Empirical Meropenem versus Piperacillin/Tazobactam for Adult Patients with Sepsis (EMPRESS) trial

OPERATIONAL GUIDELINE

For Danish sites

Operations guideline version and date
Version 1.0, 2025.06.10

Websites
www.cric.nu/empress

Applicable protocol registration numbers
Clinical Trials Information System (CTIS)
EUCT number: 2023-509703-33-00
ClinicalTrials.gov identifier: NCT06184659
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1. Overview

This document describes core areas around practical delivery of the EMPRESS protocol. For more details, the full protocol is presented at www.cric.nu/empress.

EMPRESS is a randomised, open-label, adaptive clinical trial assessing effects of empirical meropenem vs. piperacillin/tazobactam on mortality and other patient-important outcomes in critically ill adults with sepsis.

2. Screening and randomisation

Patients admitted to an active trial site should be screened for inclusion at admission and ad hoc. When they fulfil **ALL inclusion criteria** (outlined below), they should be **screened in the web-based eCRF** (app.easyrf.dk) by medical doctors, who are trained and listed in the delegation log. Patients not fulfilling all inclusion criteria can be screened later if their clinical state changes.

In fertile women under 60 years of age, human chorionic gonadotropin (**hCG**) in urine or plasma should be measured before screening (if already done under current admission, that test result can be used).

Inclusion criteria

All the following criteria must be fulfilled:

- ✓ Age ≥ 18 years
- ✓ Sepsis (including septic shock) defined as per Sepsis-3 criteria (suspected or documented infection AND worsening organ failure, including circulatory failure)
- ✓ Critical illness defined as use of at least one of the following:
  a. Invasive mechanical ventilation
  b. Non-invasive ventilation
  c. Continuous use of continuous positive airway pressure (CPAP) for hypoxia
  d. Oxygen supplementation with an oxygen flow of ≥ 10 litres (L)/minute independent of delivery system and total flows
  e. Continuous infusion of any vasopressor or inotrope (excluding strictly procedure-related infusions)
- ✓ Clinical indication for empirical treatment with either meropenem or piperacillin/tazobactam

Exclusion criteria

The exclusion criteria appear during screening in the eCRF. They are not presented here to avoid pre-exclusion where we don't get the reason for exclusion documented in the eCRF.

After screening

If a patient fulfils an exclusion criterion, the patient is permanently excluded, and no actions are to be taken.

If the patient is randomised

1. **Notify the clinical staff:** inform the clinical staff of the randomisation
2. **Initiation of trial intervention:** order in the participant's medical record the allocated trial drug (meropenem or piperacillin/tazobactam (in Sundhedsplatformen choose 'EMPRESS Meropenem' or 'EMPRESS

Piperacillin-tazobactam)) in the appropriate dose (as per the clinician's decision) as soon as possible after randomisation.

3. **In the patient's medical record:** write the inclusion note stating that the patient has been included in the trial (in Sundhedsplatformen there is a *smart phrase* (.empress)). Write what the participant is randomised to in the resumé.
4. **Consent:** as soon as possible after the above steps, inform the trial guardian, relatives, and the participant about participation (the information should be provided by a trained doctor) and obtain informed consent for continued participation (**see the consent guideline in the participant folder**). Informed consent and written consent should be documented in the medical record when conducted or obtained.
5. **Pick a participant trial folder** which holds the participant-specific documents

3. Interventions

Empiric meropenem or piperacillin/tazobactam intravenously up to 30 days from randomisation or until:

- Discharge from a participating site (with the intervention continued if relevant in case of readmissions within the intervention period)
- Termination of empirical treatment including initiation of definitive antibiotic treatment, or de-escalation to another empirical antibiotic with narrower spectrum (not including the two trial interventions), i.e., in situations where no bacteria are found in microbiological cultures, whichever comes first

Antibiotic combination therapy is allowed in both arms (e.g., empirical use of other antibiotics in addition to the trial intervention, except that meropenem and piperacillin/tazobactam cannot be used as a second antibiotic - participants cannot receive both antibiotics).

If test results from cultures and antimicrobial susceptibility tests show that de-escalation is not possible, but that there is presumed equal sensitivity to the two trial drugs, we recommend continuing the intervention as per randomisation.

Dosing will be at the discretion of the treating clinician, including reductions for impaired kidney function, low/high weight, and use of bolus or prolonged/continuous infusion.

From day 31 through 180, we recommend using the same empirical antibiotic strategy as the participant was randomised to if there is a new indication for empirical broad-spectrum antibiotic treatment, but we will not collect data on the use of antibiotics after the intervention period (i.e., day 30) and do not consider this part of the trial intervention.

Discharge

Participants who are discharged or transferred to a site participating in the EMPRESS trial will continue the allocated treatment at the new trial site if still relevant. If so, the trial-specific order should be changed to a standard order. The participant will still be followed through the electronic patient records. If the participant is readmitted to an EMPRESS trial site within 30 days of randomisation, the allocation should resume if relevant.

4. Safety reporting

Serious adverse reactions are defined as those below and will be registered daily in the eCRF within 30 days of randomisation without making inference about causality (they are known adverse reactions):

- Anaphylactic shock to IV meropenem or piperacillin/tazobactam
- Invasive fungal infection
- Pseudomembranous colitis (symptoms and signs of infection in large intestine and at least one culture or PCR-test demonstrating Clostridioides difficile in faeces)
- Toxic epidermal necrolysis

Serious adverse events

Investigator and clinicians may at any time report a serious adverse event using the paper SAE-form in the Site File folder, which is to be uploaded in the eCRF (Event folder). If the event is serious, unexpected and considered related to the trial intervention it is a **SUSAR, which must be reported to the sponsor within 24 hours**. If fatal or life-threatening, the sponsor will report it within 7 days to all trial sites and relevant authorities (via CTIS in EU, or in collaboration with national investigators elsewhere). Other SUSARs must be reported to the competent authorities within 15 days.

5. Follow-up

Follow-up at 180 days is performed by trial staff at the site or centrally collecting data on health-related quality of life (EQ-5D-5L and EQ-VAS). This is done by phone or mail as chosen by the participant.

Do not contact any participants who have withdrawn consent for follow-up.

If the participant cannot be reached at 180 days follow-up, make frequent attempts during the following two weeks to establish contact to the participant or proxy, until 180 days follow-up is obtained. It is OK to use more than 2 additional weeks – the most important thing is to get the answers.

If the participant chooses to answer by post, the time for obtaining answers can be extended by the time needed**. It is important the answers are dated and if proxy answered.**