Late vasopressor administration in ICU patients: A retrospective cohort study

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Background: Little is known about the prevalence, predictors, and outcomes of late vasopressor administration which evolves after admission to the ICU.

Methods: We retrospectively studied a cohort of Veterans admitted to the Veterans Administration ICUs for ≥ 4 days from 2014–2017. The timing of vasopressor administration was categorized as early (only within the initial 3 days), late (on ≥ day 4 and none on day 3) and continuous (within the initial 2 days through at least day 4). Regressions were performed to identify patient factors associated with late vasopressor administration and the timing of vasopressor administration with post-hospitalization discharge mortality.

Results: Among the 62,206 hospitalizations with at least 4 ICU days, late vasopressor administration occurred in 5.5% (N=3,429/62,206). Patients with greater co-morbidities (aOR: 1.02 per van Walraven point, 95% CI: 1.02-1.03) and worse severity of illness on admission (aOR: 1.01 per percentage-point risk of death, 95% CI: 1.01-1.02) were more likely to receive late vasopressor therapy. Nearly 50% of patients started a new antibiotic within 24 hours of receiving late vasopressor therapy. One-year mortality after survival to discharge was higher for patients with continuous (aHR: 1.48 95% CI: 1.33-1.65) and late vasopressor administration (aHR: 1.26 95% CI: 1.15-1.38) as compared to only early vasopressor administration.

Conclusions: Late vasopressor administration was modestly associated with co-morbidities and admission illness severity. One-year mortality was higher among those who received late vasopressor administration as compared to only early vasopressor administration. Research to understand optimization of late vasopressor therapy administration may improve long-term mortality.

Abbreviations

ICU: Intensive care unit

VA: Veterans Administration

VAPD: Veterans Affairs patient database

BCMA: Barcode Medication Administration

IQR: Interquartile range

SOFA: Sequential organ failure assessment

SD: Standard deviation

OR: Odds ratio

aOR: Adjusted odds ratio

IRR: Incidence rate ratio

HR: Hazard ratio

aHR: Adjusted hazard ratio

Early recognition and appropriate treatment of cardiovascular failure improves mortality.[1-5] Most research focused on initial presentation—particularly in the Emergency Department.[6] However, presenting diagnoses and pathophysiology on admission to the intensive care unit (ICU) become less predictive of in-hospital mortality over time as a result of events occurring in the ICU.[7-9] This suggests that caution should be used in generalizing from knowledge about early organ failures to the treatment and prognostic importance of later organ failures.

In several cases, ICU day 4 is used to pragmatically distinguish between aspects of the initial resuscitation and "ICU-acquired" problems. For example, infections occurring on ICU day 4 and beyond are distinguished from earlier occurring infections, with different recommended management and prognostic implications.[10,11] At a single center, it was shown that 78% of patients with long ICU stays develop new late organ failures, most commonly cardiovascular failure, where "late" was also defined as occurring on day 4 and beyond.[12] While the management of cardiovascular failure remains a core task of the modern ICU, the generalizability of this single center finding—the frequency and outcome of new late cardiovascular failure—is unknown.

In light of this gap, we sought to evaluate the development of cardiovascular failure in ICU patients by evaluating the administration of vasopressor agents in a large health care system—the United States Veterans Administration (VA) system. We specifically hypothesized that late cardiovascular would be common and would be driven predominately by the development of sepsis. Therefore, the objectives of the study were:

1) To quantify the number of hospitalizations and timing when patients were receiving vasopressor agents;
2) To identify patient factors associated with the development of late vasopressor administration.

3) To understand the extent to which infections are associated with the development of late vasopressor administration
4) To measure the one-year mortality of patients who received late vasopressor administration and survived to discharge and to see if it differs from those who only received early vasopressor administration.

Methods:

Study Context

The VA health system is one of the largest integrated health care delivery systems in the United States with over 9 million beneficiaries and an electronic medical record which can be leveraged to capture granular daily data.[13,14]

Study Population

Data were abstracted from the Veterans Affairs Patient Database (VAPD) 2014-2017 and represented over 100 VA hospitals.[15] The VAPD contains daily standardized physiological information for all patients hospitalized in the VA. The information is structured at the patient-facility-day and includes pharmacy and laboratory data, and diagnostic codes from the entire VA system.[15,16] Analyses from the VA were approved by the IRB of the VA Ann Arbor Health System (IRB-2016-357).

