Study protocol

Study title: A National Cross-Sectional Survey of Organizational Routines and Clinical Guidelines for Norepinephrine Administration in Sepsis (The NORA-Survey)

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1. Background

Current international guidelines strongly recommend norepinephrine (NE) as the first-line vasopressor for sepsis-induced hypotension (1). However, the optimal timing of NE initiation remains uncertain, and clinical practice varies widely (1-7). While early fluid resuscitation is a cornerstone of sepsis management, excessive fluid accumulation is increasingly recognized as an independent risk factor for adverse outcomes, including multi-organ dysfunction and death (8-12).

Recent evidence suggests that early administration of NE may reduce the total volume of fluid required for resuscitation and achieve faster hemodynamic stabilization (5, 7, 13). Despite this, central venous administration of NE is traditionally recommended due to the risk of adverse events like tissue necrosis, which can delay its initiation (14, 15). Peripheral administration is practiced, but local routines and regulations vary significantly across hospitals (15-17). This study aims to describe these differences in local routines and regulations across Swedish emergency hospitals.

2. Objectives

To characterize current clinical practices, local guidelines, and perceived barriers regarding the initiation of norepinephrine therapy in patients with sepsis and hypotension across Swedish hospitals. Additionally, the survey aims to assess the feasibility of, and national willingness to participate in, a future multicenter randomized controlled trial evaluating early norepinephrine administration.

3. Methods

3.1 Study design A national, web-based cross-sectional survey targeting Medical Lead Physicians (MLP) in both Anesthesia/Intensive Care and Emergency Medicine. The study design and reporting will adhere to the Checklist for Reporting Results of Internet E-Surveys (CHERRIES) guidelines.

3.2 Population and recruitment

Target population: All emergency hospitals in Sweden, specifically targeting both the Intensive Care Units (ICUs) and the Emergency Departments (EDs). Intermediate Care Units (IMCU/IMA) are excluded from the target population because there is currently no comprehensive national registry for these units, which precludes the systematic identification and retrieval of contact information.

Respondents: At each participating hospital, two distinct respondents will be targeted:

1. The MLP, or equivalent physician with a management role, in Anesthesia and Intensive Care.
2. The MLP, or equivalent physician with a management role, in Emergency Medicine.

By sending separate, unique survey links to both departments, the study aims to capture independent perspectives and identify potential discrepancies in perceived clinical routines, local guidelines, and inter-departmental consensus regarding early sepsis management.

Sampling: The total number of eligible emergency hospitals will be determined a priori using open public data from the Swedish Intensive Care Registry (SIR) and the National Board of Health and Welfare. Because SIR does not disclose direct personal contact information for research purposes, the email addresses for the respective MLPs will be obtained through a structured multimodal approach. This includes collaboration with the Swedish Society of Anaesthesiology and Intensive Care Medicine (SFAI) and the Swedish Society for Emergency Medicine (SWESEM), supplemented by manual networking and direct inquiries via hospital switchboards and official directories. This predetermined number of hospitals will serve as the strict denominator for reporting view, participation, and completion rates in accordance with the CHERRIES guidelines.

Distribution: The survey will be distributed via email using unique links to the electronic data capture tool REDCap. Reminders will be sent to non-responders at 2 and 4 weeks. The survey will remain open for a total of 6 weeks.

3.3 Survey design

The questionnaire consists of 24 items assessing the departments in which NE is used, prescribing specialties, administration routes, monitoring requirements, and perceived barriers to early NE initiation. The use of unique REDCap survey links will automatically prevent multiple entries from the same respondent. The REDCap survey utilizes conditional branching logic to display relevant follow-up questions based on previous responses. All items will be set as mandatory, utilizing automated completeness checks (i.e. prompting the respondent if a field is left blank). Respondents will be provided with a summary screen to review and alter their answers prior to final submission. Prior to national distribution, the survey instrument will undergo a rigorous three-step validation and pilot testing process to ensure face validity, content validity, and technical functionality:

1. **Expert Review:** An initial review by a panel of subject matter experts to evaluate clinical terminology, relevance, and the exhaustiveness of response options.
2. **Cognitive Interviewing:** The survey will be pilot-tested with a convenience sample of 3–5 senior physicians from the target specialties utilizing the 'Think Aloud' protocol and verbal probing techniques. This step aims to identify and resolve any cognitive friction, semantic ambiguity, or varying interpretations of the clinical scenarios (e.g., assessing the construct validity of perceived organizational barriers).
3. **Technical Field Pilot:** A final technical test of the REDCap instrument simulating the complete user journey to verify conditional branching logic, mandatory field constraints, and automated completeness checks, thereby minimizing the risk of survey attrition and missing data.

