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# Prehospital antibiotics and intravenous fluids for patients with sepsis: protocol for a 2×2 factorial randomised controlled trial

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## ABSTRACT

**Introduction** Prompt recognition and treatment of patients with sepsis improve survival. Patients transported to hospital with sepsis often do not receive treatment until they are assessed in emergency departments. Initiation of treatments by paramedics at the point of first contact may improve outcomes for these patients.

**Methods and analysis** The study design involves two randomised controlled trials (RCTs) conducted using a 2×2 factorial design comparing use of (1) early intramuscular ceftriaxone versus placebo and (2) an early liberal intravenous fluid strategy (up to 2 L normal saline) versus usual care resuscitation guided by paramedic medical directives. Patients who are ≥18 years of age will be eligible for inclusion if they have sepsis, defined as (1) paramedic suspicion of infection, (2) fever (temperature ≥38.0°C measured by paramedic or history of fever during the previous 24 hours), and (3) hypotension: SBP <100 mm Hg. The primary outcome is mortality prior to hospital discharge or within 90 days of admission. Secondary outcomes are all-cause mortality at 90 days after enrolment; organ dysfunction during first 24 hours (mechanical ventilation, vasopressor therapy, dialysis) and hospitalisation (mechanical ventilation; dialysis); rates and duration of hospital admission; rates of ICU admission during index hospitalisation; discharge destination; proportion of patients with positive blood cultures obtained in hospital (first 24 hours); microbiological profile including distribution of microorganism species and resistant organisms; proportion of patients receiving additional antibiotics within 6 hours and within 24 hours of hospital admission; frequency distribution of first antibiotics (if any) delivered within 24 hours of hospital arrival; mean time to antibiotics delivered within 24 hours of hospital arrival (if any); proportion of patients receiving fluid bolus (>250 mL) within 24 hours of hospital arrival; total amount of crystalloid infused during transport and first 24 hours of hospitalisation; and proportion of enrolled patients not suspected to have sepsis or infection by emergency department physicians. Safety outcomes include the proportion of patients with pulmonary oedema during transport to hospital and on initial chest X-ray and the proportion of patients with anaphylaxis or suspected allergic reactions to study medication.

**Ethics and dissemination** This study has been approved through Clinical Trials Ontario's streamlined ethics review process (board of record, Sunnybrook Health Sciences Centre). It will be conducted in accordance with the Declaration of Helsinki, Good Clinical Practice guidelines and regulatory requirements. The final results will be disseminated to participating paramedic services through educational materials, presentations and interactive training. We anticipate our trial will achieve wide dissemination through publication in a peer-reviewed medical journal and presentation at international conferences targeting the fields of prehospital and emergency medicine, resuscitation and critical care.

**Trial registration number** NCT03068741.

## STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The study design includes two randomised controlled trials using a 2×2 factorial design allowing for the evaluation of two different prehospital interventions for patients with sepsis.
⇒ The pragmatic design that involves multiple paramedic services and comparison to usual care or placebo will enhance adherence and generalisability.
⇒ The study will measure important clinical outcomes (eg, mortality) but also important secondary outcomes (eg, microbiology results, pulmonary oedema) to assess the safety of the interventions.
⇒ Masking of allocation to prehospital ceftriaxone versus placebo will reduce the risk of bias.
⇒ It is not possible to blind patients and clinicians to allocation to liberal fluids versus usual care, so all outcome assessors will be blinded to minimise the risk of bias.

## INTRODUCTION

### Sepsis is common and lethal

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection.[1 2] As sepsis progresses to septic shock (sepsis plus profound circulatory, cellular and metabolic abnormalities), it is marked by severe organ dysfunction, and eventually circulatory collapse and death.[3 4] The mortality associated with sepsis ranges from 20 to 50%[5 6] with increased mortality in patients diagnosed with septic shock. Sepsis is the tenth leading cause of death in the USA with over 200 000 deaths annually.[6] The total annual cost of sepsis in the USA is US$16.7 billion[5]. As our population ages, it is expected that the incidence (and costs) of sepsis will continue to rise.[5]

### Early goal-directed therapy and intravenous fluids

In 2001, a landmark randomised controlled trial (RCT) described markedly reduced mortality from sepsis using 'early goal-directed therapy'.[7] Early goal-directed therapy comprised early identification of sepsis, early administration of intravenous crystalloids, optimisation of oxygen delivery with blood transfusion for anaemic patients, and titration of vasopressors and inotropes to specified haemodynamic targets. Other studies have reported similar results; a systematic review identified 11 studies and 28 abstracts evaluating the efficacy of early goal-directed therapy for sepsis and septic shock and found a mean relative risk reduction for mortality of 0.46±0.26.[8 9] In particular, early intravenous crystalloids have been recommended as the most important component of early goal-directed therapy.[10]

More recent trials have failed to reproduce the dramatic mortality reductions associated with early goal-directed therapy.[11–13] However, patients in the usual care arms of these trials had already received intravenous fluids prior to randomisation. Other recent trials have also failed to demonstrate benefit to more liberal fluid resuscitation during the first 24 hours, but these also evaluated the impact of fluids after the initial resuscitation.[11 13] None of these RCTs tested whether even earlier resuscitation with intravenous fluids in the prehospital setting can reduce mortality, as has been suggested by observational studies.[14]

### Early antibiotics

In a murine model of septic shock, early compared with late antibiotics improved survival of the experimental animals.[15] An observational study involving patients with septic shock showed that the adjusted risk of death increased exponentially with each hour that antibiotics were delayed after the onset of hypotension.[16] In this study, the mean time to antibiotic administration was 6 hours. In a more recent study involving 17 990 patients from 165 ICUs in Europe, the USA and South America, the risk of dying was strongly associated with delays to first antibiotic administration.[17] Large real-world implementation studies have also demonstrated improved outcomes with earlier antibiotic administration.[18] These studies highlight the importance of avoiding antibiotic delays for patients with sepsis and septic shock. However, no RCT has directly evaluated early vs delayed antibiotics—and it is unlikely randomisation of patients into such a trial would be considered ethical once they have been assessed by physicians in the emergency department.

