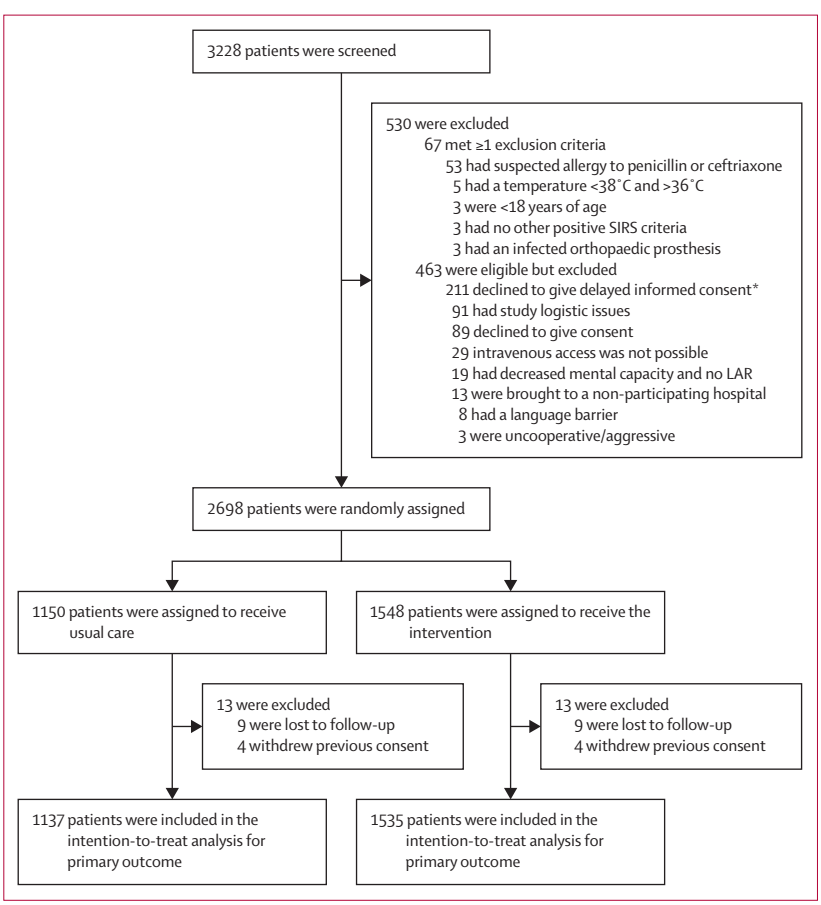

Figure 1: **Trial profile**
SIRS=systemic inflammatory response syndrome. LAR=legally authorised representative. *Informed consent could not be taken due to the severity of their illness and deferred consent was sought by the research team at a later stage.

	Usual care group (n=1137)	Intervention group (n=1535)
Age (years)	72·5 (14·1)	73·0 (13·6)
Sex		
Male	650 (57%)	885 (58%)
Female	487 (43%)	650 (42%)
Charlson comorbidity score	1 (1–3)	1 (1–3)
Method of referral		
General practitioner	816 (72%)	1126 (73%)
Other specialist	23 (2%)	36 (2%)
Self-referral	278 (24%)	344 (22%)
Unknown	20 (2%)	29 (2%)
Urgency ambulance ride		
A1: life threatening	492 (43%)	659 (43%)
A2: urgent	561 (49%)	757 (49%)
B: non-urgent	71 (6%)	107 (7%)
Unknown	13 (1%)	12 (1%)
Patients already on oral antibiotics before randomisation	255 (22%)	322 (21%)
National Early Warning Score (in the ambulance)*		
0	1 (<1%)	0
1–4	145 (19%)	192 (19%)
5–6	241 (31%)	306 (30%)
≥7	382 (50%)	521 (51%)
qSOFA score (in the ambulance)†		
<2	872 (83%)	1132 (78%)
≥2	181 (17%)	318 (22%)
DNR policy in place at admission	437 (38%)	609 (40%)
Severity of sepsis		
Non-severe sepsis	424 (37%)	579 (38%)
Severe sepsis	657 (58%)	868 (57%)
Septic shock	37 (3%)	66 (4%)
Other diagnosis	19 (2%)	22 (1%)
(Continued from previous column)		
Organ dysfunction		
Respiratory	378 (34%)	540 (35%)
Tissue perfusion	280 (25%)	276 (18%)
Neurological	239 (21%)	340 (22%)
Cardiovascular	119 (11%)	180 (12%)
Renal	79 (7%)	119 (8%)
Haematological	15 (1%)	25 (2%)
TTA before arriving at the ED (min)	..	26 (19–34)
Intravenous fluids administered prehospital		
n (%)	418 (37%)	986 (64%)
Median total (mL)	500 (500–500)	500 (300–500)
Mean total (mL)	450·7 (185·8)	447·1 (247·9)
Intravenous fluids administered at ED		
n (%)	495 (44%)	629 (41%)
Median total (mL)	1000 (500–1000)	1000 (500–1500)
Mean total (mL)	1026·3 (813·3)	1019·2 (687·0)

Data are n (%), mean (SD), or median (IQR). Intravenous fluids include crystalloids and colloids measuring more than 20 mL in volume and all blood products. DNR=do not resuscitate. qSOFA=quick Sepsis-related Organ Failure Assessment score. TTA=time to antibiotics. ED=emergency department. *n=769 in the usual care group, n=1019 in the intervention group. †n=1053 in the usual care group, n=1450 in the intervention group.

