Prescribed targets for vasopressor titration in septic shock: a retrospective cohort study

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No reprints required.

Keywords: Vasopressors, shock, titration, blood pressure, mean arterial pressure

Word count

Manuscript: 2384 words

Funding: none

Abstract

Background: Without robust clinical evidence to guide vasopressor titration in septic shock, it is unclear who adjusts the dosing of these potent medications and how. We hypothesized that explicit blood pressure targets would be missing from half of the vasopressor prescriptions in participating centers.

Methods: We conducted a multicenter, retrospective cohort study in 9 university-affiliated intensive care units (ICU) located in 3 academic hospitals in Canada and Australia. We reviewed charts of consecutive patients 18 years or older and admitted to the ICU for a presumptive diagnosis of sepsis. Other inclusion criteria were hypotension (systolic arterial pressure ≤ 90 mmHg or mean arterial pressure ≤ 65 mmHg) and continuous infusion of vasopressors for at least one hour within the initial 48 hours of ICU stay, the period of observation for this study.

Results: We included data from 369 patient charts. At least 1 target was specified in 99% of cases. The most common targets were mean arterial pressures (MAP - 73%). The median initial MAP target was 65 mmHg (range 55 to 90 mmHg). In a multivariable linear regression model, older age and center were associated with higher initial MAP targets. In 40% of patients, the treating team modified the initial target at least once.

Interpretation: When prescribing vasopressors to patients with septic shock, intensivists nearly always specify explicit targets. Age and local standards appear to influence targeted blood pressures and physicians frequently modify initial targets. Defining optimal vasopressor titration strategies adapted to individual patient characteristics demands randomized controlled trials.

Introduction:

Severe sepsis and septic shock are frequently encountered pathologies and their incidence is rising in modern intensive care units (ICU)(1, 2). With septic shock, hemodynamic instability ensues, leading to a state of circulatory failure that persists despite fluid resuscitation. In healthy individuals, autoregulation maintains blood flow to vascular beds despite variations in arterial pressure. In septic shock, based on animal studies of limited clinical relevance(3), a widespread pathophysiological model suggests that blood pressure may decrease to a critical level below which tissue perfusion becomes linearly dependant on arterial pressure(4-6). The rationale underlying vasopressor therapy in this context is to increase arterial blood pressure in order to restore and maintain adequate tissue perfusion. However, the specific blood pressure threshold below which perfusion is compromised, and the ideal target for vasopressor titration are not known. Drawing on expert opinions, current guidelines issued by the "Surviving Sepsis Campaign" recommend a minimal mean arterial pressure (MAP) of 65 mmHg in septic shock(5-7). However, no study has shown that targeting a MAP above 65 mmHg as opposed to another blood pressure value was beneficial (8-11). Accordingly, the optimal blood pressure value could vary for different patients and depend on which organ systems are monitored. Without robust clinical evidence to guide vasopressor titration in septic shock, it is unclear who adjusts the dosing of these potent medications. Moreover, given the lack of conclusive evidence on optimal vasopressor titration targets, practice variations are expected.

In a recent survey, Canadian intensivists stated that they typically aim for a mean arterial pressure of 65 mmHg in patients suffering from septic shock(12). The survey also suggests that Canadian intensivists target higher blood pressures when patients present signs of malperfusion and that patients' chronic comorbidities and acute concurrent illnesses influence their selection of blood pressure targets. However, differences may exist between actual practice and responses to a survey. The primary objectives of our study were to measure the proportion of patients with septic shock for whom physicians ordered vasopressors using explicit targets and to compare these with practice recommendations. We hypothesized that explicit blood pressure targets would be missing from half of the vasopressor prescriptions in participating centers. Secondary objectives were to describe the targets and their association with patients' chronic comorbidites and acute concurrent illnesses.

Patients and Methods:

Centers and patients

We performed a retrospective cohort study in 9 university-affiliated intensive care units located in 3 tertiary care centers in Canada and Australia. None of the centers used standardized order forms for vasopressors. The study was approved by the hospitals' research ethics boards. Informed consent was waived for this retrospective chart audit.

We screened hospital databases for consecutive patients having received vasopressors and antibiotics. We included charts of patients who were 18 years or older and who were admitted to the ICU for a presumptive diagnosis of sepsis (regardless of the final diagnosis). The dominant diagnosis at the time of admission determined the presumptive source of infection in this study. To identify cases initially considered as septic shock, we relied on explicit statements found in the medical notes from the first day in the ICU. Other inclusion criteria were hypotension (systolic arterial pressure $\leq$ 90 mmHg or mean arterial pressure $\leq$ 65 mmHg) and continuous infusion of vasopressors for at least one hour within the initial 48 hours of ICU stay. We excluded patients who were treated outside the ICU (as the coronary care and stepdown units) and patients who, although they later developed septic shock, were initially admitted to the ICU for other reasons.