Based on these and other research findings, current international guidelines recommend early goal-directed therapy for resuscitation of sepsis and septic shock, including the administration of intravenous fluids (weak, low quality of evidence) and antibiotic administration within 1 hour of recognising septic shock or a high likelihood of sepsis (strong recommendation, very low quality of evidence).[19] However, despite widespread acknowledgement of the importance of early recognition and treatment of sepsis, many patients fail to receive appropriate therapy during the first 6 hours after presentation to hospital.[20 21]

### Prehospital treatment by paramedics might represent an opportunity to improve outcomes for patients with sepsis

It is estimated that one-half of patients with sepsis are treated and transported to hospital by paramedics.[22 23] In a Seattle study, the crude incidence of sepsis was estimated to be 3.3/100 paramedic service encounters, higher than that for acute myocardial infarction or stroke.[24] The average prehospital care interval exceeded 45 min, highlighting that there is potential for early treatment to be delivered by paramedics. Paramedics already play a pivotal role in delivering time-sensitive treatments of other life-threatening conditions including ST-segment elevation myocardial infarction (STEMI),[25] acute ischaemic stroke[26 27] and trauma.[28] Paramedics may also be able to provide early treatment for patients with sepsis at the initial point of patient contact.

The PHANTASi trial evaluated prehospital intravenous ceftriaxone versus usual care[29] in 10 paramedic services and 2698 patients. No differences were observed for the primary outcome of 28-day mortality. However, only 4% of patients in PHANTASi had septic shock. The median time to antibiotics in the emergency departments of PHANTASi destination hospitals was also relatively short—only 70 min—and this may not be representative of current practice in most Canadian hospitals.[30]

### The Paramedic Initiated Treatment of Sepsis Targeting Out-of-hospital Patients (PITSTOP) trials

The objective of the PITSTOP trials is to inform the design of health systems to improve the care of patients with sepsis. If the trials are positive, our results will have broad implications for other health systems by showing that prehospital identification and treatment of sepsis increase the number of patients who survive this life-threatening condition. If the trials fail to demonstrate the effectiveness of prehospital sepsis treatment, it will ensure that resources are not needlessly invested in large-scale

implementations of paramedic sepsis protocols, as has been done in several other jurisdictions.

## METHODS AND ANALYSIS

### Study objectives

The overarching goal of this trial is to evaluate a fundamental change in the delivery of sepsis care. Currently, patients with sepsis do not receive key evidence-based therapies until they have been assessed in emergency departments—often introducing marked delays. This research tests whether integrating paramedics directly into a chain-of-survival for sepsis will improve outcomes for these critically ill patients. In essence, this research seeks to break down silos of care, delivering sepsis treatments based on *when* they are needed, rather than on *where* the patient is physically located.

### 2×2 factorial RCT design

We considered a two-arm trial that compared a bundle combining 2 L crystalloid with 1 gram of ceftriaxone (both unblinded) versus usual care. However, a factorial design also allows the effect of each intervention to be considered independently and in combination (ie, interaction).

### Primary research questions

Question 1/RCT #1: Do prehospital antibiotics delivered by paramedics improve rates of survival to hospital discharge or 90 days of admission, compared with usual care (placebo) for adult patients who are transported to hospital with suspected sepsis?

Question 2/RCT #2: Does an early liberal fluid management strategy delivered by paramedics improve survival to hospital discharge or 90 days of admission, compared with usual resuscitation guided by a medical directive for adult patients who are transported to hospital with suspected sepsis?

### Secondary research questions

**Process questions:** Does paramedic delivery of the experimental interventions (1) improve rates of survival to 90 days after enrolment; (2) decrease severity of subsequent organ dysfunction, as measured by use of life-support treatments (eg, mechanical ventilation, vasopressors, dialysis); (3) decrease use of healthcare resources (eg, rates and duration of hospital admission and ICU admission, discharge destination)? What are rates of isolation of microorganisms resistant to study antibiotics, and rates of sepsis not suspected by emergency department physicians among enrolled patients?

**Safety Questions:** Does paramedic delivery of the experimental interventions increase adverse events among enrolled patients, including rates of pulmonary oedema during transport and on initial chest X-ray; anaphylaxis or allergic reactions to study drugs?

## STUDY DESIGN

We will conduct two RCTs using a 2×2 factorial parallel group design that have common inclusion and exclusion criteria and primary and secondary outcomes and a superiority framework. Paramedics will screen and enrol eligible patients under a waiver of consent using established procedures for conducting prehospital research involving severely ill patients requiring time-sensitive therapies.

### Setting

This trial will be conducted by Paramedic Services and destination hospitals in Southern Ontario (2021 population ~6 million) with a Central Coordinating Centre located at Sunnybrook Research Institute in Toronto.

### Trial status

At the time of manuscript submission, the trial is actively recruiting patients across four large paramedic services in Ontario, Canada: Halton Region Paramedic Services, Peel Regional Paramedic Services, Toronto Paramedic Services and York Region Paramedic Services.