Table 1: **Patient characteristics at baseline**

dementia), or patients in whom it was impossible to gain rapid intravenous access. These patients were not randomly assigned and therefore were not regarded as post-randomisation exclusions.

Demographic and baseline characteristics were similar in both groups (table 1). The groups consisted primarily of patients with sepsis and severe sepsis, with a small fraction of patients having septic shock (66 [4%] in the intervention group and 37 [3%] in the usual care group). Most EMS transports were judged as urgent (A2 category, 1318 [49%]), followed by life threatening (A1, 1151 [43%]), and non-urgent (B, 178 [7%]). Retrospective chart analysis of all charts by a panel of experts, consisting of two acute physicians and an infectious disease specialist, revealed that 22 (1%) patients in the intervention group and 19 (2%) patients in the usual care group had diagnoses other than sepsis. 1942 (73%) patients were referred by a general practitioner and 577 (22%) patients were already on treatment with oral antibiotics at randomisation.

Within 28 days, 120 (8%) patients had died in the intervention group and 93 (8%) in the usual care group (0·95 [95% CI 0·74 to 1·24]; risk difference –0·37 [–2·5 to 1·7]; p=0·78; table 2). Mortality increased with increasing sepsis severity in both groups but no significant differences were found in the two groups when we accounted for these strata using a Mantel-Haenszel test (p=0·61; figure 2B). For patients in the usual care group, a longer TTA was not associated with an increase in 28 day mortality (p=0·23; appendix pp 14). Subgroup analysis for the predefined subgroups did not reveal any subgroup of patients whose 28 day mortality was significantly affected as a result of the intervention (figure 2B).

There were no significant differences in ICU admissions and length of hospital stay, nor in in-hospital or 90 day mortality (appendix p 13). Within 90 days, 178 (12%) patients in the intervention group and 134 (12%) patients in the usual care group died (p=0·87). In total, 155 (10%) patients in the intervention group and 98 (9%) patients in the usual care group (p=0·19) were admitted to the ICU. In the intervention group, 72 (5%) patients were directly admitted from the emergency department to the ICU and in the usual care group 42 (4%) were directly admitted to the ICU. The median length of stay in the hospital was 6 days for both groups.

Initially, we aimed to register time of transfer to the intensive care unit, medium care (patients are admitted to the medium care unit when they are haemodynamically

instable and require extra monitoring and medical care but do not require intubation), or to a normal care ward as a secondary outcome. However, we soon realised that this was an overambitious goal; registration of time of transfer was mostly incomplete and it was logistically difficult for the research team to record these data for all participating hospitals. Therefore, we chose to describe the number of patients who were directly admitted from the emergency department to the ICU.

366 (32%) patients in the usual care group and 517 (34%) patients in the intervention group returned the completed SF-36 form. There was no significant difference in the average physical component score and mental component score between both groups. The average physical component score was 33·8 (SD 11·3) in the usual care group compared with 34·3 (11·5) in the intervention group (p=0·06). The average mental component score was 42·8 (SD 12·7) in the usual care group and 34·3 (11·5) in the intervention group (p=0·46).

During the pilot study, the research team evaluated that the additional interventions related to the study by the EMS personnel took 5–7 min of extra time. Also, from our experience during the pilot study, we chose to use TTA before hospital arrival for the intervention group instead of time to randomisation. Time of randomisation to antibiotics was not always completely documented by the EMS personnel. Due to the acuity of the situation in which EMS personnel have to assess and treat patients, additional administrative actions that require extra time are not a priority. However, it is obligatory for EMS personnel to note any medications given, therefore documentation of the TTA was complete and easily accessible.

The median TTA before arriving at the emergency department for patients in the intervention group was 26 min (IQR 19–34). EMS personnel were able to obtain prehospital blood samples for culture and give antibiotics in 1523 patients (99%) in the intervention group.