Data collection

At each center, investigators manually reviewed every chart and extracted data using pre-piloted electronic forms with logical checks for extreme or missing values. Every investigator received a detailed instruction manual. We collected information about patient demographics, source of infection, Acute Physiology and Chronic Health Evaluation II (APACHE II) score(13) baseline chronic comorbidities, concurrent acute illnesses and targets for vasopressor titration. In order to capture all targets including those that may have been spoken instead of written by the medical team, we reviewed medical and nursing progress notes as well as written orders. We included vasopressor prescriptions made by any ICU team member within the initial 48 hours of ICU stay, but excluded prescriptions made before the patient was under the care of the intensivist (e.g. prescriptions written by the emergency physicians were excluded). To ensure data quality,

investigators received data queries when the automated data entry system identified extreme or missing values.

Definitions

In this study, we defined vasopressors as any of the following medications administered for at least 1 hour: norepinephrine, epinephrine, vasopressin, dopamine and phenylephrine. We included every target specified during the initial 48 hours of ICU stay. Chronic comorbidities correspond to pathologies diagnosed before hospital admission (peripheral vascular disease, coronary artery disease, heart failure, chronic obstructive pulmonary disease, asthma, hypertension, diabetes mellitus, chronic renal failure, cirrhosis, obesity, neoplasia and immunosuppression). We classified new illnesses diagnosed within 48 hours of ICU admission as acute concurrent illnesses (stroke, myocardial injury, cardiac arrhythmia, acute pulmonary edema, acute respiratory distress syndrome, acute lung injury, massive hemorrhage, ischemic bowel disease, acute renal failure, maximal lactic acid $\geq$ 4.0, and maximal INR $\geq$ 2.0). The supplementary appendix provides definitions for each comorbidity.

Statistical analysis

We report continuous variables as means and 95% confidence intervals (CI) or medians and interquartile ranges and categorical variables as proportions. Charts with missing baseline creatinine were excluded from the denominator. We assumed patients to be free of specific comorbidities and acute illnesses when we found no report of these. For between center comparisons of continuous variables, we used ANOVA F-test. For between center comparisons of categorical data, we used Chi-square or Fisher's exact test when the sample sizes were small.

To assess the association between chronic comorbidities and the first vasopressor titration target, we built a multivariable linear regression model with the first blood pressure target as the dependent variable. We introduced hospital center, admission APACHE II score, age, coronary artery disease, chronic heart failure, chronic hypertension, diabetes and chronic renal failure simultaneously as independent variables. In order to avoid overfitting, we ran this model strictly with targets expressed as a mean arterial pressure (MAP) since other targets like systolic arterial pressure (SAP) were rare. To assess the association between acute concurrent illnesses and

modifications of vasopressor titration targets, we built a multinomial logistic regression model with a 3-category dependent variable (initial blood pressure target decreased, unchanged or increased) using a random intercept to account extra variation among centers. Cases were included in this analysis if the initial blood pressure target was either not modified or modified numerically with no modification of the target variable (MAP to MAP or SAP to SAP). Acute renal failure, myocardial injury, serum lactate greater than 4 mmol/L and cardiac arrhythmia were the independent variables simultaneously introduced in the model.

Sample size

We assumed conservatively that we would find explicit targets for the titration of vasopressors in 50% of the charts. Following this a priori assumption, a sample size of 235 patient charts would provide 117 explicit targets and greater than 90% power to detect a 3 mmHg difference between the mean of prescribed targets and current practice guidelines to target 65 mmHg. The number of chart reviewed by site was not preset. Investigators at each center proceeded at their own pace until the total number of included charts exceeded the planned sample size. The decision to terminate data extraction was made before analysing the data (without any knowledge of the results).

Results

We screened 5571 patient charts selecting 398 for manual review. We excluded 29 charts (figure 1) ultimately including data from 369 patients in the final analysis. Mean age was 65 years (95% CI 63 - 66), 53% were males and mean APACHE II score 27 (95% CI 26 - 28). Age and gender were not different between centers but mean APACHE II score was higher in center 2 (32, 95% CI 30-33) than in centers 1 (24, 95% CI 23-25) and 3 (24, 95% CI 22-26) ($p < 0.0001$). The majority of patients were admitted directly from the emergency room (51%) and the lungs, the gastrointestinal tract and the genitourinary system were the most common sources of infection.

The most common chronic comorbidities (Table 1) were hypertension (56%), diabetes mellitus (31%) and coronary artery disease (31%). Although the type of chronic comorbidities encountered at the 3 sites varied, the total number of comorbidities per patient was similar across all centers (median 3; IQR 1-4). The most common acute concurrent illnesses (Table 2) were acute renal failure (61%), myocardial injury (35%), hyperlactatemia (35%) and acute respiratory distress syndrome or acute lung injury (31%). Again, we observed differences between centers. Overall, the median number of acute concurrent illnesses per patient in center 2 (3, IQR 2-4) was greater than in centers 1 (2, IQR 1-3) or 3 (2, IQR 1-3) ($p< 0.0001$).