We abstracted data from the VAPD for all patients who were admitted to an ICU. All patient exclusion criteria are listed in **Supplemental Appendix A.**

Identification of vasopressor administration

Vasopressor administration was defined as any intravenous receipt of norepinephrine, epinephrine, dopamine, phenylephrine,

and vasopressin as recorded in the Barcode Medication Administration (BCMA) files in the Corporate Data Warehouse. The BCMA files include all VA inpatient medication administrations and includes drug name and class. The VAPD extracted all vasopressor medications.[15] Drug infusion dose was not able to be reliably ascertained and therefore any administration on a given calendar day was utilized. Infusions in the operating room were not included.

In order to quantify the timing of vasopressor administration during an ICU admission, we sought to distinguish four time periods. Conceptually, early vasopressor administration reflects the initial resuscitation and stabilization of the patient, whereas late vasopressor administration reflects processes that "evolved" in the ICU. Unfortunately, there is no reliable way to adjudicate on an individual basis such a distinction at nationwide scale with the data available. Therefore, following past work distinguishing community- from hospital-acquired pneumonia[17] and early from late organ failure, we pragmatically define the first 3 days in the ICU as early, and day 4 and thereafter as late.[12,18] Continuous vasopressor administration was defined as use on ICU day 1 or 2 through at least ICU day 4. Vasopressor administration which was not categorized as early, late, or continuous was defined as other. **(Figure 1)**

A sensitivity analysis was performed to evaluate if admission to the ICU with sepsis was driving the administration of late vasopressor administration.[18] Sepsis was defined by the Center of Disease and Prevention (CDC) definition of sepsis which is an EHR-based, diagnostic-code independent definition.[19] *(***Supplemental Appendix B**)

A small number of patients have prolonged ICU stays in the VA, and develop persistent critical illness, which may represent a distinct syndrome of cascading organ failures. We specifically wanted to understand the development of vasopressor administration prior to the onset of persistent critical illness. Using the same methods as in previously published work in Australia and New Zealand[8] and Canada[9], we found similar patterns in the onset of persistent illness with 10.7% of the hospitalizations with an ICU LOS greater than 11 days . (**Supplemental Appendix C**) Therefore, we examined daily vasopressor administration from

ICU admission through ICU day 11, choosing day 11 for consistency with multiple cross-national sources.

Identification of late infection

Among patients who developed late vasopressor administration, antibiotic administration—new or a different class of antibiotic—was reviewed within 24 hours of initiation of vasopressors and was used as a surrogate for suspected new infection. The VAPD included extraction from the BCMA files on the administration of antibiotics.[15] Culture data was not able to be ascertained.

The VA severity score

The VA does not use the APACHE IV for severity of illness on admission. For internal risk-adjustment, the VA uses an illness severity measure (the VA ICU severity score), which predicts 30-day mortality based on several variables (age, admission diagnosis category, 29 comorbid conditions, and 11 laboratory values). We calculated the VA severity score for each patient admitted to the ICU on day of admission. This severity score performs similarly to APACHE IV, with a C-statistic of 0.874.[20]

Analysis

We present patient and hospitalization characteristics as counts (percentages), means (SDs), or medians (interquartile ranges [IQR]) as appropriate. Elixhauser comorbidities were combined using the method described by van Walraven.[21] We used hospitalization as the unit of analysis, unless otherwise specified. We used two-sided significance testing and considered a p-value less than 0.05 to be significant.

We performed logistic regression analysis to identify patient characteristics (age, gender, race, comorbidities) which were associated with late vasopressor administration (yes/no) while

adjusting for severity of illness, type of ICU, hospital length of stay prior to ICU admission, admission diagnosis and receipt of major surgery. To account for the number of days a patient could have cardiovascular organ failure, we performed a Poisson regression adjusting for the same co-variates to evaluate which patient characteristics were associated with the outcome, the number of days of late vasopressor administration.

Kaplan-Meier curves were utilized to evaluate 90-day in-hospital and one-year post discharge mortality. Among survivors, log-rank tests were performed to compare the unadjusted one-year mortality of those who received any vasopressors and those who never received any vasopressors. 90-day in-hospital and one-year post discharge mortality were evaluated using a Cox regression adjusting for patient characteristics, ICU type and severity of illness on admission. 90-day in-hospital and one-year post discharge were pragmatically chosen to understand if there was a difference in inpatient mortality and post-discharge mortality. The one-year post discharge mortality was chosen given the last cohort was admitted in 2017 and death records were only available until 2018. The data was right sided censored at the end of 2018. Only the first hospitalization was used for patients with multiple admissions during the study period.

