Evaluating the effect of chronic antihypertensive therapy on vasopressor dosing in septic shock

1. PURPOSE OF THE STUDY AND BACKGROUND

1.1. Hypothesis

- Chronic β-blocker or Angiotensin-Converting Enzyme (ACE)-inhibitor use is associated with decreased cumulative doses of vasopressors administered in the first 48 hours of septic shock

1.2. Purpose of the study

- The primary objective is to determine the effect of chronic β-blocker or ACE-inhibitor on cumulative vasopressor dosing in the first 48 hours of septic shock.

- The secondary objectives of this study
    - To determine the effect of chronic β-blocker or ACE-inhibitor on cumulative vasopressor dosing in the first 6, 12, and 24 hours of septic shock.
    - To determine the effects of chronic β-blocker or ACE-inhibitor on:
        - Adequate fluid resuscitation
        - Cumulative inotrope use (48 hours)
        - Cumulative hydrocortisone use at 6, 12, 24, and 48 hours
    - To determine cumulative vasopressor dose of patients on chronic calcium channel blocker or other antihypertensives (clonidine, hydralazine, angiotensin-receptor-blocker (ARB))

1.3. Background

Literature suggests that extended periods of tachycardia, in patients with shock, are associated with increased mortality.[1-4] Interventional trials have suggested that increased doses of catecholamines are associated with the increased mortality and the administration of esmolol infusions may improve survival in patients with shock requiring vasopressor agents.[1]

What remains unknown is the effect of home exposure to antihypertensive therapies, specifically beta-blockers and ACE-inhibitor. This study will evaluate the effects of home antihypertensive therapy with beta-blockers and ACE-inhibitor on vasopressor dose administered within the first 48 hours of septic shock.

2. STUDY DESIGN

2.1. Overview

This will be a retrospective four-cohort study. The four cohorts will be septic shock patients that were: 1) not on either a chronic β-blocker or ACE-Inhibitor, 2) on chronic β-blocker, 3) on chronic ACE-Inhibitor, and 4) on both chronic β-blocker and ACE-inhibitor

2.2. Rationale for Study Design

This study design was chosen since the primary objective is to compare cumulative vasopressor

doses. Many patients that present with septic shock have multiple comorbidities necessitating chronic therapy with either β-blocker, ACE-Inhibitor, or both. Because little is known about the effects of chronic antihypertensives on vasopressor dosing and the severity of septic shock, a retrospective study was chosen.

2.3. Rationale for Dosage

Rationale for dosage is not applicable to this study because we will only be collecting pre-existing medical data with no prospective interventions and dosing is routine care.

3. CHARACTERISTICS OF THE RESEARCH POPULATION

3.1. Subject Characteristics

Number of Subjects:

It is estimated that approximately 200 patients will be included for this study. The individual number for each group will vary based on screening.

Gender and Age of Subjects:

No restrictions apply to gender of the study subjects. Only adult, non-pregnant patients will be included, defined as 18 years of age or older.

a) **Racial and Ethnic Origin:**

No restrictions apply to race or ethnic origin of the study subjects.

3.2. Inclusion and Exclusion Criteria

a) **Inclusion Criteria:**

- Adult patients 18 years of age or older
- Diagnosis of septic shock requiring vasopressor therapy (norepinephrine, epinephrine, phenylephrine, dopamine, or vasopressin)
- Admitted to the medical intensive care unit (MICU) at Rush University Medical Center (RUMC)
- Time frame: 01/01/2012 to 08/1/2016

b) Exclusion Criteria:

- Pregnant patients
- Transfer from outside hospital on vasopressors
- Admitted in cardiopulmonary arrest
- Prior arrest within 24 hours of admission to RUMC

4. SUBJECT IDENTIFICATION, RECRUITMENT AND CONSENT

4.1. Method Of Subject Identification And Recruitment

The study will be retrospective, and collected data will be a result of routine care. Adult patients 18 years of age or older with septic shock who received treatment with a vasopressor will be assessed for inclusion. Patients will be excluded if they are pregnant, transferred from outside hospital on vasopressor, admitted in cardiopulmonary arrest, prior arrest within 24 hours of admission to RUMC or if they required neuromuscular blockade.

Patients will be reviewed from 01/01/2012 to 08/1/2016. A list of MICU patients will be generated by the corresponding ICD-9 and ICD-10 codes for septic shock. Patients will be stratified into 4 groups: 1) not on either a chronic β-blocker or ACE-Inhibitor, 2) on chronic β-blocker, 3) on chronic ACE-Inhibitor, and 4) on both chronic β-blocker and ACE-inhibitor.

4.2. Process of Consent

This study is a retrospective study and therefore it is not feasible to obtain consent. Direct patient involvement is not needed in the study and information will only be gathered from pre-existing data in the patients' medical record. All data will be de-identified to limit the chance of exposure of protected health information (PHI).

5. METHODS AND STUDY PROCEDURES

5.1. Efficacy & Safety Assessments

The electronic medical record system (EPIC) will be used to collect data, including: patient age, gender, weight, height, BMI, race, past medical history (hypertension, diabetes, heart failure, afib/flutter, arrhythmia, history of myocardial infarction, history of CVA, CAD, CKD, dyslipidemia, asthma, COPD, cancer), Charlson Comorbidity Index, hospital length of stay, medical intensive care unit (MICU) length of stay. Prior to admission medications include: beta-blockers, ACE-inhibitors, amlodipine, diltiazem, ARBs, hydralazine, clonidine, hctz, loop diruetics, amiodarone, other antiarrhythmics. Vasopressor types and cumulative doses including: norepinephrine, epinephrine, phenylephrine, dopamine, and vasopressin. Epinephrine, phenylephrine, and dopamine will be converted to norepinephrine equivalents in concordance with other literature: 100 mcg dopamine equivalent to 1 mcg norepinephrine, 1 mcg epinephrine equivalent to 1 mcg norepinephrine, and 2.2 mcg phenylephrine equivalent to 1 mcg norepinephrine.[5,6] Concomitant medications including: hydrocortisone, inotrope use, crystalloid type and amount, colloid use, albumin use, timing of antibiotics, and sedation choice if given. Clinical information collected include: Peak lactate, MAP, mechanical ventilation, in hospital mortality, 28 and 90 day mortality if available. SOFA score will be calculated as a measure of disease severity.