Table 3 presents specific targets for the titration of vasopressors. We found 604 explicit targets corresponding to the study period (within 48 hours of ICU admission). At least one explicit target was specified for 99% (365) of the patients. Most targets were values of MAP (73%), SAP (16%), a combination of MAP and SAP (8%). Table 4 presents other targets. None of the 604 prescriptions targeted urine output, lactate levels, mental status or central venous oxygen saturation. Of the 365 initial targets, 273 (75%) were MAPs. Overall, the initial MAP targets ranged from 55 to 90 mmHg and the median was 65 mmHg (IQR 65-70). Higher MAP values were initially targeted in center 3 (median MAP 70, IQR 70-75; $p<0.0001$ versus other centers). Table 5 presents the results of a multivariable linear regression model measuring the association between baseline variables and the value of initial MAP targets. The only variables associated with initial MAP values were age and hospital site with older age associated with high blood pressure targets. We found no association between the initial MAP value and the presence of chronic comorbidities.

For 40% of the patients (n=148) the medical team modified the initial target at least once. In 54% of these (80 of 148) patients, the new target consisted of different values of the same blood pressure variable (MAP to MAP or SAP to SAP). We found that, of these modifications, 41% (33 of 80) represented an increase from the original prescription while 58% (47 of 80) were reductions in blood pressure (table 6). In a multivariable logistic regression, we found no association between the acute concurrent illnesses and target modifications in either direction (table 7).

Discussion

In this multicenter retrospective study conducted in Australia and Canada, we found that an explicit titration target accompanied nearly every vasopressor prescription. A MAP value of 65 mmHg was the most frequent vasopressor titration target, though somewhat higher targets (typically 70 mmHg) were also common and the range was wide (55 to 90 mmHg). We found differences between centers in the prescribed blood pressure variables (MAP vs. SAP vs. combination of MAP and SAP) and in the blood pressure values. Our data suggest that physicians (and not other health professionals) intend to control the targets for vasopressor dosing adjustments. Older age and local culture (the center effect) are predictors of higher blood pressure targets. We found no association between chronic comorbidities and blood pressure targets. Clinicians often changed targets in the first 48 hours of ICU stay. A multivariable analysis identified no association between acute concurrent illnesses and the direction of target blood pressure modifications when they occurred (in either direction).

This study constitutes the only observational description of actual practices regarding the titration of vasopressors. The advantage of an observational approach, as opposed to a survey of stated practices, is that it allows highlighting discrepancies between actual practices and physicians' perceptions. Other strengths of our study include a data extraction process that involved rigorous manual review of every included chart as well as detailed instructions and pre-piloted electronic data forms with logical checks ensuring data integrity. The multicenter nature of the study improves the generalizability of our results.

Limitations include our reliance on information available in medical records. Chart completeness regarding chronic comorbidities and vasopressor titration targets as well as the intensity of diagnostic workups may have varied across participating centers and between patients. Although ultimately, the decision to include or exclude data from a given chart involved a careful manual review of eligibility criteria, different hospitals use different databases and the screening process may have resulted in different patient populations in different centers.

The data refuted our initial hypothesis that many vasopressor prescriptions would not follow explicit titration orders. Physicians apparently agree on the need to explicitly describe how to titrate vasopressors and this consistently involves setting a blood pressure target. The fact that chronic comorbidities, illness severity and individual acute concurrent illnesses are not associated with how physicians prescribe vasopressors in septic shock could mean that, contrary to perceptions and the results of a survey recently published by our group, these variables are not taken into consideration.(12) Alternately, they may play an important role in the selection of titration targets but this signal may disappear due to disagreement between physicians in their interpretation. The frequent target modifications suggest that physicians adjust vasopressors based on their perception of the patients' requirements. This implies that clinical decisions rely on surrogate endpoints although we could not identify them.

To the extent that vasopressors are potent medications with significant adverse effect profiles and that they are systematically prescribed to the most vulnerable patients, identifying a titration strategy that will maximise benefit and minimise harm constitutes a research priority. Future steps should involve 1) developing a better understanding of the rationale underlying vasopressor titration strategies in real time, 2) observing if actual blood pressures correspond to set targets, 3) validating that different titration strategies lead to predictable results regarding surrogate endpoints of organ perfusion and function and 4) comparing the effects of different titration strategies on clinically important endpoints. All of these objectives are best achieved with prospective studies.

Conclusion

In treating patients with septic shock, intensivists from participating sites nearly always write prescriptions for vasopressors accompanied by explicit titration targets. These targets may vary with local standards more than with individual patient characteristics. Defining optimal vasopressor titration strategies adapted to individual patient characteristics demands randomized controlled trials.

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Figure legend

Figure 1: Flow diagram of charts included for review.