In the intervention group, 61 (4%) patients were discharged home from the emergency department, of whom 21 (34%) patients were discharged home with antibiotics. In the usual care group, 923 (81%) of 1137 patients received antibiotics at the emergency department, of which 789 (85%) of 923 received antibiotics within 3 h; 148 (13%) of 1137 patients did not receive antibiotics until arriving at the ward; 16 were discharged without receiving antibiotics at the ED nor received a prescription for antibiotics. 66 (6%) of 1137 patients in the usual care group were discharged home from the emergency department; 28 (42%) of these patients had received one dose of antibiotics at the emergency department and 22 (33%) of these 66 patients were discharged with a prescription for antibiotics.

TTA after arriving at the emergency department in the usual care group was 70 min (IQR 36–128). The median TTA during the baseline measurements before training in the three largest regions was 93 min (IQR 39–140; n=130, p=0·142). This means a shortening of the TTA by 23 min.

	Usual care group (n=1137)	Intervention group (n=1535)	Relative risk (95% CI)	Risk difference (%, 95% CI)	p value
28 day mortality	93 (8%)*	120 (8%)	0·95 (0·74 to 1·24)	–0·37 (–2·5 to 1·7)	0·78
90 day mortality	134 (12%)*	178 (12%)	0·98 (0·80 to 1·21)	–0·20 (–2·7 to 2·3)	0·87
Median TTA in the ED (min)	70 (36–128)	..	..	..	..
TTA in the ED (min)					
0–60	410 (42%)	..	..	..	..
61–120	254 (26%)	..	..	..	..
121–180	125 (13%)	..	..	..	..
181–240	78 (8%)	..	..	..	..
>240	56 (6%)	..	..	..	..
Missing	50 (5%)	..	..	..	..
No antibiotics in the ED	164 (14%)	..	..	..	..
Intensive care unit admission	98 (9%)	155 (10%)	1·17 (0·92 to 1·49)	1·5 (–0·73 to 3·7)	0·19
28 day re-admission	119 (10%)	102 (7%)	..	..	0·0004
Median length of stay (days)					
Intensive care unit	3 (2–8)	4 (2–10)	..	..	0·28
Hospital	6 (3–9)	6 (4–10)	..	..	0·12

Data are n (%) or median (IQR) unless otherwise stated. TTA=time to antibiotics. ED=emergency department. *n=1136.

Table 2: **Outcomes**

1397 (91%) patients in the intervention group and 1030 (91%) patients in the usual care group received antibiotics during the hospital stay. 107 patients in the intervention group and 85 patients in the usual care group did not receive antibiotics in hospital or were discharged from the emergency department without an antibiotic prescription, mainly because a viral infection was suspected. We did not have information on antibiotic use for 31 patients in the intervention group and 22 patients in the control group. Amoxicillin–clavulanic acid was the most frequently used antibiotic, with ciprofloxacin and ceftriaxone the second and third most common (appendix p 17). 986 (64%) patients in the intervention group and 418 (37%) patients in the usual care group received fluids in the ambulance; the mean volume of administered fluids was 447·1 mL (247·9) and 450·7 mL (185·8), respectively (table 1).

The most common foci of infection were the lungs and the urinary tract (appendix p 16). Prehospital blood cultures were positive in 389 (35%) patients in the intervention group compared with 279 (26%) patients in the usual care group (p<0·0001). More Gram-positive bacteria were found in the intervention group than in the usual care group, indicative of a higher contamination risk of blood culture analysis in the prehospital setting. Positive urine cultures were less frequent in the intervention group than in the usual care group (25 [25%] of 1048 *vs* 295 [37%] of 801; p<0·0001), suggesting that