### Eligibility criteria

Paramedics will identify eligible patients using the traditional criteria for sepsis, including clinical suspicion of infection, and evidence of hypotension,[3] similar to the approach that has been used in hospital trials.[7 12] To improve the specificity of this definition, we will require that all enrolled patients have measured fever by paramedics or history of measured fever during the previous 24 hours.[31] Recent consensus statements have suggested using the quick Sequential Organ Failure Assessment (qSOFA) criteria (ie, any 2 of respiratory rate >22, altered mentation, or SBP <100) to identify patients with sepsis who have higher mortality risk.[2] However, these criteria have not been prospectively validated. We will therefore measure these among enrolled patients, but will use the following established features to recruit into the PITSTOP trials:

#### Inclusion criteria

1. Patients with sepsis, defined as (all three must be present):
   i. Paramedic suspects possible infection: for example, suspected pneumonia, urinary tract infection, skin infection, bone and joint infection, intra-abdominal infection, meningitis;
   ii. Fever: temperature ≥38.0°C measured by paramedic, OR measured during the previous 24 hours;
   iii. Presence of hypotension: SBP <100 mm Hg.
2. Age ≥18 years.

#### Exclusion criteria

We will exclude patients with any of the following:

1. Post cardiac arrest.
2. Suspected STEMI.
3. Suspected acute cerebrovascular accident.
4. Acute severe trauma.
5. Obvious severe non-traumatic bleeding.
6. Signs of fluid overload.

7. Suspected acute congestive heart failure.
8. Known *Clostridiodes difficile* infection within the last 6 weeks.
9. Known pregnancy or breastfeeding.
10. Known allergy or sensitivity to penicillin or cephalosporin.
11. Known to be receiving oral or subcutaneous anticoagulants (eg, warfarin, direct oral anticoagulants; aspirin and clopidogrel are accepted) or low molecular weight heparin.
12. Paramedic is unable to identify patient by first and last name and/or health card number.

**Prehospital lactate:** We considered but rejected using prehospital lactate meters to identify patients with septic shock because these point-of-care devices have not been approved for prehospital use by Health Canada. Furthermore, only ~5% of patients with sepsis present with elevated lactate alone and without hypotension.[32]

### Eligible non-randomised Patients

When eligible patients (ie, those meeting all inclusion criteria yet no exclusion criteria) are not enrolled, we will classify and record reason(s) for non-enrolment.

## Interventions

Two RCTs will be conducted simultaneously using a 2×2 factorial design comparing use of (1) early antibiotics (1 g ceftriaxone intramuscular) versus placebo (0.9% NaCl) for patients with sepsis, and (2) 2 L of intravenous crystalloid saline (0.9% NaCl) given carefully checking every 250 mL for early pulmonary oedema versus usual care resuscitation guided by Ontario Advanced Life Support Patient Care Standards. All eligible patients can participate in the first RCT of early antibiotics. Only patients who have intravenous access established can participate in the second RCT of early liberal intravenous fluid management.

### RCT#1: experimental strategy—prehospital antibiotics (blinded)

1 g of ceftriaxone by intramuscular injection. The drug is provided in a sterile and completely covered vial as a white, odourless powder to be reconstituted with 4.4 mL 0.9% saline. The administered dose is 2.8 mL delivered intramuscular for a total of 1 g ceftriaxone.

### RCT#1: control treatment—placebo to antibiotic (blinded)

Placebo intramuscular 0.9% saline. The placebo vial is an empty completely covered vial that will have 4.4 mL 0.9% saline added to it. The administered dose is 2.8 mL delivered intramuscular for a total of 2.8 mL 0.9% saline.

### RCT#2: experimental strategy—early liberal fluid management (unblinded)

2 L of intravenous crystalloid saline (0.9% NaCl) suggested to be infused using an infusion pump or pressure bag. Paramedics will monitor for pulmonary oedema after each additional 250 mL intravenous is infused. In the absence of suspected pulmonary oedema, paramedics will be instructed to continue the saline infusion up to 2 L in total regardless of blood pressure.

### RCT#2: control strategy—usual care fluid management (unblinded)

Intravenous crystalloid saline (0.9% NaCl) infused for persistent hypotension only, up to a maximum of 2 L. According to the Ontario Advanced Life Support Patient Care Standards for paramedics, intravenous fluids should only be provided when SBP<90 mm Hg, held when SBP ≥ 100mmHg and reassessed after each 250–500 mL is infused.

### Procedures common to all groups (experiment and control, both comparisons)

The study ends on arrival in the ED. Paramedics will provide an information sheet that describes the study to in-hospital clinicians but maintains allocation concealment for the antibiotic comparison. Subsequent treatment decisions are at the discretion of the in-hospital team.

### Experimental strategy—rationale and considerations

Choice of antibiotic: ceftriaxone was approved by the US Food and Drug Agency in 1984 and is now a generic antibiotic (~CAD$1.65 per 1 g dose) approved by Health Canada for initial empiric therapy of lower respiratory tract infections; complicated and uncomplicated urinary tract infections; septicemia; skin, bone and joint infections; intra-abdominal infections; and meningitis.[33] It is suitable for prehospital administration because it does not require prolonged refrigeration or complex reconstitution[34 35] and can be given rapidly as a single dose.[36 37] It is a bactericidal, third-generation cephalosporin with a broad spectrum of activity, making it suitable for initial empiric monotherapy as recommended by sepsis guidelines issued by the Infectious Disease Society of America, Canadian Critical Care Society[10] and Canadian Association of Emergency Physicians.[38]

Choice of route of administration: we considered intravenous administration, but rejected this route of administration in favour of intramuscular injection. Intramuscular injection of ceftriaxone offers several advantages over intravenous administration. Patients in the field can receive the medication much faster with intramuscular administration, and without the need to first obtain intravenous access. All paramedics can administer intramuscular ceftriaxone, whereas only paramedics who are trained to insert intravenous catheters can administer intravenous ceftriaxone. Using intramuscular ceftriaxone therefore allows for participation of a much larger group of paramedics while providing a consistent intervention. A further drawback to intravenous administration is that the product monograph approved by Health Canada requires that infusions of this medication be administered over 20 to 30 min in adults, creating additional delays and potential feasibility problems if hospital transport times are shorter than this interval.[33] In contrast, intramuscular ceftriaxone can be administered as an immediate bolus

dose following reconstitution; all patients should therefore receive the study drug prior to hospital arrival.

