Position Paper on the Reporting of Norepinephrine Formulations in Critical Care from the Society of Critical Care Medicine and European Society of Intensive Care Medicine Joint Task Force

OBJECTIVES: To provide guidance on the reporting of norepinephrine formulation labeling, reporting in publications, and use in clinical practice.

DESIGN: Review and task force position statements with necessary guidance.

SETTING: A series of group conference calls were conducted from August 2023 to October 2023, along with a review of the available evidence and scope of the problem.

SUBJECTS: A task force of multinational and multidisciplinary critical care experts assembled by the Society of Critical Care Medicine and the European Society of Intensive Care Medicine.

INTERVENTIONS: The implications of a variation in norepinephrine labeled as conjugated salt (i.e., bitartrate or tartrate) or base drug in terms of effective concentration of norepinephrine were examined, and guidance was provided.

MEASUREMENTS AND MAIN RESULTS: There were significant implications for clinical care, dose calculations for enrollment in clinical trials, and results of datasets reporting maximal norepinephrine equivalents. These differences were especially important in the setting of collaborative efforts across countries with reported differences.

CONCLUSIONS: A joint task force position statement was created outlining the scope of norepinephrine-dose formulation variations, and implications for research, patient safety, and clinical care. The task force advocated for a uniform norepinephrine-base formulation for global use, and offered advice aimed at appropriate stakeholders.

KEYWORDS: hypotension; norepinephrine; patient safety; research methods; shock; vasopressor

Patrick M. Wieruszewski, PharmD, BCCCP[1,2]

Marc Leone, MD, PhD[3]

Benjamin Skov Kaas-Hansen, MD, MSc, PhD[4]

Siddharth Dugar, MD, FCCP, FCCM, FASE[5,6]

Matthieu Legrand, MD, PhD[7]

Cathrine A. McKenzie, BPharm, PhD[8]

Brittany D. Bissell Turpin, BCCCP, PharmD, PhD, FCCM[9,10]

Antonio Messina, MD, PhD[11,12]

Prashant Nasa, MD, EDIC[13]

Christa A. Schorr, DNP, MSN, RN, FCCM[14,15]

Jan J. De Waele, MD, PhD[16,17]

Ashish K. Khanna, MD, MS, FCCP, FASA, FCCM[18,19]

Norepinephrine (also named noradrenaline), a catecholamine vasopressor, is ubiquitous in contemporary critical care practice. This agent is recommended by the Surviving Sepsis Campaign as a first-line vasopressor and most providers report using this agent for the correction of hypotension in septic shock (1–4). Although mortality rates from septic shock have improved, the global incidence is rising (5), increasing the usage of norepinephrine in ICUs across the world. The impact of norepinephrine in critical care practice was evident when septic shock in-hospital mortality rates increased during a brief 6-month period of critical shortage of norepinephrine in the United States, resulting in clinicians resorting to alternatives (6). Accurate and transparent handling and reporting of norepinephrine use at

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the bedside and in research is of utmost importance. We identified an important variation in the presentation of norepinephrine formulations across geographically distinct areas of the world. We present a Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine (ESICM) joint task force position statement, discuss the concept of different norepinephrine-salt formulations, its implications for critical care practice and research, and provide global guidance on uniform practices related to norepinephrine formulation production and reporting.

Scope and Task Force Composition

The concept of total dose of norepinephrine as a single agent or, in some cases, as norepinephrine equivalence has been used as a threshold to guide clinical care, prognostication for organ system injury and mortality, and as an enrollment criterion for important randomized trials (2, 7–10). Based on recent publications highlighting potential variation and lack of necessary details surrounding the reporting of norepinephrine-dose formulations in research (11, 12), the SCCM and ESICM commissioned a joint task force. The task force was composed of a multidisciplinary group of experts that were identified by each society based on clinical and research expertise in shock and vasopressors while ensuring diverse geographical representation within the societies' jurisdictions. The task force was charged with detailing the scope of norepinephrine-salt formulation reporting on approved pharmaceuticals, implications for clinical care and research, and formal guidance for institutions, pharmaceutical industry, critical care staff, and researchers.