Figure 2: Histograms of blood pressure targets.

Table 1: Chronic comorbidities

	All Patients (n=369)	Centre 1 (n=174)	Centre 2 (n=114)	Centre 3 (n=81)	*P*
Hypertension % (N)	56% (205)	51% (88)	66% (75)	52% (42)	0,03
Diabetes mellitus % (N)	31% (115)	29% (51)	31% (35)	36% (29)	0,58
Coronary artery disease % (N)	31% (113)	30% (52)	38% (43)	22% (18)	0,07
Chronic obstructive pulmonary disease % (N)	26% (94)	28% (49)	21% (24)	26% (21)	0,4
Peripheral vascular disease % (N)	19% (71)	22% (38)	24% (27)	7% (6)	0,01
Immunosuppression % (N)	18% (68)	17% (30)	11% (13)	31% (25)	0,002
Chronic renal failure % (N)	18% (66)	14% (25)	13% (15)	32% (26)	0,001
Heart failure % (N)	18% (65)	15% (26)	21% (24)	19% (15)	0,4
Neoplasia % (N)	17% (64)	21% (36)	8% (9)	24% (19)	0,01
Cirrhosis % (N)	8% (29)	5% (9)	11% (12)	10% (8)	0,19
Asthma % (N)	4% (16)	2% (3)	3% (3)	12% (10)	0,001
Number of comorbidies per patient - median (IQR)	3 (1 - 4)	2 (1 - 4)	3 (1 - 4)	3 (2 - 4)	0,97
Patients with no chronic comorbidity % (N)	10% (38)	12% (21)	11% (13)	5% (4)	0,19
Patients with ≥ 1 chronic comorbidity % (N)	90% (331)	88% (153)	89% (101)	95% (77)	0,19
Patients with ≥ 2 chronic comorbidity % (N)	71% (263)	67% (117)	70% (80)	81% (66)	0,06

Table 2: Concurrent acute illnesses

	All Patients (n=369)	Centre 1 (n=174)	Centre 2 (n=114)	Centre 3 (n=81)	*P*
Acute renal failure % (N)	61% (224)	62% (108)	72% (82)	42% (34)	0,0001
Myocardial infarction % (N)	35% (128)	33% (57)	59% (67)	5% (4)	< 0.0001
Maximal serum lactic acid ≥ 4.0 % (N)	35% (128)	24% (41)	48% (55)	40% (32)	< 0.0001
ARDS/ALI % (N)	31% (115)	31% (53)	39% (44)	22% (18)	0,0499
Cardiac arrhythmia % (N)	24% (89)	18% (32)	22% (25)	40% (32)	0,001
Maximal INR ≥ 2.0 % (N)	23% (84)	14% (24)	34% (39)	26% (21)	0,0002
Acute pulmonary edema % (N)	17% (61)	17% (29)	11% (13)	24% (19)	0,08
Massive hemorrhage % (N)	13% (48)	21% (37)	9% (10)	1% (1)	< 0.0001
Ischemic bowel disease % (N)	6% (23)	8% (14)	4% (5)	5% (4)	0,46
Stroke % (N)	3% (10)	2% (4)	4% (5)	1% (1)	0,45
Number of acute illnesses per patient - median (IQR)	2 (1 - 3)	2 (1 - 3)	3 (2 - 4)	2 (1 - 3)	< 0.0001
Patients with no concurrent acute illness % (N)	9% (34)	9% (15)	4% (4)	19% (15)	0,002
Patients with ≥ 1 concurrent acute illness % (N)	91% (335)	91% (159)	96% (110)	81% (66)	0,002
Patients with ≥ 2 concurrent acute illness % (N)	72% (265)	70% (121)	85% (97)	58% (47)	0,0001