The bioavailability of ceftriaxone by the intramuscular route is approximately 100%.[33] Pharmacokinetic studies in humans demonstrate intravenous administration leads to higher initial peak drug concentrations at 30 min, but both routes of administration achieve serum levels that exceed the minimum inhibitory concentration (MIC) for susceptible organisms within 15 min,[39 40] and serum drug levels exceeding the MIC are sustained for 24 hours regardless of route of administration.[41 42] Concentrations in extracellular spaces also exceed the MIC following one time per day intramuscular administration, including pleural fluid, abdominal tissues, ascitic fluid, soft tissues, bile and gall bladder, and cerebrospinal fluid.[43 44] Furthermore, intramuscular ceftriaxone achieves a higher peak concentration compared with intravenous ceftriaxone at 2 hours, and concentrations subsequently remain higher than intravenous administration through to 24 hours.[39] The ease and rapidity of administration followed by sustained serum drug concentrations have made intramuscular ceftriaxone an appealing approach for treatment outside of the hospital setting.[45]

Microbiological testing: we considered obtaining blood cultures prior to delivery of prehospital antibiotics (grade 1C, low quality evidence).[10] The key arguments for obtaining cultures are to assist with subsequent tailoring of antibiotics to agents with narrower spectrum, and to ensure adequate antimicrobial coverage for infections caused by antibiotic-resistant strains. We rejected this strategy for several reasons. Obtaining prehospital blood cultures presents significant logistical challenges (sample collection and labelling, processing in destination hospitals which use different microbiologic equipment). The utility of blood cultures for immunocompetent patients presenting to emergency departments with sepsis has been questioned,[46 47] with some reports estimating that <2% of emergency department blood cultures affect therapy.[48] The guidelines acknowledge the limited evidence supporting blood cultures and advise against obtaining these if it will delay antibiotic delivery. Finally, we believe that blood cultures obtained after the study-directed single dose of ceftriaxone will still provide useful information. Modern blood culture systems contain resins that 'neutralise' the presence of antibiotics. Therefore, prehospital ceftriaxone should not decrease the yield of in-hospital tests to isolate ceftriaxone-resistant strains.[49 50] We also considered but rejected the option of new point-of-care microbiological tests, as these have not yet been adequately validated and are not sufficiently robust for use in the field.

**Group separation—intravenous fluids:** It will be important to achieve separation between groups in the RCT comparing liberal fluid management versus usual care. The intervention arm should receive 2 L of intravenous crystalloid regardless of blood pressure unless pulmonary oedema is present; we will suggest use of infusion pumps or pressure bags for these infusions as was done in previous trials,[51] to ensure these volumes are delivered even if transport times are relatively short. In the control arm, the paramedics will infuse fluid to treat SBP <90 mm Hg according to Ontario Advanced Life Support Patient Care Standards. Using this approach, and based on our observed data from participating paramedic services, we anticipate that most control patients will receive approximately 250 mL, and few will receive more than 1 L. We anticipate that most intervention group patients will receive 2 L using the infusion pump or pressure bag, providing adequate separation between groups.

## Outcomes

### Primary outcome

The primary outcome is mortality prior to hospital discharge to day 90.

### Secondary process outcomes

- Mortality at 90 days after enrolment.
- Organ dysfunction during (1) first 24 hours (mechanical ventilation, vasopressor therapy (any), dialysis) and (2) hospitalisation (mechanical ventilation).
- Healthcare resources: rates and duration of hospital admission, ICU admission during index hospitalisation, discharge destination (home vs not).
- Proportion of patients with positive blood cultures obtained in hospital (first 24 hours); microbiological profile including frequency distribution of microorganism species and resistant organisms.
- Proportion of patients receiving additional antibiotics within 6 hours and within 24 hours of hospital admission; frequency distribution of first antibiotics (if any) delivered within first 24 hours of hospital arrival; mean time to antibiotics delivered within first 24 hours of hospital arrival (if any).
- Proportion of patients receiving fluid bolus (>250 mL) within first 24 hours of hospital arrival; total amount of intravenous crystalloid infused during transport and first 24 hours of hospitalisation
- Proportion of patients with blood, urine and sputum cultures obtained during first 24 hours that grow organisms resistant to ceftriaxone (ie, inappropriate antibiotic therapy).
- Proportion of enrolled patients suspected to have sepsis or infection by emergency department physician
- Proportion of hospitalised patients who grow any antibiotic-resistant organism (eg, methicillin-resistant *Staphylococcus aureus, C. difficile*, extended beta-lactamase resistance organisms) during the first 24 hours.

### Safety outcomes

- Proportion of patients with pulmonary oedema documented during transport to hospital and on initial chest X-ray.
- Proportion of patients with anaphylaxis or suspected allergic reactions to study medication.

### Study schedule and duration

We will follow all enrolled patients using chart review at those destination hospitals with research ethics board (REB) approval until the time of hospital discharge, 90 days or death, whichever comes first, to collect relevant process of care and clinical outcome measures. All enrolled patients whose records can be linked to ICES will have all-cause mortality measured to 90 days; secondary outcomes will also be collected using available ICES data.