Available electronic databases of approved/licensed pharmaceuticals in North American, European, Australasian, and Middle Eastern regions were manually queried for regulatory documents related to norepinephrine and noradrenaline. The task force retrieved additional documents by contacting local experts in countries in which electronic databases were not accessible. The medical literature was searched via MEDLINE and Ovid by task force members to identify relevant research potentially impacted by norepinephrine dosage reporting. The recommendations produced by the task force were based on expert opinion with the information identified rather than specific certainty in evidence procedures (e.g., Grading of Recommendations, Assessment, Development, and Evaluations). Lastly, a brief survey was distributed to the principal investigators from participating centers in the ongoing ANDROMEDA SHOCK-2 trial, an international, multicontinental, randomized controlled trial (RCT) of peripheral perfusion-guided septic shock resuscitation (**Supplemental Table 1**, http://links.lww.com/CCM/H477) (13). This served as a contemporary representative sample of current practices and intensivist knowledge and opinions related to differences in norepinephrine formulations. Significant heterogeneity was identified to deal with, which the ANDROMEDA SHOCK-2 study required participating centers to report norepinephrine doses only in μg/kg/min. In addition, the database included the reporting of the formulation of norepinephrine available at each center with an automatic homogenization to the drug's base equivalent.

Norepinephrine-Salt Formulations

Active pharmaceutical ingredients (i.e., chemical molecules) require processing to enable administration to humans. For injectable medications, processing molecules as salt formulations, that is, an anionic or cationic conjugated form of the molecule, is common during manufacturing. In the United States, for example, nearly two-thirds of all injectable products are processed as salt formulations (14). Such salt formulations are critical for addressing a variety of biological and physicochemical issues with medicinal products, including stability, absorption, toxicity, manufacturing, and most commonly, increasing the aqueous solubility of active pharmaceutical ingredients, thereby facilitating IV administration of the salt–drug compound (15).

Norepinephrine, a trihydroxy-substituted phenethylamine, is poorly soluble in water, alcohol, and ether, but is very soluble in acid (16). Thus, norepinephrine is unavailable for clinical use in its pure molecular form and, as such, must be processed to a salt formulation through solubilization in acids, which ultimately enables its administration by IV infusion in humans (**Table 1**). For the purposes of simplistic illustration in this article, all notations of "salt formulation" further on will specifically be referenced to norepinephrine tartrate. In an injectable solution, salt formulations of norepinephrine, on a weight-by-volume basis, weigh more due to the conjugated salt presence. For example, 2 mg of norepinephrine

TABLE 1.
Available Norepinephrine-Salt Formulations and their Dose Equivalency

Salt Formulation	Salt Formulation Dosage (mg)	Base Molecule Equivalency (mg)
Norepinephrine hydrochloride	1.22	1
Norepinephrine bitartrate (anhydrous basis)[a]	1.89	1
Norepinephrine tartrate	2	1

[a]Also commonly referred to as "acid tartrate."

Salt formulation equivalent dosages are calculated using molecular weights of compounds and taken as a ratio to the molecular weight of norepinephrine base. Compound structure and molecular weight information obtained from PubChem, National Institutes of Health, and National Library of Medicine (https://pubchem.ncbi.nlm.nih.gov/).

tartrate "salt formulation" contains 1 mg of norepinephrine "base molecule." Whether norepinephrine is expressed as "base (norepinephrine)" or "salt (e.g., bitartrate or tartrate)" is critical, as this can dramatically impact the actual norepinephrine dosage prescribed and administered to a patient (**Fig. 1**). For example, if vial labeling reflects salt formulation concentration and is inadvertently perceived and used as base concentration, a prescribed, administered, and reported dose of norepinephrine at "1 µg/kg/min would in fact only constitute 0.5 µg/kg/min of norepinephrine base" (Fig. 1).

Although there has been significant attention surrounding norepinephrine infusion concentrations and efforts to standardize concentrations across ICUs for enhanced patient safety, there has been little attention or education surrounding whether the drug is expressed as a salt or base formulation (17). In a survey of intensivists across 75 countries worldwide, half of respondents were unaware of which norepinephrine salt formulation was used in their ICUs (4), implying a lack of awareness of how norepinephrine dosage is reported on the products prepared for administration at the bedside.

IMPLICATIONS

Norepinephrine, with its vasoconstrictive and positive inotropic effect, is the preferred agent in patients with acute hemodynamic failure. The higher likelihood of dying in these patients emphasizes the need for rigor and accuracy when prescribing and administering this agent. At the bedside, most ICU teams define their hemodynamic goals in patients with shock and set the