ARDS/ALI: acute respiratory distress syndrome or acute lung injury

INR: international normalized ratio

Table 3: Prescribed vasopressors targets

	All sites	Centre 1	Centre 2	Centre 3	P value
Number of patients	369	174	114	81	-
Total number of targets analyzed	604	277	176	151	-
Patients with ≥ 1 target % (N), (95% CI)	99% (365), (98 - 100)	99% (173), (97 - 100)	99% (113), (95 - 100)	98% (79), (94 - 100)	0,35
All targets					< 0.0001
SAP is only target % (N), (95% CI)	16% (95), (13 - 19)	7% (18), (4 - 9)	43% (75), (35 - 49)	1% (2), (0 - 3)	
MAP is only target % (N), (95% CI)	73% (438), (69 - 76)	79% (220), (75 - 84)	39% (69), (33 - 47)	99% (149), (97 - 100)	
SAP and MAP combined % (N), (95% CI)	8% (50), (6 -11)	14% (38), (10 - 18)	7% (12), (3 - 11)	0% (0), (0 - 0)	
Other % (N), (95% CI)	3% (21), (2 - 5)	0.4% (1), (0 - 2)	11% (20), (7 - 16)	0% (0), (0 - 0)	
First target only					< 0.0001
SAP is only target % (N), (95% CI)	16% (58), (12 - 20)	4% (6), (1 - 6)	45% (51), (36 - 54)	1% (1), (0 - 4)	
MAP is only target % (N), (95% CI)	75% (273), (70 - 79)	83% (144), (78 - 89)	45% (51), (36 - 54)	99% (78), (96 - 100)	
SAP and MAP combined % (N), (95% CI)	7% (27), (5 - 10)	13% (23), (8 - 18)	4% (4), (0 - 7)	0% (0), (0 - 0)	
Other % (N), (95% CI)	2% (7), (1 - 3)	0% (0), (0 - 0)	6% (7), (3 - 12)	0% (0), (0 - 0)	
Target value (first targets only)					
SAP only - median mmHg (N), (IQR)	100 (58), (90 - 100)	100 (6), (90 - 100)	100 (51), (90 - 100)	120 (1), (120 - 120)	0,04
MAP only - median mmHg (N), (IQR)	65 (273), (65 - 70)	65 (144), (65 - 65)	65 (51), (65 - 70)	70 (78), (70 - 75)	< 0.0001

Table 4: Other vasopressor titration targets

	All sites
Blood pressure range % (N)	2% (15)
Systemic vascular index of resistance % (N)	0.5% (3)
Heart rate > 50 bpm % (N)	0.2% (1)
Heart rate > 95 bpm % (N)	0.2% (1)
Dopamine at fixed "renal" dose % (N)	0.2% (1)

Table 5: Multivariable anaysis of the association between the first prescribed MAP target as a continuous value and the patients' baseline comorbidities

Multivariable model comparing the first prescribed MAP target as a continous value with patients' baseline comorbidities		
Parameters	**Estimate (95%CI)**	**P value**
Centre* 1 vs 3	- 6.93 (-7.94 ~ 5.92)	< 0.0001
Centre 2 vs 3	- 4.37 (-5.74 ~ -3.00)	< 0.0001
APACHE II score	-0.02 (-0.07~0.04)	0.54
Age	0.04 (0.01~0.07)	0.01
Coronary artery disease	0.40(-0.68 ~ 1.47)	0.47
Chronic heart failure	-0.48 (-1.69 ~ 0.72)	0.43
Hypertension	-0.17 (-1.15 ~ 0.80)	0.72
Diabetes	0.08 (-0.87 ~ 1.04)	0.86
Chronic renal failure	-1.11 (-2.26 ~ 0.04)	0.06

R-square=0.43

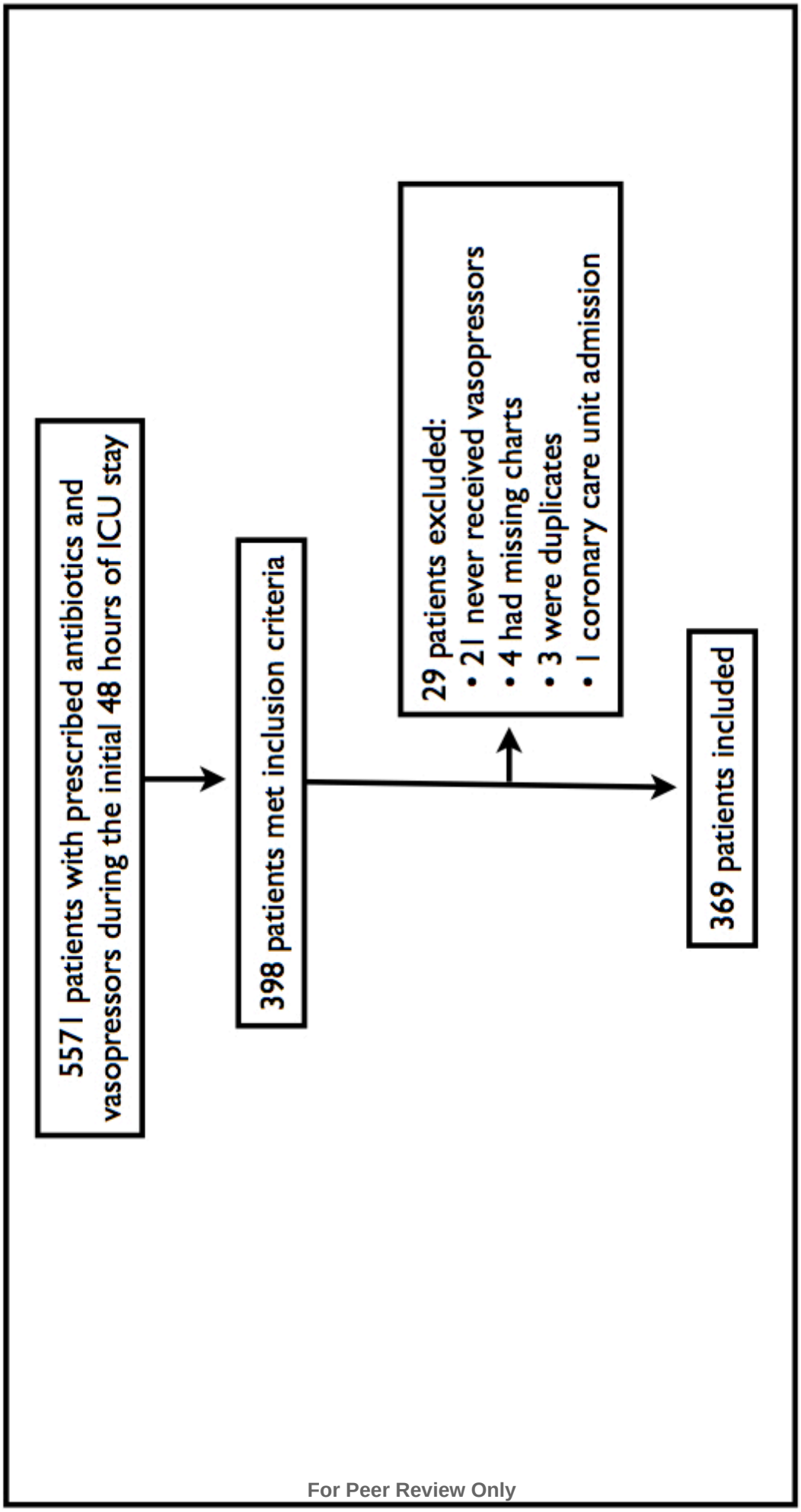
Table 6: Modifications to initial targets