Based on our experience with other multicentre RCTs in post-arrest care, we anticipate a follow-up rate of over 99%.[52] In previous clinical trials employing similar outcome measures in cardiac arrest patients, we have <1% loss to follow-up for our primary and secondary outcomes at discharge, and at 30 days.[53–56] We anticipate the trial will take 5–6 years to complete after enrolment commences.

## Sample size

The baseline hospital mortality of patients with suspected sepsis who are transported by paramedics ranges from 17% to 23%.[24] Based on previous trials of critically ill patients with sepsis, we will search for a plausible absolute reduction in hospital mortality of 5%.[57] To detect this difference (80% power, two-sided testing, alpha error 5%), we will require between 780 and 1020 patients per group. Based on our experience with other prehospital trials, we believe this sample size (n=2040) to be a feasible target.

We anticipate that not all paramedics will be trained to insert intravenous cannulas or will be able to successfully obtain intravenous access. In these situations, patients will only be included in the analysis for the prehospital antibiotic RCT and will not be included in the analysis for the prehospital intravenous fluids RCT. This is expected to result in fewer patients enrolled in the prehospital intravenous fluids RCT compared with the prehospital antibiotics RCT. If only half of the entire study population (eg, 1020 patients) can participate in the prehospital intravenous fluids RCT because intravenous access can be obtained, we will still have 80% power to detect a decrease in baseline mortality from 23% to 16%, or from 17% to 11%. These differences are both clinically relevant and plausible based on previous research.

Factorial designs provide an efficient method of evaluating more than one intervention in the absence of interactions. While there is no established biological rationale to expect an interaction between fluids and antibiotic administration, our anticipated sample size should provide sufficient power to detect an interaction effect that is twice as large as the treatment effect (ie, a 10% mortality difference).[58]

### Assessment of subject compliance with study intervention

We will institute the following strategies that allowed us to achieve high levels of protocol adherence in previous trials:

1. Formal paramedic education.
2. Refresher education sessions, as required.
3. Regular protocol compliance checks by Coordinating Centre staff.
4. Ongoing identification of protocol violations.
5. Regular study progress updates to participating paramedic services.
6. We also will provide on-scene visual reminders including lists of inclusion/exclusion criteria.

## Randomisation and blinding

We will randomise patients 1:1:1:1 (2×2 factorial) stratified by paramedic service and using permuted blocks of variable sizes to avoid substantial imbalance in the number of patients assigned to each group. The randomisation schedule will be prepared by the study statistician (RP) and study kits (small sealed, numbered opaque study boxes) will be prepared by Coordinating Centre personnel working with the study pharmacists.

Two techniques will be employed to maintain allocation concealment. For the RCT of prehospital antibiotics (ceftriaxone vs placebo), study drug and placebo will be prepared by the pharmacy in identical vials and placed into numbered, opaque, sealed boxes, according to the randomisation schedule. Within each box, study personnel will also insert a label stating the randomisation allocation to the prehospital intravenous fluids RCT (early liberal fluid management strategy or usual fluid management strategy).[59] All clinicians will remain blinded to group assignment in the prehospital antibiotics RCT, whereas group assignment in the prehospital intravenous fluids RCT will be known once study kits are opened.

Paramedics will screen all patients for eligibility. Once a patient is deemed to be eligible, the paramedic will open the opaque study box to retrieve the study vial for the antibiotic versus placebo RCT. If the patient has received an intravenous catheter, the paramedic will also follow the randomisation allocation for the aggressive fluids versus usual care trial.

Numbering on the outside of the sealed, opaque boxes will also allow trial personnel to track and monitor the integrity of the random allocation process and ensure that study kits are opened appropriately. This approach is an accepted method for maintaining allocation concealment,[60] and is the method currently favoured by participating paramedic services including those who participated in the ICEPACS RCT (NCT01528475).[53 61]

## Statistical analysis plan

The 2×2 factorial trial will result in different final study cohorts for each RCT, as all patients meeting eligibility criteria can receive the antibiotic intervention versus placebo, but only patients with intravenous access can receive the liberal intravenous fluids intervention versus usual care. The results of PITSTOP will therefore be analysed as two separate trials: 'PITSTOP-antibiotics' and 'PITSTOP-fluids'. The cohort size and composition in these two trials are expected to differ slightly, but the

primary and secondary outcomes, analytical approach and presentation of results will be kept consistent.

The primary analyses of the RCTs will be intention-to-treat and will include patients who met all inclusion criteria, were enrolled by paramedics and received at least one of the study interventions. In addition:

- Patients who received a study intervention, but did not meet all inclusion criteria, will not have outcome data collected and will not be included in the intention-to-treat analysis, as these represent screening and enrolment errors (ie, ineligible patients).
- Patients who were enrolled into the trial, but for whom one or more exclusion criteria were subsequently deemed to have been present, will still have outcome data collected and will be included in the intention-to-treat analysis. However, these patients will be removed in a secondary sensitivity analysis (ie, modified intention-to-treat analysis).
- Patients who met all eligibility criteria but did not receive any study intervention will also be reported in the Consolidated Standards of Reporting Trials diagram but excluded from the intention-to-treat analysis (ie, no intervention applied).
- Patients for whom no intravenous access could be obtained will be excluded from the intention-to-treat analysis of the liberal intravenous fluids versus usual care trial (ie, ineligible for intravenous fluids).
- Patients for whom no intramuscular injection of study investigational product could be administered will be excluded from the intention-to-treat analysis of the antibiotics versus placebo trial (ie, ineligible for intramuscular antibiotics).