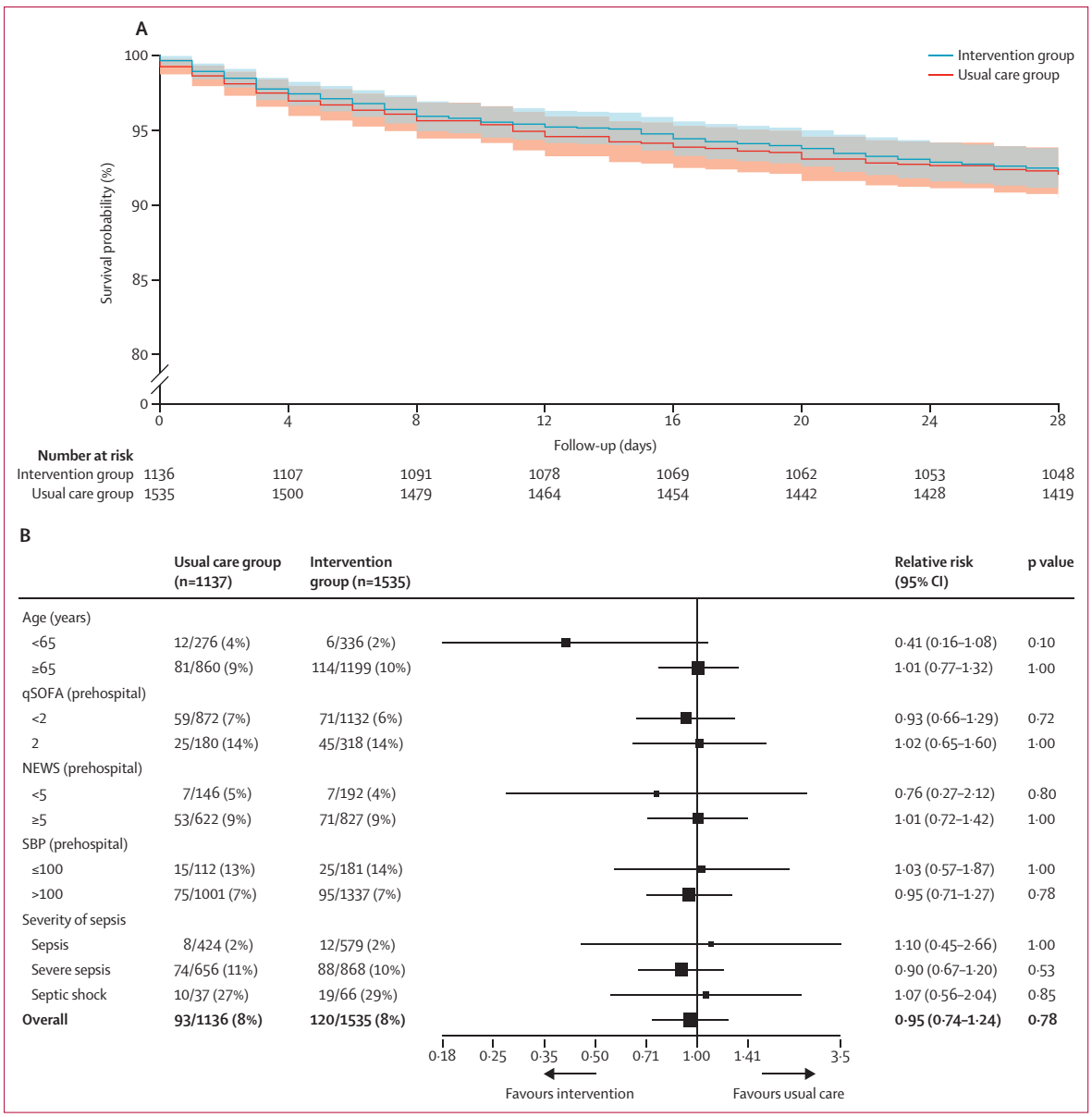

Figure 2: **Probability of survival and subgroup analyses of 28 day mortality**
(A) Kaplan-Meier estimates for the probability of survival at 28 days for patients in the intervention or usual care group. (B) Relative risk for 28 day mortality in the predefined subgroups. Horizontal bar represents 95% CIs. qSOFA=quick Sepsis-related Organ Failure Assessment score. NEWS=National Early Warning Score. SBP=systolic blood pressure (mm Hg).

even one dose of antibiotic can negatively influence culture results. More Gram-negative bacteria were found in cultures from the usual care group, which might be due to the higher number of positive urine cultures with *Escherichia coli*.

Data for the number of blood cultures with bacteria resistant to ceftriaxone in the total population are currently being collected and processed.

There were no serious adverse events, such as anaphylactic shock, in the intervention group. We considered re-admission within 28 days and an allergic reaction as adverse events. 221 patients (8%) were re-admitted within 28 days, 102 (7%) in the intervention group and 119 (10%) in the usual care group (p=0·0004). Seven mild allergic reactions occurred, of which none could be attributed to ceftriaxone.

The predominant protocol violations were randomisation and treatment violations, seen mainly during the first few months of the trial. Randomisation violations resulted in more patients being included in the intervention group; the probable reason for this was the overenthusiasm of EMS personnel wanting to treat as

many patients as possible with antibiotics in the ambulance as this was an open-label study. To achieve this, some EMS personnel purposefully opened the envelopes until they found an envelope instructing randomisation to the intervention group. The research team gave extensive explanation of the importance of randomisation, which led to a subsequent improvement in randomisation. At the end of the study the total number of patients in the intervention group outnumbered the patients in the usual care group by 398. However, in spite of this, there were no differences in baseline characteristics between the groups (table 1). A subanalysis restricted to the approximately 800 patients included in two large ambulance regions where inclusions were more equally distributed between the intervention and usual care groups did not show any significant difference in primary outcome measures (appendix pp 19, 20). Additionally, this analysis yielded estimates for risk difference and relative risk that were in line with the analysis in the whole sample (appendix pp 19, 20). Treatment violations occurred in 40 patients in the usual care group who were given antibiotics and 12 patients in the intervention group who did not receive antibiotics in the ambulance.