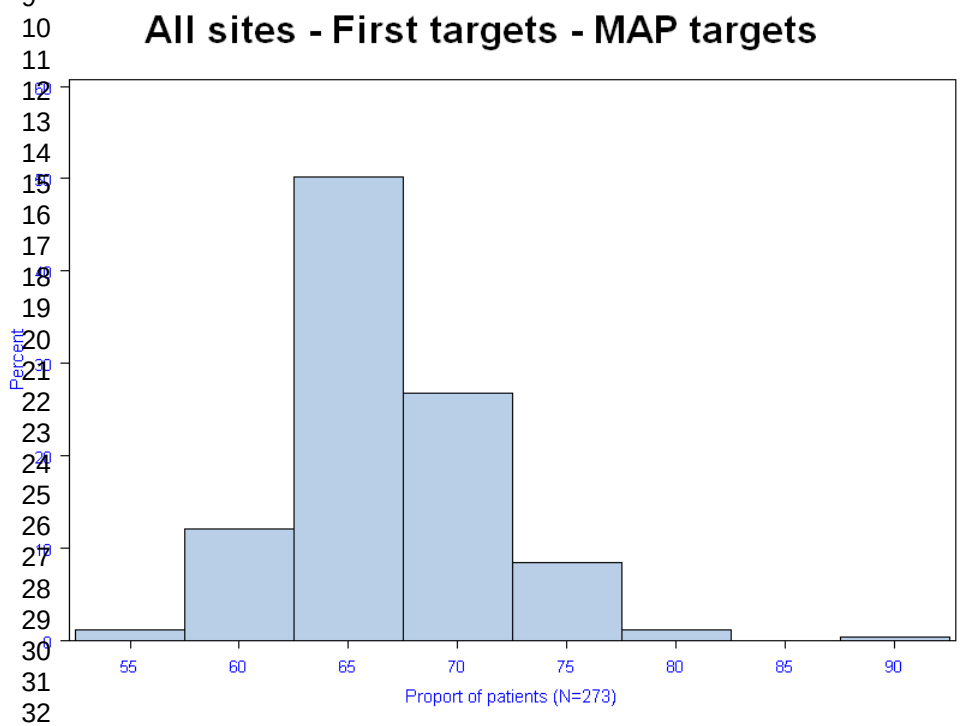
	All sites
Number of patients	369
Total number of targets analyzed	604
Patients with at least one explicit target % (N), (95% CI)	99% (365), (98 - 100)
Target modifications	
Patients with 0 modification (only 1 target) % (N)	54% (199)
Patients with at least one modification of initial target % (N)	40% (148)
Direction of target modifications	
Proportion of target changes in the same category that represent an INCREASE in the target value %, (N)	41% (33)
SAP - SAP increase - median mmHg (IQR)	+10 (10 , 10)
MAP - MAP increase - median mmHg (IQR)	+5 (5 , 5)
Proportion of target changes in the same category that represent a DECREMENT in target value	58% (47)
SAP - SAP decrease - median mmHg (IQR)	-10 (-15 , -7.5)
MAP - MAP decrease - median mmHg (IQR)	-5 (-5, -5)