For both RCTs, baseline characteristics will be summarised by descriptive statistics. The primary outcome (binary) in both trials will be compared using regression models that include terms for both experimental interventions and interaction terms to account for the 2×2 factorial design and any potential for effect modification. If significant interactions exist at $\alpha<0.10$, then the effect of each treatment will be estimated in each subgroup corresponding to each of the allocations into the 2×2 factorial trial and reported in both trials using the full sample size comprised of patients enrolled into both trials. If no significant interactions are detected, then the interaction will be dropped from the models and the main effects of each intervention assessed in separate models. The primary outcome will be analysed using a log-binomial model or if convergence not achieved modified Poisson regression. The significance level for these analyses will be 5% (two-sided) and treatment effects will be expressed as relative risks and 95% CI. Stratification by paramedic service will be considered in the models. Secondary binary outcomes (continuous and binary) will also be analysed and reported using relative risks with 95% CIs and/or differences in means or medians with SD or IQRs. In secondary analyses, mortality will be adjusted for important baseline variables (eg, age, sex, comorbidities) using multivariable regression modelling. Time to death will be summarised by Kaplan–Meier curves and compared using Cox proportional hazard models including the main treatment effects and considering potential for interactions between the interventions as explained above, and the treatment effects expressed as HR and 95% CI with censoring at 90 days. Secondary hypothesis-generating analyses will also be conducted considering any potential effect modification of baseline patient, and hospital variables on the primary and secondary outcomes.[62] We will conduct subgroup analyses to determine whether any of the following factors modify the effect of prehospital sepsis treatment on subsequent patient outcomes: sex (male vs female); age (<65 vs ≥65 years); sepsis hospital volume (high vs low).

### Frequency of analyses

Our Data Safety Monitoring Committee (DSMC) will conduct two blinded interim analyses to assess for harm at pre-specified enrolment landmarks: after recruitment of one-third (n=340 per group) and two-thirds (n=680 per group) of patients. The DSMC will consider stopping the trial early for harm if there are important differences favouring either study group (at a significance level of $p<0.001$, according to the criteria of Haybittle-Peto[63]) for the following pre-specified endpoints: proportion of patients dying during transport to hospital and proportion of patients dying before hospital discharge. The DSMC will also review all adverse events that are potentially related to prehospital sepsis treatment that are identified by study coordinators.

### Blinding and protecting against bias

Blinding of antibiotic group assignment was possible, but blinding of fluid management assignment was considered to be infeasible. For both comparisons, all outcome assessors will be blinded to group assignment to ensure that outcomes are not subject to measurement error. To further protect against bias, we will use explicit criteria when measuring study endpoints including the primary outcome of hospital mortality. We will minimise contamination through explicit protocols and careful monitoring of protocol adherence. Every effort will be made to randomise patients as quickly as possible after they meet eligibility criteria, prior to arrival at the destination hospital. To account for outcome differences that arise due to the use of other therapies that may impact on mortality, we will document important procedures during the first 24 hours.

## Study administration

### Organisation and participating centres

The trials will be conducted with the participation of regional paramedic services. Primary and secondary outcomes will be obtained from population-based administrative databases. Approval to conduct a chart review to ascertain some outcomes for enrolled patients will also be sought from relevant destination hospitals.

### Committee members

The steering committee will comprise the principal investigator and all co-investigators and collaborators. They will meet by teleconference regularly to review study progress and operational issues. The study DSMC will include three individuals with expertise in the following: (1) large-scale prehospital research, (2) statistical analysis, and (3) sepsis.

## Trial management

DS is the principal investigator. AR is the project manager. The Centre for Clinical Trial Support is the coordinating centre, which will convene regular progress meetings involving the project manager, data abstractors, paramedic service study leads, investigators and additional participants, as applicable. These meetings will include updates about patient recruitment and discussions of trial operational details. The project coordinator/manager and principal investigator will also liaise frequently with each paramedic service. Protocol violations will be audited by the Coordinating Centre and recorded on designated Protocol Violation Forms. The Coordinating Centre will respond to queries from paramedic services and hospitals, and work with paramedic services on study activities (REB applications; study contracts; organising study materials; education sessions and in-services, as applicable).

Paramedics can also communicate directly with Coordinating Centre staff about patient eligibility and study protocols. Each paramedic service will have a dedicated individual who is specially trained in this protocol to answer paramedic inquiries.

A chart insert will be provided to in-hospital clinicians containing phone numbers and email addresses of our investigators should enrolled participants or their healthcare providers have questions or concerns.

## Data management

### Confidentiality and security

Information about study participants will be kept confidential and managed according to the requirements of Canada's federal privacy law, the *Personal Information Protection and Electronic Documents Act 2000* (PIPEDA), provincial privacy legislation and the REB. PIPEDA outlines the rules for the collection, use and disclosure of personal health information (PHI). PHI is the terminology used in the legislation and serves as important research data as well. All health data are considered to be highly sensitive; thus, health information protection is paramount. Safeguards are in place to protect PHI against loss, theft and unauthorised access, disclosure, copying, use or modification. The nature of the safeguards will vary depending on the format of the information and the method of storage.

Data collection in the prehospital environment will occur directly on the ambulance electronic patient care records (ePCR), using study-related fields approved by each paramedic service. These data will be transferred via a secure pathway and stored in the trial database. This secure, validated, password-protected web-based database has restricted access in compliance with the privacy and ethical practices of Sunnybrook Research Institute and will only contain data fields that are directly relevant to the PITSTOP trials. The following designated individuals will have access to this database: the principal investigator, Coordinating Centre staff, study statistician, and the data abstractors.