We conducted all analysis with Stata software 15.1 (StataCorp, College Station, TX) and SAS 9.4 (SAS Institute, Cary, NC).

Results:

Of the 160,855 patients admitted to VA ICUs from 2014-2017, 62,206 had an ICU LOS $\geq$ 4 days. (**Figure 2)** Such patients had a median age of 68 (IQR: 62, 73), were predominately male, and white. **(Table 1)**

Overall, 18,057 hospitalizations (11.2% of 160,855) required vasopressor administration. Most were long stay hospitalizations (**Figure 2)**, 13,099 (21.1% of 62,206) with ICU LOS $\geq$ 4 days versus 4,958 (5.0% of 98,649) with ICU LOS < 4 days. Among all ICU patients,

vasopressors were given only on ICU days 1-3 in 11,939 hospitalizations (4,958 with ICU LOS < 4 days and 6,981 with ICU LOS ≥ 4 days), whereas 5,347 received them on day 4 or after.

Among patients admitted to the ICU for at least 4 days, late vasopressor administration occurred in 5.5% (N=3,429/62,206). Late vasopressor administration occurred in 9.4% (N=1,690/9,048) and 4.8% (N=2,574/53,158) among patients with and without sepsis on admission. (**Figure 1** for "late" definitions, **Supplemental Appendix B** for additional information on analysis stratified by sepsis present on admission.) The median ICU day for the start of late vasopressor administration was ICU day 6 (IQR: 5, 7 days) with a median duration of 1 day (IQR: 1, 2 days).

Of the patients with late vasopressor administration, nearly half (N=1,639/3,429) transitioned to a new antibiotic or a new class of antibiotic within 24 hours of the receipt of new vasopressors. The median duration of the new antibiotic was 3 days (IQR: 2, 5 days).

Among patients with at least 4 ICU days, patients with more co-morbidities (aOR: 1.02 per van Walraven point, 95% CI:1.02-1.03: IRR 1.02, 95% CI:1.02-1.03) and higher severity of illness (aOR: 1.01 per percent, 95% CI: 1.01-1.02; IRR: 1.01, 95% CI: 1.01-1.02) at hospital admission had higher odds and higher rates of late vasopressor administration. Neither age (aOR: 0.98 per year, 95% CI: 0.94-1.01; IRR: 0.98, 95% CI: 0.95-1.01) nor gender (aOR:1.03 for female vs male, 95%, CI: 0.84-1.26; IRR: 1.03, 95% CI: 0.84-1.26) were associated with higher odds or rates of late vasopressor administration. (**Table 2**)

When stratifying patients by timing of vasopressor administration, in an unadjusted model, in-hospital 90-day mortality was higher among patients with late and continuous vasopressor administration as compared to patients with only early vasopressor administration. In an adjusted Cox regression model controlling for patient characteristics on admission, ICU type and severity of illness on admission, the adjusted hazard ratio (aHR) for in-hospital mortality was higher for patients who received continuous (aHR: 2.53, 95% CI: 2.26-2.84) or late

vasopressor administration (aHR: 2.09, 95% CI: 1.88-2.33) as compared to patients who only received early vasopressor administration.

Among those who survived to hospital discharge, patients who received any vasopressor administration had a worse one-year mortality as compared to those with no vasopressor requirements (unadjusted log-rank p < 0.01**).** (**Figure 3a**) In an unadjusted model, when stratifying patients by timing of vasopressor administration, patients with late and continuous vasopressor administration, had higher one-year post-discharge mortality as compared to those with only early vasopressor administration. (**Figure 3b**). Among those who survived to hospital discharge, in an adjusted Cox regression model controlling for patient characteristics, ICU type and severity of illness on admission, the aHR for mortality in the one year was higher for patients who received continuous (aHR: 1.48, 95% CI: 1.33-1.65) or late vasopressor administration (aHR: 1.26, 95% CI: 1.15-1.38) as compared to patients who only received early vasopressor administration.