Discussion

In this first prospective randomised controlled open-label trial that compared the effects of early prehospital antibiotics with usual care in patients with suspected sepsis, as well as training of EMS personnel, we found that giving prehospital antibiotics led to a time gain of 96 min, but did not lead to a difference in in-hospital, 28 day, or 90 day mortality. Only a small proportion of patients diagnosed with sepsis in the ambulance by EMS personnel had an alternative diagnosis during chart review after hospital discharge. There was a 22 min shortening in the TTA in the emergency department after EMS and emergency department personnel were trained, although this decrease was not statistically significant.

In this trial, we found no beneficial effect of early prehospital antibiotics on mortality. Additionally, we did not find any significant differences in secondary outcomes between the groups. However, unplanned re-admissions within 28 days were significantly lower in the intervention group than in the usual care group. There was no significant difference in the age, comorbidity, and disease severity between the re-admitted patients in both groups and we cannot provide an alternative explanation for the significantly lower unplanned re-admissions in the intervention group. As expected, the quality-of-life score (SF-36) after 1 month was well below that of the general population.[39] However, quality-of-life scores did not differ significantly between the groups.

Global initiatives, such as the international SSC guidelines, have contributed greatly to improving awareness and management of patients with sepsis. The SSC guidelines strongly recommend early administration of antibiotics in patients with suspected or proven (severe) sepsis and septic shock because delayed antibiotic administration is thought to be associated with increased mortality.[15,17,26] In previous studies, the time to (appropriate) antibiotic treatment varied between 115 min and 360 min,[15,17,27,29] whereas most patients in our usual care group received antibiotics within 1 h of presentation to the emergency department. Compliance with SSC guidelines regarding antibiotic therapy was therefore much better in all participating centres compared with other studies.[40–42] For example, the median difference in the TTA in the treatment and usual care group was 96 min which is much smaller than in other studies.[43]

We had a much lower mortality rate in our trial than the predicted mortality of 40%, which was based on large epidemiological studies done mostly in ICU settings and in patients with severe sepsis and septic shock.[16,44] Our study focused on patients with varying degrees of sepsis severity who were brought in by ambulances to the emergency department, whereas previous sepsis studies have focused on intensive care populations with patients mainly with septic shock. Epidemiological data on sepsis, severe sepsis, and septic shock in the prehospital setting in the Netherlands was largely unknown at the time of developing the concept and design of the PHANTASi trial. Despite the fact that our population consisted of only a small fraction of septic shock cases, nearly 80% of the population in the intervention and the usual care group had an overall NEWS of 5 or more, a marker of disease severity at presentation to the emergency department.[45–47] Although our focus on patients presenting to the emergency department makes our study less comparable with previous studies, our study population is a better reflection of the overall emergency department population. Studies showing that early antibiotic treatment is beneficial for reducing mortality found this positive association mainly in patients with more severe illness and a TTA of more than 5–6 h.[48,49] The benefit in survival resulting from early recognition and initiation of antibiotic therapy might not have reached significant levels due to the relatively small number of patients with septic shock in our prehospital population as well as the relatively short TTA in our usual care group. This finding is in accordance with studies that included a general emergency department population of patients with varying severity of disease[20] and with lower mortality rates.[21] Another point that should be taken into consideration is that the TTA describes the TTA administration from the triage time (arrival time at the hospital) and not from time zero, when the infection initially commenced. Time zero, which might be biologically more relevant, is usually unknown and can vary greatly between patients, ranging from hours to days, depending on the severity of the illness.

Before the start of the trial, we did an observational study that showed recognition and documentation of

sepsis by EMS personnel was very poor.[13] However, after training EMS personnel in the Amsterdam region (the largest ambulance region in the Netherlands), we found a statistically significant improvement in sepsis recognition;[25] after training, 41% of cases were correctly identified and documented compared with 14% of cases before training. Additionally, in the present study, a shortening of TTA in the usual care group after training compared with the baseline measurements before training (70 min [IQR 36–128] *vs* 93 min [39–140]) was seen. Previous studies have shown that improvement in prehospital recognition and initiation of treatment has a positive effect on patient outcomes and processes of care in the hospital.[21,22,28] In our opinion, there was an improvement in the recognition of sepsis and TTA, with resultant improvement in usual care, which might have decreased the power of our study. Increasing awareness of sepsis among health-care workers by training EMS personnel, promoting the trial through newsletters, articles, and blogs in national medical journals, regular briefings, and site visits to the emergency departments of the hospitals in the study might have contributed to this improvement in usual care. Additionally, the EMS in the Netherlands is robustly organised with relative short response times and arrival times to the emergency department. In 93% of cases, an ambulance reaches the scene of the emergency within 15 min,[35] and has an average of 40 min from dispatch call to arrival at the emergency department. Further information regarding the general EMS system in the Netherlands can be found in the appendix (p 18).