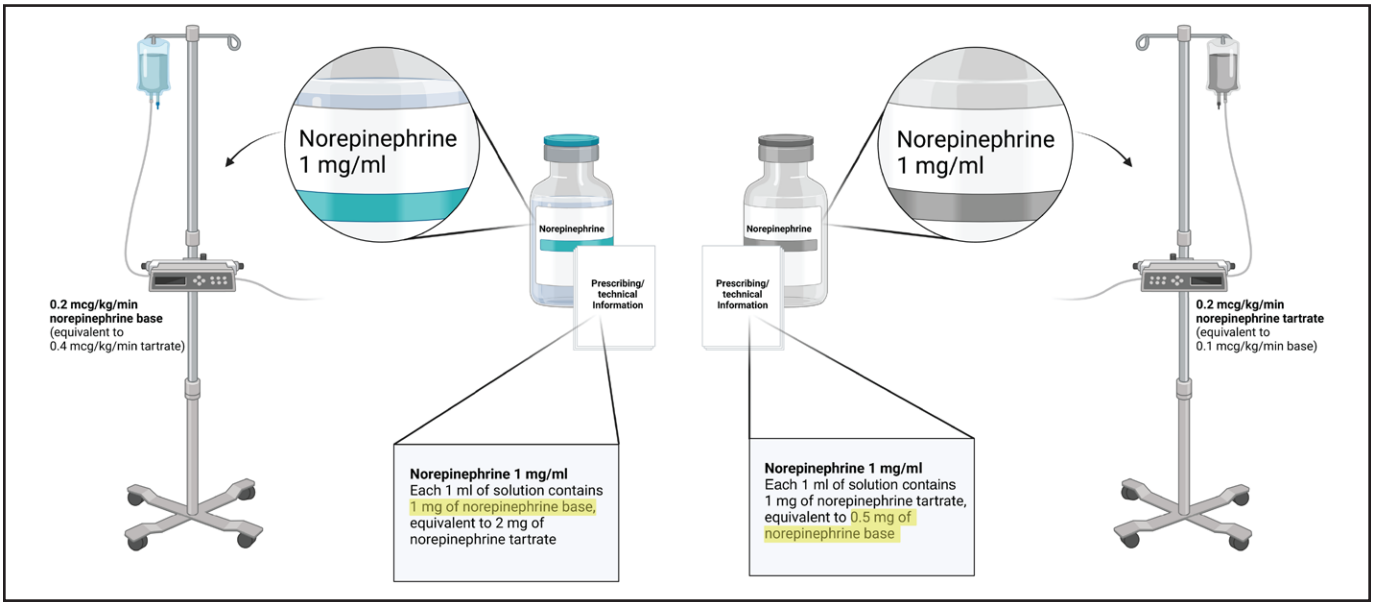

Figure 1. Examples of norepinephrine (NE) vials labeled with base molecule formulation (*left*) and salt formulation (*right*), with their respective prescribing or technical information details and downstream effects on clinician dosing.

starting infusion dose and titration intervals to achieve those goals, commonly mean arterial pressure (4). However, the norepinephrine dose itself is a clinically meaningful metric with a number of important considerations. Specifically, knowing the global variations in norepinephrine reporting as base or salt formulation changes the meaning of different doses of norepinephrine and clinical dose responses compared across hospitals and countries (**Fig. 2**).

Severity Assessment

The large granularity of data from ICU patients makes critical care a natural habitat of artificial intelligence (18), and although many modern machine learning-based scores exploit this granularity for better prognostication (19, 20), several conventional models exist that are used (21). Regardless of methodology, erroneous norepinephrine dosing information hampers development and validation of severity scores: if multiple datasets are used with different dosing information, the resulting model is unlikely to express a genuine relationship between dose and outcome if such differences are not explicitly harmonized, and if norepinephrine base and apparent dosing differ, a model cannot be expected to perform well in external data which would defeat the purpose of external validation.

Overall, the hampered performance of severity scores will undermine their utility. The Sequential Organ Failure Assessment (SOFA) score, for example, is widely used for adjusting for disease severity across populations (22, 23). Receiving greater than or equal to 0.1 norepinephrine μg/kg/min adds 1 point to the overall SOFA score, leaving a gray area around this cutoff with potential for erroneous scoring (**Fig. 3**). Multinational studies can provide inconsistent results if the norepinephrine dose differs across centers from different countries (25).