Discussion

Key findings

In a national cohort of Veterans admitted to the ICU, we found that 1 in 9 received any vasopressors and this increased to 1 in 5 among those with an ICU LOS of at least 4 days. Patients with a higher initial comorbidity burden and severity of illness, but not greater age, were somewhat more likely to be administered late vasopressors. Nearly 50% of patients with late vasopressor administration had a new antibiotic or a different class of antibiotic initiated within 24 hours, suggesting that vasopressor administration was frequently associated with clinical concerns for recurrent or new sepsis. Late vasopressor therapy was associated with an increased in-hospital mortality and, among survivors, one-year post-discharge mortality among survivors, compared to those who used vasopressors only in the first 3 days of an ICU stay.

Relationship to previous studies

Previous work on cardiovascular failure focused on the early presentation of cardiovascular failure—e.g. early goal directed therapy for sepsis and early re-vascularization for cardiogenic shock.[1-5] Mortality rates from early cardiovascular failure have improved with the advancement of early detection strategies and the initiation of the appropriate treatment.[22,23] Consequently, more patients have survived their initial pathologies but have continued to remain in the ICU. Recent work has focused on identifying ways to limit the duration of intravenous vasopressors as a way of shortening ICU stays. For example, corticosteroids have reduced the duration of vasopressors but with potential adverse consequences.[24,25] Midodrine has been shown in several small studies to be a beneficial adjunct in stopping intravenous vasopressors and is currently being evaluated in a clinical trial.[26-29] These adjuncts (corticosteroids and midodrine) have been studied early in the ICU course.[24-26]

There has been little past work systematically studying the epidemiology of late cardiovascular failure. Using data from the 1990s, Rosenberg *et al* showed that organ failures present later in an ICU stay (e.g. after inter-hospital transfer) had a different association with in-hospital mortality than did those present on initial ICU presentation.[7] More recently, in a single center cohort study, 50 patients with prolonged ICU stays were found to frequently develop new late organ failures on and after ICU day 4. The most common organ failure was cardiovascular failure.[12] Our results validate and expand this concept by evaluating a large, national cohort of patients admitted to the ICU for at least four days. This national scope offers generalizability, while still maintaining a high level of clinical granularity with linked one-year mortality outcomes.

Study Implications

Cardiovascular failure which occurs later in the ICU course may have been assumed to have implications similar to cardiovascular failure which occurred on presentation. Our work questions this assumption. These data demonstrate that *when* a patient develops the need for

vasopressors in their ICU stay has important mortality implications—even if the patient survives the hospitalization. Similar elevated post-discharge mortality has been found in sepsis, and to a lesser degree, acute hypoxic respiratory failure.[30-32]

New late vasopressor administration, in this large national health system, is not rare—and may benefit from targeted research with a more nuanced understanding of the physiology driving the administration of late vasopressor utilization in the ICU, rather than being treated by analogy to hypotension newly presenting to the emergency department. Our data raise an urgent question about the extent to which the in-ICU and post-discharge mortality, that may be attributable to late cardiovascular failure, are modifiable by differences in practice.

Our findings also imply that certain patient characteristics on admission (e.g. severity of illness, comorbidities, race, hospital LOS prior to admission to ICU, ICU type) are associated with late vasopressor administration. However, the individual effect sizes are very small. Whether these can be meaningfully aggregated into a useful context-specific risk stratification tool should be a subject of future work.[33,34]

Our findings demonstrate a higher mortality during and after hospitalizations with late vasopressor administration as compared to those hospitalizations with early vasopressor administration. This implies that the timing of cardiovascular failure during the ICU stay matters and has different survival implications. The mechanisms driving this mortality difference needs to be discerned while in the ICU and in the post-hospitalization period (e.g. Post-ICU clinics).

Additionally, our findings of associated changes in antibiotic therapy imply that sepsis—or clinical concern for sepsis—may be partially driving the development of late vasopressor administration as nearly half of the patients receive a new antibiotic class within 24 hours of developing a requirement for vasopressors. However, this interpretation must be tempered by the high propensity of U.S. hospitals to administer antibiotics, and emphasizes the need for more accurate point-of-care sepsis diagnostics.[35] Future work would benefit from targeted

prospective research with a more nuanced understanding of how infections are being worked up in the ICU, rather than being identified by analogy to the administration of antibiotics.

Strengths and Limitations

Our study has several strengths. We examined a national cohort with detailed daily physiologic data collected over a three-year period encompassing 62,346 hospitalizations with linked mortality data. These granular data allowed us to relate the timing of the need for vasopressors use with long-term mortality and explore the development of late vasopressor administration with the development of new infections. Second, we have shown that few patient characteristics are associated with late vasopressor therapy administration.