Ambulances in the Netherlands are staffed by nurses with years of experience in treating critically ill patients and who have followed additional specialised training before applying to qualify as a registered ambulance nurse. Primary care services (general practice) in the Netherlands are well organised and almost 75% of the patients in this study were referred by general practitioners; 20% of these patients were already on antibiotics before presentation. This makes it difficult to apply the results of our study to communities with different health-care settings, where the response and arrival times are much longer[36] and general practitioner services are not as well organised. Whether including more patients with septic shock or doing this study in a prehospital setting with longer arrival times would have led to positive results is unclear. Nonetheless, this study showed that even in a populated country, such as the Netherlands, with short hospital arrival times, EMS personnel are able to recognise sepsis, obtain blood cultures, give antibiotics, and thereby shorten delays in the hospital.

There are some other limitations to our study beyond those already discussed. First, more patients were included in the intervention group, especially during the initial months of the study due to randomisation violations. However, there were no differences in baseline characteristics between the two groups. Second, we had initially planned to do a stepped-wedge design to assess the effects of training of EMS personnel. However, due to the complex nature of the trial, it was logistically and ethically not possible to extract the necessary data from all participating hospitals. Therefore, we chose to compare pre-training and post-training data in three participating regions. The multivariate analyses originally planned to compare outcomes between pre-training and post-training took into account the phased implementation, which is typical for the stepped-wedge design. Due to this change in design, the statistical analysis for comparison of TTA before and after training could be simplified and some other comparisons had to be descriptive only. We also did two studies before and after training EMS personnel in the Amsterdam region with the aim of investigating the recognition of sepsis and antibiotic administration in the ambulances and at the emergency department.[12,29] Third, all patients in the intervention group received ceftriaxone which is a broad-spectrum antibiotic. Preferably, a narrower spectrum antibiotic such as amoxicillin–clavulanate would have been given. However, due to the large number of hospitals in this study with different antibiotic regimens, we chose to use ceftriaxone for sepsis of unknown origin. This choice was made in close collaboration with microbiologists involved in developing national sepsis guidelines. Additionally, all participating hospitals were instructed to switch to narrow-spectrum antibiotics as soon as possible once the blood culture results were received. We were well aware that the choice for a third-generation cephalosporin does raise some questions, especially with the growing problem of antibiotic resistance. However, we opted for ceftriaxone as we wanted to minimise the risk of serious adverse events, such as a major anaphylactic reaction. Fourth, in patients with suspected or proven infection, the diagnosis of sepsis in the ambulance was made using the systemic inflammatory response syndrome criteria,[50] which were established to diagnose sepsis. However, in 2016, qSOFA criteria[38] were introduced with the aim of identifying patients with suspected infection who are at greater risk of developing a poor outcome outside the ICU (a prognostic criterion). If the current trial was done using qSOFA criteria, many patients would not have been eligible for inclusion in the study and would therefore not have received antibiotics. However, the value of qSOFA criteria in the prehospital and the emergency department setting is still a matter of debate. Fifth, as mentioned before, our population had an overall lower mortality rate than expected and only a small percentage of our patients had septic shock. Therefore, it is possible that for this group of patients early (prehospital) antibiotics might not make a significant difference compared with giving early antibiotics to patients with more severe illness, such as septic shock.

In conclusion, training EMS personnel in early recognition of sepsis does seem to have benefits by

improving the care in the whole acute care chain for patients with sepsis. EMS personnel are able to recognise sepsis, obtain blood cultures, give antibiotics, and help shorten delays in the hospital. However, we currently do not advise antibiotic administration in the ambulance to patients with suspected sepsis.

Contributors

NA is the coordinating investigator and PWBN is the principal investigator of the study. NA, PWBN, EO, PvE, and PMS conceived the study. NA, PWBN, PMS, and MHHK participated in study design and obtained funding for the study. EO and the team of the Albert Schweitzer Hospital did the feasibility study before initiation of the trial. NA, PWBN, EO, PMvdV, PvE, HRH, FH, AvZ, HvLN, VB, RSNP, and the collaborators of participating centres (appendix) enrolled patients and collected the data. NA and PWBN were responsible for study supervision. NA, RSNP, and BAMD were responsible for the database, including checking data entry and checking the database for accuracy. PMvdV is the statistician for the study and prepared the statistical analysis plan. NA, PvE, BAMD, RSNP, and PWBN analysed and interpreted the data. NA, PWBN, and PMvdV drafted the manuscript. All authors read, revised, and approved the manuscript.

Declaration of interests

We declare no competing interests.

Acknowledgments

We would like to thank all the patients who took part in the study. Special thanks to the EMS personnel, emergency department health-care workers, research staff, and all members of the ORCA (Onderzoeks Consortium Acute Geneeskunde) Research Consortium the Netherlands for their patience and cooperation. We are indebted to our sponsors, the NutsOhra Foundation and the Netherlands Society of Internal Medicine (NIV), for their support. Finally, we would also like to thank Coen Stehouwer (Maastricht University Medical Centre, Netherlands) and Rene van den Dorpel (Maastad Hospital Rotterdam, Netherlands) for their intellectual input.