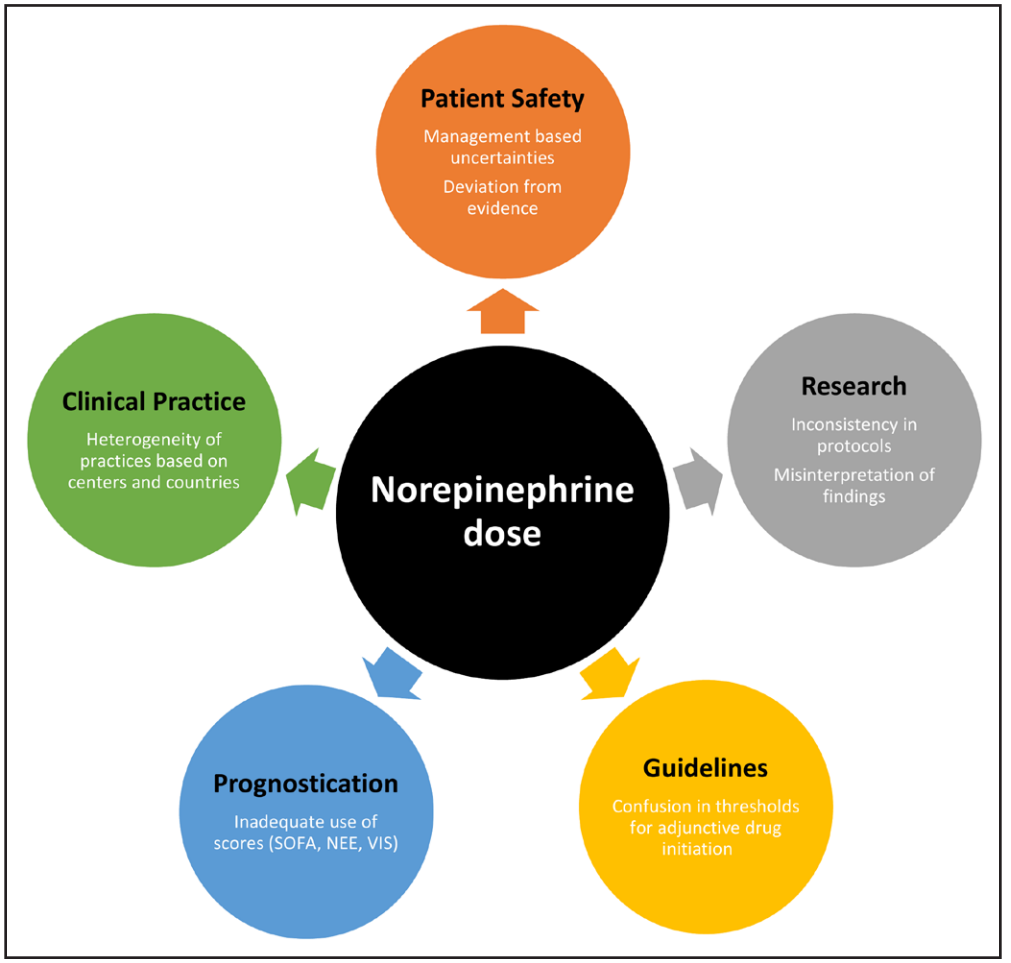

Figure 2. Global implications of using different norepinephrine formulations when using and reporting doses in critical care. NEE = norepinephrine equivalents, SOFA = Sequential Organ Failure Assessment, VIS = vasoactive-inotropic score.

Research Reporting and Estimates

The lack of clear reporting of norepinephrine formulations is significant in research literature. The prime purpose of RCTs is to quantify (or refute) causal effects of select exposures on pertinent outcomes. Observational epidemiology often has the same aspirations, commonly in the form of case–control and cohort studies.

Study Enrollment and Enrichment

Eligibility criteria serve to align study and target populations. Enrichment can be used to maximize statistical power by including patients likely to respond to the exposure and/or experience the outcome (26). Although the distinction

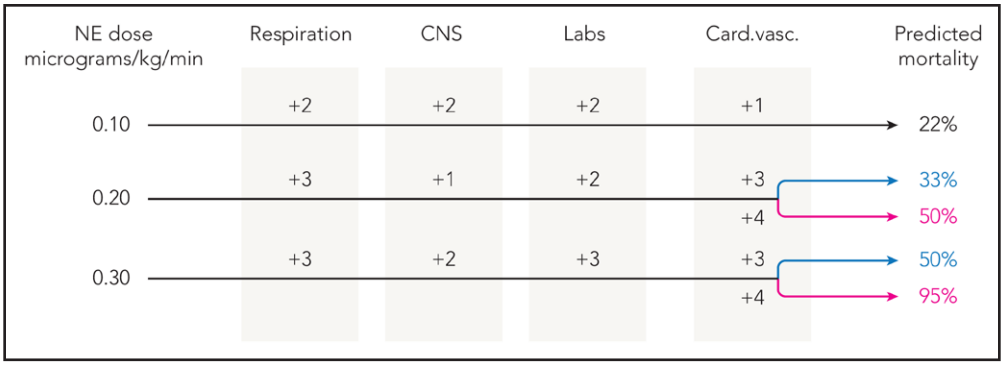

Figure 3. The effect of using different norepinephrine (NE) formulations in calculating the initial Sequential Organ Failure Assessment score. *Blue* and *pink lines* show the predicted mortality if the dose (first column on the *left*) is NE base and NE tartrate, respectively. The predicted mortality rates are based on those reported by Ferreira et al (24).

between these two may be ill-defined (27), inconsistent norepinephrine-dose information across sites or data sources will introduce irreparable heterogeneity in the study population and, thus, noise in the statistical analysis that will likely bias results in unpredictable ways and preclude actionable insights.