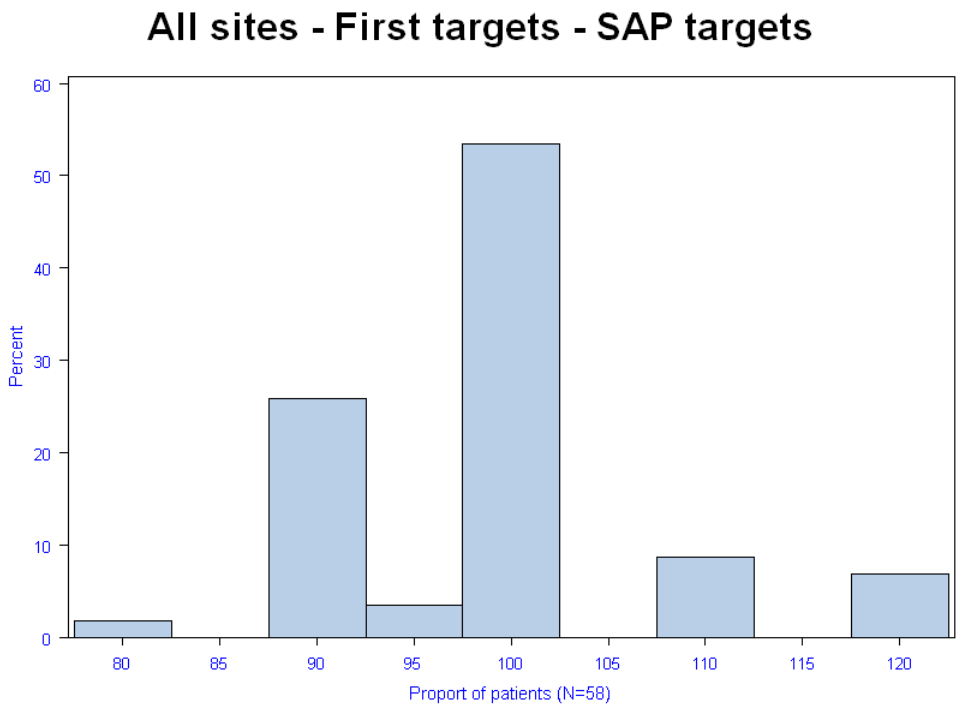
Table 7: Multivariable logistical model measuring the association between concurrent acute illnesses and the direction of blood pressure target modifications

Logistic regression (N = 277)		
	OR - SAP or MAP **increased** (n=33) vs. **no change (n=197)**	P value
Acute renal failure vs. NO acute renal failure	1.46 (0.65, 3.28)	0,36
Myocardial infarction vs. no myocardial infarction	1.06 (0.43, 2.64)	0,9
Lactic acid greater than 4 vs. NO lactic acid greater than 4	0.75 (0.32, 1.78)	0,52
Cardiac arrhythmia vs. NO arrhythmia	0.97 (0.39, 3.27)	0,94
	OR - SAP or MAP **decreased (n=47)** vs. **no change**	P value
Acute renal failure vs. NO acute renal failure	1.19 (0.60, 2.39)	0,61
Myocardial infarction vs. no myocardial infarction	0.68 (0.30, 1.52)	0,35
Lactic acid greater than 4 vs. NO lactic acid greater than 4	1.44 90.72, 2.88)	0,31
Cardiac arrhythmia vs. NO arrhythmia	1.15 90.54, 2.45)	0,71

*p-value for site effect=0.36


5571 patients with prescribed antibiotics and vasopressors during the initial 48 hours of ICU stay
398 patients met inclusion criteria
29 patients excluded:
• 21 never received vasopressors
• 4 had missing charts
• 3 were duplicates
• 1 coronary care unit admission
369 patients included





Supplementary appendix

Chronic comorbidities

Any comorbidity present upon hospital admission prior to the development of septic shock

- Peripheral vascular disease: history of stroke, transient ischemic attack, thoracic or abdominal aortic surgery, peripheral arterial bypass surgery, peripheral angioplasty, claudication.
- Coronary artery disease: history of myocardial infarction, coronary angioplasty, coronary artery bypass, coronary artery stenosis ≥ 50% measured during coronarography.
- Heart failure: cardiac ejection fraction ≤ 50% or diastolic dysfunction on echocardiography.
- Chronic obstructive pulmonary disease: FEV1 ≤ 80% and FEV1/FVC ≤ 0.7.
- Asthma: Methacholine challenge positive/FEV1 variation ≥ 12%/180ml after bronchodilators.
- Hypertension: history of hypertension or any patient receiving more than 3 anti-hypertensive medications; included anti-hypertensive medications are beta-blockers, alpha blockers, alpha2 agonists, ACEi, ARB, renin inhibitor, calcium channel blockers, loop diuretics, thiazide diuretics, potassium sparing diuretics, vasodilators.
- Diabetes mellitus: use of oral hypoglycemic medications (metfomine, glyburide, chlorpropamide, tolbutamide, glimepiride, gliclazide, repaglinide, nateglinide, acarbose, rosiglitazone, pioglitazone) or use of insulin.
- Chronic renal failure: defined according to the recommendations of the "National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI)": estimated glomerular clearance ≤ 60ml/min as per the MDRD method; patients on chronic dialysis are automatically included.
- Cirrhosis: proven cirrhosis on hepatic biopsy, child B or C cirrhosis, history of hepatic encephalopathy or history of upper gastrointestinal tract hemorrhage secondary to esophageal/gastric variceal bleeding.
- Active neoplasia: any patient diagnosed with neoplasia within 5 years prior to admission or any patient having received chemotherapy/radiotherapy within 5 years prior to admission.