4. Ethical considerations

The survey investigates organizational routines and local clinical guidelines, and no sensitive personal health data or patient-level data will be collected. Prior to accessing the questionnaire, respondents will be presented with an introductory information screen outlining the study purpose, data management procedures, investigator contact information, and an estimated completion time of approximately 5 minutes. Informed consent will be obtained electronically; by actively proceeding beyond the introductory screen and completing the survey, participants consent to the use of their anonymized responses for research purposes. To enhance usability, the survey items will be presented across multiple screens rather than a single scrolling page. Because the study does not involve human subjects research as defined by the Swedish Ethical Review Act (SFS 2003:460), no formal ethical permit is required and none will be sought. No financial or material incentives will be offered for participation.

5. Data management and statistical analysis

Data will be securely collected and stored in a REDCap database hosted by Region Stockholm behind institutional firewalls. Access to the raw dataset will be strictly restricted to the core research group. Responses will be analyzed at the hospital level. Categorical variables will be presented as frequencies and percentages. Subgroup analyses (e.g., University/Regional hospitals vs. County hospitals vs. District hospitals, according to the SKR classification) will be performed using Pearson's Chi-squared test or Fisher's exact test, as appropriate. As the REDCap survey requires mandatory responses for all items, missing data will only occur in the event of a premature survey drop-out. Available data from such incomplete (abandoned) surveys will be analyzed for the answered items; missing data will not be imputed. To prevent duplicate data, each participating hospital will be issued a single, designated REDCap survey link directed to each MLP. Consequently, up to two final responses per hospital (one representing the ICU and one representing the ED) will be recorded. Responses will be analyzed both aggregately and comparatively to identify intra-hospital discrepancies in perceived routines.

6. References

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Appendix: Survey items

Important Note: All questions in this survey refer exclusively to local routines and clinical guidelines for adult patients (≥ 18 years of age).

Q_Hospital: Please enter the name of your hospital: [Free text field]

Q1: Which category best describes your hospital?

[ ] University / Regional Hospital

[ ] County Hospital

[ ] District / Smaller Emergency Hospital

Q2: What type of intensive care is provided at your hospital? (Select all that apply)

[ ] General ICU

[ ] Neuro ICU

[ ] Thoracic ICU

[ ] Burn ICU

[ ] Other specialized ICU (please specify): _____

Q3: What is your primary clinical role?

[ ] Consultant in Anesthesia and Intensive Care

[ ] Consultant in Emergency Medicine

[ ] Senior Consultant in Anesthesia and Intensive Care

[ ] Senior Consultant in Emergency Medicine

[ ] Other (please specify): _____

Q4: In which departments does the initiation of norepinephrine for sepsis patients occur at your hospital? (Select all that apply)

[ ] Emergency Department

[ ] Intermediate Care Unit

[ ] Intensive Care Unit

[ ] Operating Room

[ ] Regular Ward

[ ] Other (please specify): _____

Q5: Which medical specialties usually prescribe and initiate norepinephrine at your hospital? (Select all that apply)

[ ] Anesthesiology and Intensive Care

[ ] Emergency Medicine (Independent initiation)

[ ] Emergency Medicine (Only after ICU consult)

[ ] Internal Medicine

[ ] Infectious Diseases

[ ] Cardiology

[ ] Other (please specify): _____

Q6: Is peripheral intravenous administration of norepinephrine permitted at your hospital?

[ ] Yes, routinely

[ ] Yes, but only in life-threatening emergencies or while waiting for central line

[ ] No, central venous access is strictly required

Q6b: Additional comments regarding local permissions for peripheral administration (optional): [Free text field]

Q7: If peripheral administration is permitted, what is the maximum allowed concentration of norepinephrine?

[ ] 0.008 mg/ml (8 µg/ml)

[ ] 0.01 mg/ml (10 µg/ml)

[ ] 0.04 mg/ml (40 µg/ml)

[ ] 0.08 mg/ml (80 µg/ml)

[ ] No standardized maximum concentration

[ ] Other (please specify): _____

Q7b: What is the maximum dose of norepinephrine permitted peripherally?

[ ] 0.05 microg/kg/min

[ ] 0.1 microg/kg/min

[ ] 0.2 microg/kg/min

[ ] Other (please specify):_____

Q8: Is there a specific maximum time limit for how long norepinephrine can be administered peripherally before a central line must be inserted?

[ ] Yes, maximum 12 hours

[ ] Yes, maximum 24 hours

[ ] Yes, until a central line can be safely inserted

[ ] No specific time limit

[ ] Other (please specify): _____

Q9: What are the minimum monitoring requirements for peripheral administration of norepinephrine at your hospital? (Select all that apply)

[ ] Continuous ECG monitoring

[ ] Arterial catheter

[ ] NIBP cycling at maximum 5-minute intervals

[ ] Documented peripheral IV site checks

[ ] Other (please specify): _____

Q10: Does your hospital have a specific written protocol or action plan for managing norepinephrine extravasation?

[ ] Yes

[ ] No

[ ] I don't know / Other (please specify): _____

Q11: What is the hemodynamic target (trigger) for initiating norepinephrine according to your local sepsis guidelines?