References

1 Jawad I, Lukšić I, Rafnsson SB. Assessing available information on the burden of sepsis: global estimates of incidence, prevalence and mortality. *J Glob Health* 2012; **2:** 010404.

2 Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. *Crit Care Med* 2001; **29:** 1303–10.

3 Gaieski DF, Edwards JM, Kallan MJ, Carr BG. Benchmarking the incidence and mortality of severe sepsis in the United States. *Crit Care Med* 2013; **41:** 1167–74.

4 Kumar G, Kumar N, Taneja A, et al. Nationwide trends of severe sepsis in the 21st century (2000–2007). *Chest* 2011; **140:** 1223–31.

5 Martin GS, Mannino DM, Eaton S, Moss M. The epidemiology of sepsis in the United States from 1979 through 2000. *N Engl J Med* 2003; **348:** 1546–54.

6 Stevenson EK, Rubenstein AR, Radin GT, Wiener RS, Walkey AJ. Two decades of mortality trends among patients with severe sepsis: a comparative meta-analysis. *Crit Care Med* 2014; **42:** 625–31.

7 Gohil SK, Cao C, Phelan M, et al. Impact of policies on the rise in sepsis incidence, 2000–2010. *Clin Infect Dis* 2016; **62:** 695–703.

8 Hall MJ, Williams SN, DeFrances CJ, Golosinskiy A. Inpatient care for septicemia or sepsis: a challenge for patients and hospitals. *NCHS Data Brief* 2011: 1–8.

9 Cuthbertson BH, Elders A, Hall S, et al. Mortality and quality of life in the five years after severe sepsis. *Crit Care* 2013; **17:** R70.

10 Torio CM, Moore BJ. National inpatient hospital costs: the most expensive conditions by payer, 2013: statistical brief #204. Healthcare Cost and Utilization Project (HCUP) Statistical Briefs. Rockville, MD: Agency for Healthcare Research and Quality, 2006.

11 Wang HE, Shapiro NI, Angus DC, Yealy DM. National estimates of severe sepsis in United States emergency departments. *Crit Care Med* 2007; **35:** 1928–36.

12 Smyth MA, Brace-McDonnell SJ, Perkins GD. Identification of adults with sepsis in the prehospital environment: a systematic review. *BMJ Open* 2016; **6:** e011218.

13 Groenewoudt M, Roest AA, Leijten FM, Stassen PM. Septic patients arriving with emergency medical services: a seriously ill population. *Eur J Emerg Med* 2014; **21:** 330–35.

14 van der Wekken LC, Alam N, Holleman F, van Exter P, Kramer MH, Nanayakkara PW. Epidemiology of sepsis and its recognition by emergency medical services personnel in the Netherlands. *Prehosp Emerg Care* 2016; **20:** 90–96.

15 Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: international guidelines for management of sepsis and septic shock: 2016. *Crit Care Med* 2017; **45:** 486–552.

16 Kumar A, Roberts D, Wood KE, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit Care Med* 2006; **34:** 1589–96.

17 Ferrer R, Martin-Loeches I, Phillips G, et al. Empiric antibiotic treatment reduces mortality in severe sepsis and septic shock from the first hour: results from a guideline-based performance improvement program. *Crit Care Med* 2014; **42:** 1749–55.

18 Gaieski DF, Mikkelsen ME, Band RA, et al. Impact of time to antibiotics on survival in patients with severe sepsis or septic shock in whom early goal-directed therapy was initiated in the emergency department. *Crit Care Med* 2010; **38:** 1045–53.

19 Ryoo SM, Kim WY, Sohn CH, et al. Prognostic value of timing of antibiotic administration in patients with septic shock treated with early quantitative resuscitation. *Am J Med Sci* 2015; **349:** 328–33.

20 de Groot B, Ansems A, Gerling DH, et al. The association between time to antibiotics and relevant clinical outcomes in emergency department patients with various stages of sepsis: a prospective multi-center study. *Crit Care* 2015; **19:** 194.

21 Puskarich MA, Trzeciak S, Shapiro NI, et al. Association between timing of antibiotic administration and mortality from septic shock in patients treated with a quantitative resuscitation protocol. *Crit Care Med* 2011; **39:** 2066–71.

22 Singer M. Antibiotics for sepsis—does each hour really count? Or is it incestuous amplification? *Am J Respir Crit Care Med* 2017; **196:** 800–02.

23 Moyer P, Ornato JP, Brady WJ Jr, et al. Development of systems of care for ST-elevation myocardial infarction patients: the emergency medical services and emergency department perspective. *Circulation* 2007; **116:** e43–48.