A separate and secure database will be created that links the participant's PHI (including date of birth, health card number and first and last name) with a unique PITSTOP trial identifier. The PHI is required to identify and retrieve the participant's information in administrative health databases and their corresponding chart at the destination hospital. The participant's address will also be collected so that the study notification letter can be mailed to the participant after enrolment. The Coordinating Centre will contact the Health Records Department of those destination hospitals in which the REBs have approved the PITSTOP protocol to request that the participant's chart is retrieved for review (remotely or in-hospital).

When chart abstraction for data collection is done remotely or in-hospital, it will be performed by trained abstractors and entered into the trial database that will only contain the unique PITSTOP trial identifier and no PHI. Typographical errors noted in the PHI (eg, name, OHIP number or date of birth) received from the participating paramedic services may also be corrected at this point when cross-checked against the in-hospital record.

At the time of analysis, the database linking PHI to the PITSTOP trial identifier and the PITSTOP trial database will be transferred to the agency that oversees population health databases in that region for linkage to obtain primary and secondary outcomes (eg, ICES in Ontario). In Ontario, ICES is a prescribed entity for the purposes of section 45 of Ontario's Personal Health Information Protection Act and contains multiple administrative health databases. The records of each randomised patient will be deterministically and/or probabilistically linked to these administrative databases using PHI as outlined in the agreements with ICES, including, but not limited to the health card number, date of birth, admission date and/or first and last name. Once these records have been linked, analyses will only occur according to existing privacy and security procedures in place in these organisations. These databases include, but are not limited to, the Canadian Institute for Health Information Discharge Abstract Database, National Ambulatory Care Reporting System, Ontario Lab Information System and Registered Persons Database. The purpose of this linkage is to ensure that the primary outcome (hospital mortality) and several secondary outcomes can be collected on all patients, even if the hospital charts from some patients are unavailable for review. A secondary aim is to facilitate the conduct of a cost-effectiveness analysis at the conclusion of the trial.

As per institutional requirements for the retention of research study records, all electronic and paper files will

be retained in an identifiable form for 10 years prior to destruction.

### Source documents and data abstraction

Paramedics in participating paramedic services are required to collect basic demographic information and clinical details about treated patients on an ePCR, including treatments delivered and adverse/critical events during transport. The only additional information not already collected that will be required for this trial will be data related to sepsis screening, reasons for non-enrolment of eligible patients, randomisation allocation (study kit number for antibiotics intervention, treatment assignment for fluid intervention), whether study drug was administered and how much fluid was delivered, and development of adverse events including pulmonary oedema, allergic reactions or anaphylaxis. These data elements will be captured by variables on the electronic software interface already used by paramedics. Randomisation allocation will be captured by a variable on the electronic software interface used by paramedics to capture clinical data.

In addition, in destination hospitals in which the REBs have approved the PITSTOP protocol, data abstractors will complete chart abstraction (either in-hospital or remotely) of variables related to in-hospital sepsis treatment, microbiology results for and other outcome variables for enrolled patients. If a participant is transferred to another institution that is not participating in this trial, then the data abstractors will collect only the available outcome data from the original institution and the vital status of the participant will be assumed to be 'alive'. Data will be entered electronically into the web-based trial database. The web-based database will facilitate data collection across the geographical regions involved in this study.

To ensure uniform collection of the primary outcome and most secondary outcomes, the trial database will be securely transferred to the entity that oversees administrative population health databases in that province (eg, IC/ES in Ontario). Secure linkage with these administrative health databases will allow for measurement of hospital mortality and some but not all secondary outcomes (eg, intensive care unit admission) for all enrolled patients.

### Quality assurance

Data quality assurance for the PITSTOP trial will follow usual Coordinating Centre quality assurance procedures. Validation checks are built into the database to screen for abnormal values and flagged values are re-evaluated.

## Ethical considerations and dissemination

### Research ethics board approvals

The PITSTOP RCT has been approved by the following REBs:

1. Clinical Trials Ontario—Board of Record Sunnybrook Health Sciences Centre Research Ethics Board—REB Approval reference #0774, covering the following centres:
   - Oak Valley Health (Markham Stouffville Hospital)
   - Lunenfield Tanenbaum Research Institute (Mt. Sinai Hospital)
   - Southlake Regional Health Centre
   - Hamilton Health Sciences (Hamilton General and Juravinski Hospitals)
   - Sunnybrook Research Institute (Sunnybrook Health Science Centre and Sunnybrook Centre for Prehospital Medicine)
   - Humber River Hospital
   - William Osler Health System (Etobicoke and Brampton Civic Hospitals)
   - North York General Hospital
   - University Health Network (Toronto General and Toronto Western Hospitals)
   - Unity Health (St. Michael's Hospital and St. Joseph's Health Centre Toronto)
   - Mackenzie Health
2. Joseph Brant Hospital Research Ethics Board—REB reference ID: 000-032-16
3. Halton Healthcare Research Ethics Board—REB reference ID: N/A
   - Oakville Trafalgar, Milton District and Georgetown Hospitals
4. William Osler Health System Research Ethics Board Headwaters Hospital—REB reference ID: 16-0053/0235
5. Lakeridge Health Research Ethics Board—REB reference ID: 2016-023
6. Michael Garron Hospital Research Ethics Board—REB reference ID: 695-1610-Mis-301- RS
7. Scarborough Health Network Research Ethics Board—REB reference ID: EME-16-027
   - Scarborough General, Centenary and Grace Hospitals

### Risk to study subjects

The prehospital intravenous fluids RCT involves delivery of a 2 L intravenous crystalloid bolus to patients with sepsis, versus administration of intravenous fluids only as specified by the (usual care) Ontario Advanced Life Support Patient Care Standards for hypotension. This treatment with intravenous crystalloid has become standard of care in emergency departments and therefore poses minimal incremental risk when provided earlier by paramedics. In routine clinical practice, risks of crystalloid infusions include the development of pulmonary oedema and respiratory failure. Paramedics are trained to detect and treat pulmonary oedema and will stop the crystalloid infusion if any signs of this complication develop.