[ ] MAP < 65 mmHg

[ ] SBP < 90 mmHg

[ ] Individualized targets only

[ ] No specific target is defined

[ ] Other (please specify): _____

Q12: Do your local sepsis guidelines include a specific time target for initiating vasopressors?

[ ] Yes, within 1 hour

[ ] Yes, another specific time target (please specify): _____

[ ] No specific time target

[ ] Other (please specify): _____

Q13: Do your local guidelines require a specific volume of intravenous fluid to be administered before initiating norepinephrine?

[ ] Yes, a fixed volume is recommended *Hidden/branching if "Yes": If yes, what is the required volume?*

[ ] < 15 ml/kg

[ ] 15 – 25 ml/kg

[ ] 30 ml/kg

[ ] > 30 ml/kg

[ ] No, a fixed volume is recommended

[ ] No, treatment is individualized

[ ] No, concurrent initiation is encouraged

[ ] Other (please specify): _____

Q14: Are other vasopressors routinely used in the Emergency Department as a bridge while preparing the norepinephrine infusion? (select all that apply)

[ ] Yes, ephedrine boluses

[ ] Yes, phenylephrine boluses

[ ] Yes, epinephrine boluses

[ ] Yes, norepinephrine boluses

[ ] No, bridging is not routinely used

[ ] Other (please specify): _____

Q15: Is the weaning (step-down) of norepinephrine infusions permitted outside the Intensive Care Unit?

[ ] Yes, routinely permitted in Intermediate Care Unit

[ ] Yes, under strict conditions

[ ] No, must be managed in Intensive Care Unit

[ ] We do not have an Intermediate Care Unit

[ ] Other (please specify): _____

Q16: Primary barriers to early initiation of norepinephrine (Select all that apply)

[ ] Insufficient physician staffing/competence in Emergency Department

[ ] Insufficient nursing staffing/competence in Emergency Department

[ ] Lack of suitable beds with adequate monitoring and equipment in the Emergency Department

[ ] Lack of Intermediate Care Unit beds

[ ] Lack of Intensive Care Unit beds

[ ] Strict local requirements for central lines

[ ] Safety concerns

[ ] Lack of clear local protocols

[ ] Lack of clinical consensus/boundary dispute

[ ] Other (please specify): _____

Q16a: Of the primary barriers chosen in the last question, which single barrier is most important?

[ ] Insufficient physician staffing/competence in Emergency Department

[ ] Insufficient nursing staffing/competence in Emergency Department

[ ] Lack of suitable beds with adequate monitoring and equipment in the Emergency Department

[ ] Lack of Intermediate Care Unit beds

[ ] Lack of Intensive Care Unit beds

[ ] Strict local requirements for central lines

[ ] Safety concerns

[ ] Lack of clear local protocols

[ ] Lack of clinical consensus/boundary dispute

[ ] Other (please specify): _____

Q17: How frequently is norepinephrine initiated peripherally in the Emergency Department?

[ ] Routinely

[ ] Occasionally

[ ] Rarely

[ ] Never

Q18: How would you rate the clinical compliance with your local sepsis guidelines regarding initiation of norepinephrine?

[ ] Excellent

[ ] Good

[ ] Fair

[ ] Poor

Q19a: We are planning a future randomized multicenter trial (RCT) where patients with sepsis-induced hypotension are randomized to either an intervention group (early peripheral norepinephrine initiated in the Emergency Department simultaneously with the first fluid bolus) or a control group (standard care defined as: norepinephrine initiation is delayed until Intensive Care Unit admission). The study workflow will involve the on-call Intermediate Care (IMA) and/or Intensive Care (ICU/IVA) physician. Based on the current situation at your hospital, would your department find it clinically and ethically acceptable to participate and randomize patients to these two arms?

[ ] Yes, we find both the intervention and control arms acceptable

[ ] No, we have clinical/ethical concerns regarding the intervention arm (early Emergency Department start)

[ ] No, we have clinical/ethical concerns regarding the control arm (delaying start until Intensive Care Unit admission)

[ ] No, our department cannot participate for other administrative or logistical reasons
[ ] I don't know / Cannot answer at this time

Q19b: What would be the primary barriers to conducting this specific trial design at your hospital? (Select up to 2)

[ ] Lack of research resources (e.g., shortage of study nurses, time, or administrative support)

[ ] Safety concerns regarding peripheral administration of vasoactive drugs in the Emergency Department

[ ] Ethical concerns regarding peripheral administration of vasoactive drugs in the Emergency Department

[ ] Practical concerns regarding peripheral administration of vasoactive drugs in the Emergency Department (e.g, lack of training, lack of equipment such as monitoring and infusion pumps)

[ ] Ethical concerns regarding delaying norepinephrine to the Intensive Care Unit (e.g., if the hospital already routinely practices early Emergency Department initiation)

[ ] Difficulties in reaching consensus between Emergency Medicine and Anesthesia/Intensive Care Unit regarding adherence to the protocol

[ ] Low patient volumes or competing trials

[ ] No obvious barriers exist