The resulting premature enrollment based on perceived dose can have a number of consequences that distort outcome data from such sites (28) (**Fig. 4**).

Exposure Quantification, Dose Response Relationships, and Outcomes

When the effect of norepinephrine on mortality is assessed (7, 9, 29), erroneous norepinephrine-dose information could both reduce and increase separation through systematic differences in RCTs, and cause misclassification of exposure (30) in observational studies, which can bias estimates toward the null.

The association between maximum required norepinephrine dose and organ system failure has consistently been demonstrated (21). Specifically, the appropriate choice and timing of second- and third-line vasopressors (more often noncatecholamine agents) have been questioned. Early initiation of vasopressin was recently determined to be helpful (31). Similarly, a substantial part of early-multimodal vasopressor therapy comes from prior published large datasets demonstrating a dose-dependent relationship between exclusive monotherapy with catecholamines (mainly norepinephrine) and adverse outcomes (22, 32). These observational studies are clouded by confounding and are liable to become further unreliable, especially if they work across countries or areas with different norepinephrine formulations.

Similarly, norepinephrine equivalents (NEE) are sometimes used as screening and enrollment thresholds. NEE calculation per se is complicated and has been questioned as to its correlation with a dose–response relationship across vasopressor classes and organ system injury (10, 33). This notwithstanding, NEE is still the basis of quantification of a "vasopressor or vasoregulatory dose burden" in many prospective interventional studies. Several landmark trials have used NEE thresholds for eligibility and/or subgroup analyses (8, 34–39). Doing so may introduce noise and regional variability such as that seen in the Angiotensin II for the Treatment of High-Output Shock (ATHOS-3) trial (40). Even when norepinephrine is not the exposure of interest, correct norepinephrine dose information is key for drawing valid conclusions. For example, due to its relationship with adverse outcomes, patients who require higher norepinephrine doses might respond more strongly to auxiliary treatment for septic shock because the potential for improvement in such patients is, a priori, greater. Similarly, patients who receive high doses of norepinephrine (and are eligible for a particular study) may respond more strongly to interventions that target other pathways than those of norepinephrine because the latter may already be saturated. Correct norepinephrine dose information is obviously crucial to correctly recognize and quantify such effect modifications.

Thus, reassessment of results from international studies using norepinephrine doses for inclusion or to trigger auxiliary treatments may be warranted to recalibrate exposure and ensure external validity. In addition, meta-analyses assessing dose–response effects would necessitate consistency in norepinephrine dose information. For example, combining North American (7) and French (30) patients in meta-analysis without confirming consistent norepinephrine formulations may render accurate comparison and interpretation of results unfeasible.

Bedside Care and Guidelines

Enacting guidelines correctly at the bedside is crucial to patient safety and clinical effectiveness.