Study Timeline:

Date	Activity
September 2016	Rush University Medical Center IRB approval
October - November 2016	Data collection
December 2016	Data analysis
January 2017	Study presentation and manuscript preparation

5.2. Costs to the Subject

There will be no costs to the subjects as this is an evaluation of pre-existing medical data.

5.3. Payment for Participation

Subjects will not receive compensation for their participation in this study.

6. CONCOMITANT AND DISALLOWED MEDICATIONS

Concomitant and disallowed medications are not applicable to this study design.

7. SUBJECT WITHDRAWALS

Given the design of this study, subject withdrawal will not be an issue encountered.

8. STUDY DRUG/DEVICE/BIOLOGIC ADMINISTRATION/ASSIGNMENT

This study does not involve the implementation of a study drug, device, or biologic.

9. SAFETY AND REPORTABLE EVENTS

Given the design of this study we will not be prospectively collecting adverse events that require reporting.

10. RISK/BENEFIT ASSESSMENT

10.1. Potential Risks

There are minimal risks to the study subjects. The only potential risk is invasion of privacy since medical records will be accessed. All data will be de-identified to limit the chance of exposure of PHI.

10.2. Protection Against Risks

It will be the responsibility of the primary investigator (PI) for data collection and storage in a safe, secure area and password protected computer when identifying eligible patients. Research Electronic Data Capture (REDCap) will be used for data collection and storage. Patient confidentiality will be maintained by recording only de-identified data onto the data collection form. Although the data collected and stored in REDCap will be exported for analysis, the exported data will contain no unique, patient-identifying information.

10.3. Potential Benefits to Subjects

There are no potential benefits to patients in this study

10.4. Alternatives to Participation

There are no alternatives to participation available for study subjects given the design of the study

11. CONFIDENTIALIATY OF DATA AND INFORMATION STORAGE

It will be the responsibility of the primary investigator (PI) for data collection and storage in a safe, secure area and password protected computer when identifying eligible patients. Research Electronic Data Capture (REDCap) will be used for data collection and storage. Patient confidentiality will be maintained by recording only de-identified data onto the data collection form. Although the data collected and stored in REDCap will be exported for analysis, the exported data will contain no unique, patient-identifying information.

12. RESEARCH INFORMATION IN MEDICAL RECORDS

No research information will be included in the patient's medical record.

13. DATA ANALYSIS AND MONITORING

13.1. Sample Size Determination

There are limited data for proper evaluation of a sample size. However, there was a smaller presented study that had a dramatic decrease in norepinephrine dose in patients on a β-blockers or ACE-inhibitors prior to admission for patients in circulatory shock of any kind.[7] Using these data, estimated 48h cumulative mean dose for norepinephrine patients not on anti-hypertensives will be 50 mg (SD = 10) and estimated 48h cumulative mean dose for norepinephrine for beta blocker, ACE-Inhibitor, and beta-blocker + ACE-Inhibitor groups will be 25 mg (SD = 10). Using a 4-way fixed effects ANOVA power calculation with estimated effect size from previous study (f = 1.08) the total sample size would be 16

F tests – ANOVA: Fixed effects, omnibus, one-way
Analysis: A priori: Compute required sample size

Input: Effect size f	=	1.0825318
α err prob	=	0.05
Power (1−β err prob)	=	0.95
Number of groups	=	4
Output: Noncentrality parameter λ	=	23.4375020
Critical F	=	3.2388715
Numerator df	=	3
Denominator df	=	16
Total sample size	=	20
Actual power	=	0.9609969

However, the current proposed study is specifically looking at septic shock and the anticipated effect is unknown. Therefore, using a 4-way fixed effects ANOVA power calculation with a medium effect (f = 0.25) has a total sample size of 180 patients.

F tests – ANOVA: Fixed effects, omnibus, one-way
Analysis: A priori: Compute required sample size

Input: Effect size f	=	0.25
α err prob	=	0.05
Power (1−β err prob)	=	0.80
Number of groups	=	4
Output: Noncentrality parameter λ	=	11.2500000
Critical F	=	2.6559389
Numerator df	=	3

Denominator df	=	176
Total sample size	=	180
Actual power	=	0.8039869

A list of ICU patients will be generated by the corresponding ICD-9 and ICD-10 codes for septic shock during the inclusion time frame, randomized and screened until reaching the minimum power and equal groups (n = 200, 50 patients in each group)

13.2. **Planned Statistical Analysis**

All data will be reported using descriptive statistics with mean (SD) used to describe normally distributed data and median (interquartile range [IQR]) used for non-normal data or data with a significant number of outliers. Distribution of data and assessment of normality will be analyzed. Chi-squared, Fisher's Exact and Student's t-test as appropriate will be used to assess differences among the study cohorts. A 4-way fixed effects ANOVA will be utilized for the primary outcome, cumulative vasopressor dose at 48 hours. *Post hoc* pairwise comparisons will be completed between groups using Bonferroni's, Turkey, or Hochberg's GT2 depending on final group size and variance. Statistical support for data evaluation will be sought out if necessary.

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