There are several limitations to our study. First, we used a cohort of Veterans who are disproportionately white men and may not be representative of other cohorts. However, our cohort also included 3.6% (N=2,236) female patients and 27.7% (N=17,203) non-white patients, numbers that would be substantial by themselves in many contexts. Second, we utilized vasopressor administration as a surrogate for cardiovascular failure. Third, it is unknown if changes in patient's code status or limitations of care contributed to the differences in mortality and if those changes were related to the ICU admission. Fourth, we do not know if the patients had a documented infection when antibiotics were initiated.

Conclusion

In patients admitted to the ICU for at least 4 days, late vasopressor therapy administration was not uncommon and one-year mortality was higher for patients who received late vasopressor therapy and survived to hospital discharge compared to those who only received vasopressors early. Research aimed at understanding what is driving late vasopressor therapy administration may be a target for improving long term mortality.

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Authorship contributions: E.M.V designed the study, performed the statistical analyses, interpreted the results, compiled the manuscript. S.M.B provided critical revisions for the manuscript. R.B provided critical revisions of the manuscript. J.M.P. provided critical revisions for the manuscript. D.J.M. performed statistical analyses and provided critical revisions for the manuscript. X.Q.W performed statistical analyses and provided critical revisions for the manuscript. S.S. performed statistical analyses and provided critical revisions for the manuscript. T.J.I. designed the study, refined the analyses, assisted in interpreting the findings, and provided critical revisions of the manuscript.

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Table 1: Demographic and clinical features of patients who remained in the ICU ≥4 days

	N=62,206
Male, % (N)	96.4 (59,970)
Age, median, (IQR)	68 (62, 73)
Race, % (N)	
White	72.3 (45,003)
African American	20.3 (12,597)
Other	7.4 (4,606)
Type of ICU % (N)	
Medical	55.2 (34,329)
Surgical	38.0 (23,651)
Other	6.8 (4,226)
Elixhauser co-morbidity, median (IQR)	4 (2, 5)
ICU LOS, median (IQR)	5 (4, 8)
Hospital LOS, median (IQR)	9 (6,15)
In-hospital death, % (N)	7.9 (4,931)
Discharge location, % (N)	
Home	89.2 (55,480)
Transfer to another acute care facility	3.1 (1,926)
Other/death	7.7 (4,800)

ICU: Intensive Care Unit; LOS: Length of stay; IQR: Interquartile range

Table 2: Predictors of late vasopressor administration. Association of patient-level characteristics comparing patients who received late vasopressors to those who did not receive late vasopressors.

	Logistic Regression					Poisson Regression		
Variable	**Unadjusted OR**	**p-value**	**Adjusted OR**	**95% CI**	**p-value**	**IRR**	**95% CI**	**p-value**
Age (per Decade)	1.09	<0.01	0.98	0.94-1.01	0.19	0.98	0.95-1.01	0.17
Female (vs Male)	0.85	0.10	1.03	0.84-1.26	0.80	1.03	0.84-1.26	0.80
Race (vs White)								
African American	0.84	<0.01	0.87	0.79-0.95	<0.01	0.87	0.79-0.95	<0.01
Other	1.27	<0.01	1.18	1.04-1.33	0.01	1.18	1.04-1.33	0.01
ICU type (vs Medical)								
Surgical	0.91	<0.01	1.14	1.03-1.25	0.01	1.13	1.02-1.26	0.02
Others	0.77	<0.01	0.74	0.63-0.87	<0.01	0.74	0.63-0.87	<0.01
Elixhauser (per van Walraven point)	1.03	<0.01	1.02	1.02-1.03	<0.01	1.02	1.02-1.03	<0.01
VA risk score (per percent)	1.02	<0.01	1.01	1.01-1.02	<0.01	1.01	1.01-1.02	<0.01
Operations	2.54	<0.01	2.36	2.19-2.54	<0.01	2.36	2.18-2.55	<0.01
Hospital LOS prior to ICU admission (per Day)	1.03	<0.01	1.03	1.02-1.04	<0.01	1.03	1.01-1.04	<0.01

ICU: Intensive care unit; VA: Veterans Administration; LOS: Length of stay; OR: Odds ratio; CI: Confidence interval; IRR: Incidence rate ratio

Figure Legend

1. The distribution of vasopressor administration by ICU day

2. Flow diagram of hospitalizations from 2014-2017

3. Kaplan-Meier Survival Curves one year after hospitalization discharge among those with an ICU LOS $\geq$ 4 days