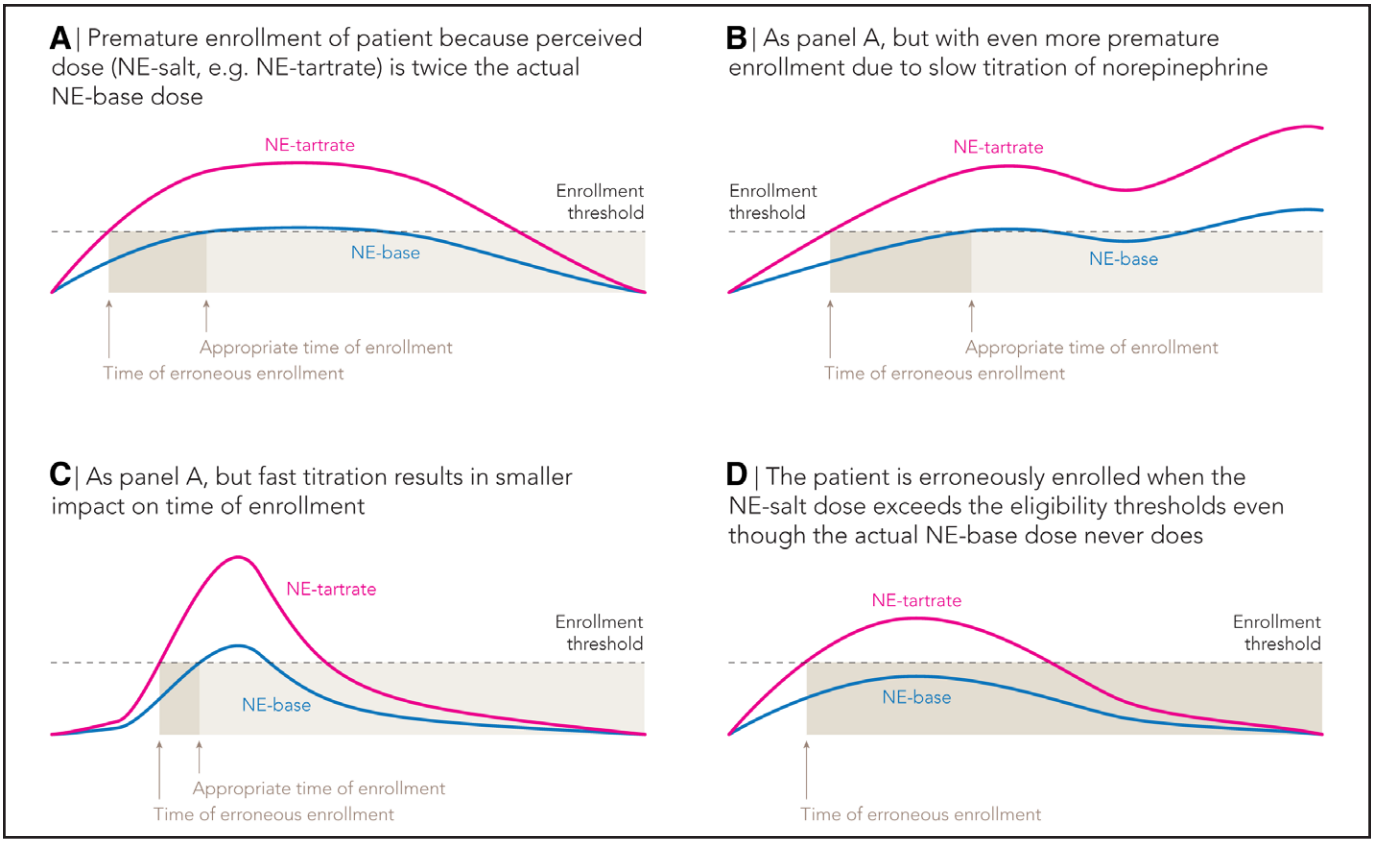

Figure 4. Implications of using different norepinephrine (NE) formulations on patient enrollment based on norepinephrine thresholds as inclusion criteria.

Several illustrative examples exist for when erroneous norepinephrine dose information jeopardizes this; here, we choose to exemplify the challenges in dose-equivalence estimation and augmenting vasopressor therapy in patients with refractory shock.

Dose Equivalence. Several methods exist for quantifying vasopressor load, for example, the vasoactive-inotropic score (VIS), NEE, and cumulative vasopressor index (10, 41, 42). The VIS was built to predict morbidity and mortality in infants after cardiopulmonary bypass (43) and seeks to quantify the degree of hemodynamic support in patients with shock receiving mechanical circulatory support (44–46). Similarly, NEE, which has been used in RCTs to define inclusion criteria, comparing baseline characteristics and reporting outcomes is a standardized method of describing the degree of vasopressor support in patients receiving multiple vasoactive agents (35, 47, 48). Both VIS and NEE handle norepinephrine doses on a continuous scale, and VIS and NEE from two centers will be inherently incomparable unless both are based on base-norepinephrine dose. Even if they both use norepinephrine-salt doses, they may not be comparable as the base equivalence differs between different salt formulations (Table 1). Indeed, a site using norepinephrine-salt formulation will overshoot NEE doses by 0.1 μg/kg/min for patient receiving an infusion of 0.2 μg norepinephrine-tartrate/kg/min (equivalent to 0.1 norepinephrine base μg/kg/min), while the VIS will be erroneously high by 10.

Refractory Shock. Norepinephrine dose plays a key role in the definition of refractory shock. Although there is no established criterion, a common threshold in clinical practice is inadequate mean arterial pressure despite infusion of greater than or equal to 0.8 to 1 μg/kg/min NEE (49). Thus, inconsistent norepinephrine-dose information will introduce different de facto thresholds for when a patient is deemed to suffer from refractory shock and, consequently, when initiation of auxiliary treatment is indicated. As an example, the Surviving Sepsis Campaign guidelines suggest starting corticosteroids when the norepinephrine dose exceeds 0.25 μg/kg/min at least 4 hours after initiation. Similarly, the panelists state that, in their practice, vasopressin is usually added when the dose of norepinephrine is between 0.25 and 0.5 μg/kg/min (50).

Depending on the evidence base of this recommendation and the formulation used at the institution of a given clinician, this range could represent anything between 0.125 norepinephrine base (equivalent to 0.25 norepinephrine-tartrate/2) and 1.0 norepinephrine-tartrate (equivalent to 0.5 norepinephrine-base × 2) micrograms norepinephrine/kg/min (**Fig. 5**).