- Immunosuppression: any patient receiving an immunosuppressant agent. Any patient having received a form of chemotherapy within 6 weeks prior to admission. Any patient known with a hematologic neoplasia (lymphoma or leukemia). Any patient having a past history of solid organ transplantation or bone marrow transplantation (excluding corneal transplant). Any HIV + patient. Immunosupressant agents are 6-mercaptopurine, azathioprine, systemic corticosteroid (prednisone, hydrocortisone, methylprenisolone, dexamethasone), methotrexate, cyclosporine, cyclophosphamide, hydroxychloroquine, mycophenolate mofetil, AntiTNF (infliximab, adalimumab, etanercept, certolizumab pegol), anakinra, rituximab.

Concurrent acute illnesses

Any organ insult or complication occurring within the initial 48 hours of ICU admission. Included if present upon ICU admission.

- Myocardial injury: serum troponins above upper limit of normal and above baseline value if available.
- Cardiac arrhythmia: history of atrial fibrillation, atrial flutter, supraventricular tachycardia, ventricular tachycardia, ventricular fibrillation, torsade de pointes. Chronic atrial fibrillation of atrial flutter is not considered an acute comorbidity.
- Acute pulmonary edema: diagnosis written in the progress notes and with at least 1 objective element present (lung imaging suggestive of edema, improvement after diuretics/dialysis, left heart failure on cardiac echocardiography).
- ARDS/ALI: PaO2/FiO2 ≤ 300mmHg with bilateral lung infiltrates on a chest x-ray. Use the radiologist's interpretation of the chest x-ray.
- Massive hemorrhage: deadly bleed or a symptomatic bleed in a critical region or organ (intracranial, spinal, ocular, retroperitoneal, articular, pericardial, or intramuscular with compartment syndrome) or bleed causing a ↓ Hb 20g/l or leading to a transfusion of ≥ 2 units of packed RBCs.
- Ischemic or hemorrhagic stroke proven on head CT/MRI. If the symptoms were present during the study period but imaging was done within 24 hours after the end of the study period, the event is included.

- Ischemic bowel disease: clinical suspicion mentioned in the progress notes and supported by a radiology exam (abdominal CT, abdominal angiography), endoscopic exam, or by operating room (OR) findings. OR findings are included if surgery performed immediately before the ICU admission.
- Acute renal failure: hemodialysis or CVVH in the ICU or a serum creatinine ↑ 1.5X baseline value or urine output ≤ 0.5ml/kg/hr x ≥ 6 hours or serum creatinine ≥350 μmol/L (only if new creatinine is ≥44 μmol/L compared to baseline value).
- Maximal INR > 2.0. If the patient was on vitamin K antagonist with a therapeutic INR (> 2.0) prior to ICU admission, we do not consider this as being an acute comorbidity.

STROBE Statement; Checklist for Prescribed targets for vasopressor titration in septic shock: aretrospective cohort study

	Item No	Recommendation	Checklist
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	√
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	√
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	√
Objectives	3	State specific objectives, including any prespecified hypotheses	√
Methods			
Study design	4	Present key elements of study design early in the paper	√
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	□ (period of recruitment missing)
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	√ (Follow up NA)
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	√
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	√
Bias	9	Describe any efforts to address potential sources of bias	√
Study size	10	Explain how the study size was arrived at	√
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	√
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	√
		(*b*) Describe any methods used to examine subgroups and interactions	√
		(*c*) Explain how missing data were addressed	√
		(*d*) If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	NA
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	√ (Details in figure 1)
		(b) Give reasons for non-participation at each stage	√
		(c) Consider use of a flow diagram	√
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	√
		(b) Indicate number of participants with missing data for each variable of interest	No missing data for primary outcome; missing baseline creatinine values not reported
		(c) Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	Report numbers of outcome events or summary measures over time	√
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	√
		(*b*) Report category boundaries when continuous variables were categorized	√
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	√
Discussion			
Key results	18	Summarise key results with reference to study objectives	√
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	√
Generalisability	21	Discuss the generalisability (external validity) of the study results	√
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	No funding provided for this study

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely

available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.