24 Abdullah AR, Smith EE, Biddinger PD, Kalenderian D, Schwamm LH. Advance hospital notification by EMS in acute stroke is associated with shorter door-to-computed tomography time and increased likelihood of administration of tissue-plasminogen activator. *Prehosp Emerg Care* 2008; **12:** 426–31.

25 American College of Emergency Physicans. Trauma care systems development, evaluation, and funding. Policy statement. *Ann Emerg Med* 2012; **60:** 249–50.

26 Studnek JR, Artho MR, Garner CL Jr, Jones AE. The impact of emergency medical services on the ED care of severe sepsis. *Am J Emerg Med* 2012; **30:** 51–56.

27 Band RA, Gaieski DF, Hylton JH, Shofer FS, Goyal M, Meisel ZF. Arriving by emergency medical services improves time to treatment endpoints for patients with severe sepsis or septic shock. *Acad Emerg Med* 2011; **18:** 934–40.

28 Seymour CW, Carlbom D, Engelberg RA, et al. Understanding of sepsis among emergency medical services: a survey study. *J Emerg Med* 2012; **42:** 666–77.

29 van der Wekken AJ, Hiltermann TJ, Groen HJ. The value of proteomics in lung cancer. *Ann Transl Med* 2015; **3:** 29.

30 Roest AA, Stoffers J, Pijpers E, Jansen J, Stassen PM. Ambulance patients with nondocumented sepsis have a high mortality risk: a retrospective study. *Eur J Emerg Med* 2017; **24:** 36–43.

31 Kommer GJ, Gijsen R, Lemmens LC, Kooistra M, Deuning C. Beschikbaarheid, specialisatie en bereikbaarheid van Spoedeisende hulp in Nederland; Analyse gevoelige ziekenhuizen. Bilthoven: Rijksinstituut voor Volksgezondheid en Milieu (RIVM), 2015.

32 Levy MM, Fink MP, Marshall JC, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Crit Care Med* 2003; **31:** 1250–56.

33 Committee for Human Medicinal Products. Guideline for good clinical practice E6 (R2). London: European Medicines Agency, 2017.

34 Alam N, de Ven PM, Oskam E, et al. 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. *Acute Med* 2016; **15:** 176–84.

35 Ambulancezorg Nederland. Ambulances-in-zicht 2015. 2016.

36 Bakker RH, Verhage V, Tuinstra J, Bouma J. Triage op de Meldkamer. Tijdschrift voor gezondheidswetenschappen 2014: 125–30.

37 Royal College of Physicians. National Early Warning Score (NEWS): standardising the assessment of acute illness severity in the NHS. Report of a Working Party. 2012.

38 Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* 2016; **315:** 801–10.

39 Winters BD, Eberlein M, Leung J, Needham DM, Pronovost PJ, Sevransky JE. Long-term mortality and quality of life in sepsis: a systematic review. *Crit Care Med* 2010; **38:** 1276–83.

40 Vilella AL, Seifert CF. Timing and appropriateness of initial antibiotic therapy in newly presenting septic patients. *Am J Emerg Med* 2014; **32:** 7–13.

41 Tromp M, Tjan DH, van Zanten AR, et al. The effects of implementation of the Surviving Sepsis Campaign in the Netherlands. *Neth J Med* 2011; **69:** 292–98.

42 de Miguel-Yanes JM, Andueza-Lillo JA, Gonzalez-Ramallo VJ, Pastor L, Munoz J. Failure to implement evidence-based clinical guidelines for sepsis at the ED. *Am J Emerg Med* 2006; **24:** 553–59.

43 Seymour CW, Kahn JM, Martin-Gill C, et al. Delays from first medical contact to antibiotic administration for sepsis. *Crit Care Med* 2017; **45:** 759–65.

44 Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001; **345:** 1368–77.

45 Alam N, Vegting IL, Houben E, et al. Exploring the performance of the National Early Warning Score (NEWS) in a European emergency department. *Resuscitation* 2015; **90:** 111–15.

46 Corfield AR, Lees F, Zealley I, et al. Utility of a single early warning score in patients with sepsis in the emergency department. *Emerg Med J* 2014; **31:** 482–87.

47 Silcock DJ, Corfield AR, Gowens PA, Rooney KD. Validation of the National Early Warning Score in the prehospital setting. *Resuscitation* 2015; **89:** 31–35.

48 Liu VX, Fielding-Singh V, Greene JD, et al. The timing of early antibiotics and hospital mortality in sepsis. *Am J Respir Crit Care Med* 2017; **196:** 856–63.

49 Seymour CW, Gesten F, Prescott HC, et al. Time to treatment and mortality during mandated emergency care for sepsis. *N Engl J Med* 2017; **376:** 2235–44.

50 Levy MM, Fink MP, Marshall JC, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Crit Care Med* 2003; **31:** 1250–56