Other auxiliary treatments are more invasive and may result in serious complications. For example, the Extracorporeal Life Support guidelines recommend weaning from venoarterial extracorporeal membrane oxygenation should be attempted upon reaching minimal vasoactive therapy, defined as less than 0.06 μg/kg/min (51). Thus, weaning attempts may be started later than recommended if performed when a patient is receiving, for example, 0.06 μg norepinephrine-salt/kg/min instead of 0.06 μg norepinephrine-base/kg/min (equivalent to 0.12 μg norepinephrine-salt/kg/min) (Fig. 5).

GUIDANCE FROM THE TASK FORCE

This international, multidisciplinary task force recommends that a uniform, global standard method of using and reporting norepinephrine doses and formulations be adopted. The task force also recommends that norepinephrine base (i.e., norepinephrine) should be used over norepinephrine-salt (e.g., norepinephrine-tartrate or -bitartrate). This guidance applies to hospital organizations, clinical care, research, and drug manufacturers, as detailed below, and summarized in **Table 2**.

Hospital Organization

Hospital organizations (including hospital pharmacies and drug formulary) should use a uniform method of reporting norepinephrine product concentrations and doses used in infusions in their policies and procedures. The staff training on the policies or procedures should advocate for the uniform reporting of norepinephrine as base within the organization.

Clinical Care

Uniform reporting of norepinephrine concentration as a norepinephrine base should be used for drug prescription, drug dilution, labeling and compounding, dispensing, administration, and medical records documentation. A uniform reporting method of norepinephrine-base formulation should be used for communication among stakeholders such as pharmacists, nurses, and clinicians at the bedside. The integration of uniformly reporting norepinephrine doses in base formulation in the patient data management system reduces the risk of error.

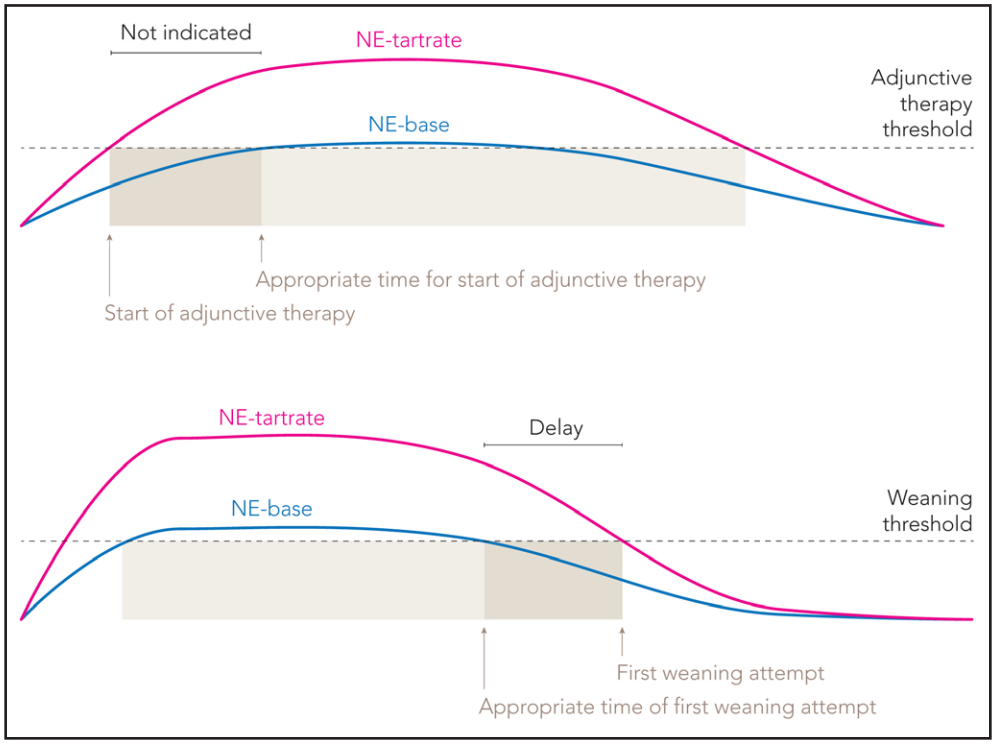

Figure 5. Implications of using different norepinephrine (NE) formulations leading to inappropriately delayed weaning from venoarterial extracorporeal membrane oxygenation (*top*) and premature addition of adjunctive therapy (*bottom*).