The prehospital antibiotics RCT involves the intramuscular administration of ceftriaxone or placebo by paramedics. The most common adverse event associated with intramuscular injection of ceftriaxone according to the product monograph is pain at the injection site (10%) and induration and tenderness (1–2%); however, one

trial reported injection site pain that lasted more than 24 hours in 20% of children with typhoid fever.[64] This pain is typically mild and transient. Other adverse drug effects from ceftriaxone are uncommon (<5%), most commonly diarrhoea or fever, and anaphylactic reactions are rare (0.1–1.0%).[33] Paramedics have the training and tools necessary to treat these most severe reactions. Some patients' infections may be caused by organisms that are resistant to empiric ceftriaxone, rendering initial therapy ineffective; this situation is similar to usual emergency department care. The delivery of prehospital antibiotics may theoretically decrease the yield of subsequent microbiological testing in hospital; we will therefore track rates of positive body fluid cultures obtained within 24 hours of hospital arrival. Patients in the experimental arm may receive an additional dose of open-label ceftriaxone (or other antibiotic) after arrival in the emergency department; such doses should seldom exceed 2 g (in addition to the 1 g administered prehospital) for a total of 3 g, doses which are considered safe in humans.[33]

### Dissemination

The final results of the trial will be disseminated to participating paramedic services through educational materials, presentations and interactive training. We anticipate our trial will achieve wide dissemination through publication in a peer-reviewed medical journal and presentation at international conferences targeting the fields of prehospital and emergency medicine, resuscitation and critical care. It will not be possible to share the final database at ICES with the public. The full protocol will be made publicly available as a peer-reviewed publication. The statistical code will be made available upon request, if/where feasible.

## Informed consent

### Patient waiver of consent

This study requires timely implementation of the study interventions, and individual patient consent will be infeasible prior to randomisation due to the limited time window available, and because most participants with sepsis lack capacity due to the severity of their illness. The trial has been granted a waiver of consent in accordance with the Tri-Council Agreement from the REBs of Sunnybrook Health Sciences Centre and participating hospitals.[42–46 65] While we believe this study will pose only minimal risk to participants compared to usual care, our DSMC is empowered to stop the trial early if any signal for harm is detected. Paramedics will provide an information card to all eligible patients or their relatives that explains the trial, and any patients that decline participation will not proceed in the study but will receive standard treatment. In situations where the patient declines participation after the study kit has already been opened, the patient will not proceed in the study and will also not be included in the primary intention-to-treat analysis; these post-randomisation exclusions will be reported in the study patient flow diagram.[66] All patients who are enrolled in the trial with an available mailing address will also be sent a letter of notification (online supplemental appendix) by mail containing more information about the study and explaining that they were enrolled in the trial under waiver of consent. This approach has been approved by our REBs for patients with severe illness, including for emergency conditions with varying degrees of incapacity.

## Safety

### Unblinding

Paramedics and study personnel will be blinded to treatment allocation for the prehospital antibiotics trial. Any severe adverse events will be treated according to usual procedures by paramedics. If unblinding is required for safety or treatment purposes during the course of the study, a mechanism will be in place to allow the identity of the study drug to be promptly disclosed. An example of an event that may warrant unblinding is the development of an allergic reaction after receiving the study drug and a desire to confirm that the reaction occurred due to ceftriaxone rather than placebo. Paramedics will have a call number, and if unblinding is required, the treatment allocation can be quickly identified (24/7). A study notification card will be provided to the in-hospital clinicians upon admission to the Emergency Department; this also contains the call number.

### Steering Committee and Data Safety and Monitoring Committee (DSMC)

The Steering Committee will comprise the principal investigator and all co-investigators and collaborators. They will meet by teleconference regularly to review study progress and operational issues. The study DSMC will include three individuals with expertise in the following: (1) large-scale prehospital research; (2) statistical analysis; (3) sepsis. The DSMC will review all data and communicate directly with the trial principal investigators as outlined in the DSMC charter. The DSMC can also make recommendations to the Steering Committee. As described earlier, the DSMC will conduct two blinded interim analyses of the data to consider early stopping for harm at pre-specified enrolment landmarks. The DSMC will also review all adverse events that are potentially related to prehospital sepsis treatment that are identified by study coordinators.

### Access to data

The trial statistician will have full access to the study dataset. The full study dataset will be stored at ICES, where linkage of individual study subject records to health administrative datasets will occur. The principal investigator will have responsibility for assessing requests to access study datasets.

## Patient and public involvement

We have built our study on a highly integrated knowledge translation foundation by including collaborators who will be end-users of our prehospital sepsis intervention.

The interventions, including logistics and implementation planning, have been developed in direct collaboration with representatives from all participating paramedic services. Furthermore, we have involved leaders and paramedics from each paramedic service and in-hospital clinicians to develop the research question, determine the methodology and develop data collection tools. These individuals will also be involved in interpreting the research findings, to ensure our results are relevant to other stakeholders and health systems. A patient representative has been recruited to help with interpretation and reporting of the results. We plan to circulate a clear message to practitioners, target institutions and the public about our findings regarding the effectiveness of prehospital sepsis treatment.

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