Research

Researchers should explicitly state the norepinephrine formulation used during RCTs, observational analyses, and all other contributions to scientific literature. Wherever possible the equivalent drug dosing should be defined as

TABLE 2.
Task Force Guidance on Norepinephrine Formulations

1. Norepinephrine base should be adopted as the uniform, global standard for norepinephrine dosing and formulations in ICUs.
2. Hospital formularies and pharmacies should adopt a uniform reporting policy across countries.
3. ICU workflow teams, including but not limited to bedside nurses, pharmacists, and clinicians should report and chart norepinephrine in the medical record, drug dispensing systems and infusion pumps as norepinephrine base.
4. Researchers and research literature should clearly state norepinephrine formulation used in the investigation and include conversion to norepinephrine base for analysis.
5. Manufacturers should explicitly state norepinephrine formulation on drug vials as norepinephrine base.
6. Uniform norepinephrine formulation labeling and reporting globally is urgently needed to ensure patient safety, optimize clinical care and research. There is no reason to delay the implementation of the guidance developed by this task force.

norepinephrine base. Various scoring systems involving norepinephrine should also include drug dosing based on norepinephrine base, and explicitly mention this in any guidance developed to calculate these scores. Clinical guidance documents, medical journals, and textbooks should be aligned to similar reporting standards for norepinephrine concentration as a norepinephrine base. Codified medication data should be used to enable disambiguation of norepinephrine dosing, for example, via drug classifications that reach product levels and not just chemical compounds.

Manufacturers and Product

The manufacturer should explicitly label the norepinephrine formulation on drug vials as norepinephrine base. Globally, a uniform method of norepinephrine formulation includes labeling drug vials and diluting or dispensing information should be used to avoid errors during disruption of supply chain (**Fig. 1**).

Urgency

The variations in norepinephrine dose formulations are an issue with far-reaching implications for care of the critically ill. Although this joint position statement is by no means exhaustive of the scope of the variations in every country or geographical region, we believe that this issue is representative of a problem that has the potential to influence care and scientific investigation all over the world. The task force recommends that uniform norepinephrine formulation labeling and reporting globally is urgently needed to ensure patient safety, and to optimize clinical care and research. There is no reason to delay the implementation of the guidance developed by this task force.

CONCLUSIONS

A multinational, multidisciplinary task force of the SCCM and ESICM recommends a global uniformity in norepinephrine reporting used for formulation, dispensing, research, and clinical use. Norepinephrine base is the preferred form for reporting compared with the conjugated acid salt formulation.

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1 *Department of Pharmacy, Mayo Clinic, Rochester, MN.*
2 *Department of Anesthesiology, Mayo Clinic, Rochester, MN.*
3 *Department of Anesthesiology and Intensive Care Medicine, Nord Hospital, Assistance Publique Hôpitaux Universitaires de Marseille, Aix Marseille University, Marseille, France.*
4 *Department of Intensive Care, Copenhagen University Hospital–Rigshospitalet, Copenhagen, Denmark.*
5 *Department of Critical Care, Respiratory Institute, Cleveland Clinic, Cleveland, OH.*
6 *Cleveland Clinic Lerner College of Medicine, Cleveland, OH.*
7 *Division of Critical Care Medicine, Department of Anesthesiology and Perioperative Care, University of California San Francisco, San Francisco, CA.*

8 *Department of Clinical and Experimental Medicine, School of Medicine, University of Southampton, National Institute of Health and Care Research (NIHR), Southampton Biomedical Research Centre, Perioperative and Critical Care Theme, and NIHR Wessex Applied Research Collaborative, Southampton, United Kingdom.*

9 *Ephraim McDowell Regional Medical Center, Danville, KY.*

10 *Department of Pharmacy, University of Kentucky, Lexington, KY.*

11 *Department of Anesthesia and Intensive Care, IRCCS Humanitas Research Hospital, Rozzano (MI), Italy.*

12 *Department of Biomedical Sciences, Humanitas University, Pieve Emanuele (MI), Italy.*

13 *Department of Critical Care Medicine, NMC Specialty Hospital, Dhabi, United Arab Emirates.*

14 *Cooper Department of Medicine, Cooper Research Institute, Cooper University Hospital, Camden, NJ.*

15 *Cooper Medical School at Rowan University, Camden, NJ.*

16 *Department of Intensive Care Medicine, Ghent University Hospital, Ghent, Belgium.*

17 *Department of Internal Medicine and Pediatrics, Faculty of Medicine and Health Sciences, Ghent University, Ghent, Belgium.*

18 *Department of Anesthesiology, Section on Critical Care Medicine, Wake Forest University School of Medicine, Atrium Health Wake Forest Baptist Medical Center, Winston-Salem, NC.*

19 *Outcomes Research Consortium, Cleveland, OH.*

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Wieruszewski and Leone share joint first authorship.

De Waele and Khanna share joint senior authorship.

De Waele and Khanna share joint task force co-chairs.

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For information regarding this article, E-mail: akhanna@wakehealth.edu

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