

Predictors of Acute Hemodynamic Decompensation in Early Sepsis: An Observational Study

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Abstract

Background: The study of sepsis is hindered by its heterogeneous time course and evolution. A subgroup of patients with severe sepsis develops shock soon after the initiation of treatment while others present hypotensive. We sought to determine the incidence of hypotension after the initiation of treatment for sepsis, and characterize their clinical features and course.

Methods: A retrospective review of electronic medical record of all septic patients (n = 542) that met the definition of septic shock within 24 hours of admission (2011 - 2012) at an urban Veteran Affairs Hospital was performed. Subjects either had 1) initial normotension (INT) with hypotension developing within 24 hours or 2) initial hypotension (IH). Logistic regression was used to model associated factors of INT/IH.

Results: INT occurred in 62 patients (11%) with average initial blood pressure of 120/71 mm Hg and developed hypotension to 79/48 mm Hg. IH was identified in 52 patients (10%) with average presenting blood pressure of 81/46 mm Hg. INT showed evidence of increased sympathetic tone with significantly higher heart rate, blood pressure and temperature. INT patients were younger, more frequently on alpha-blockers, and more likely septic from pneumonia compared to IH patients. INT and IH patients had similar timing of antibiotic initiation, amount of 24-hour fluid resuscitation, vasopressor use, organ dysfunction and mortality at 28 days. Using alpha-blockers, being Caucasian, and having higher temperatures were independent predictors of INT.

Conclusion: INT is a distinctive presentation of septic shock char-

acterized by rapid deterioration during early treatment. By further studying this subgroup, mediators of septic shock may be identified that clarify pathophysiology and provide timely targeted treatment.

Keywords: Sepsis; Septic shock; Vascular hypotension; Rehydration solutions; Fluid therapy; Adrenergic effects

Introduction

Sepsis remains a challenge to the healthcare system and is associated with frequent hospitalizations and high mortality [1-3]. The pathophysiology of sepsis has been intensively studied [2, 4]. However, clinical studies of sepsis are often hindered by its heterogeneous time course [4, 5]. Sepsis treatment studies have emphasized early recognition and treatment is critical to successful outcomes [6-8]. The effectiveness of interventions, such as fluid or antibiotic administration, is time-dependent [7-10]. The patient with sepsis who presents with hypotension is intuitively a different clinical phenotype than the patient who presents over a more prolonged time course [8, 10-12]. This distinction may be important in terms of prognosis and may influence the interventions deployed. We examined these two phenotypes of septic shock presentation within the first day of hospital admission and their response to standard of care (SOC).

We performed a retrospective review of patients presenting with sepsis, severe sepsis, and septic shock. We compared patients who presented with initial hemodynamic stability before evolving into septic shock to those who presented initially with septic shock in terms of initial findings, management, and outcomes. We investigated the associated patient-specific and treatment factors involved with the evolution of severe sepsis to septic shock. Early recognition of patients with severe sepsis who are at risk for deterioration into septic shock could potentially be useful in management decisions.

Materials and Methods

Study design and population

We conducted a retrospective cohort study at the Veterans

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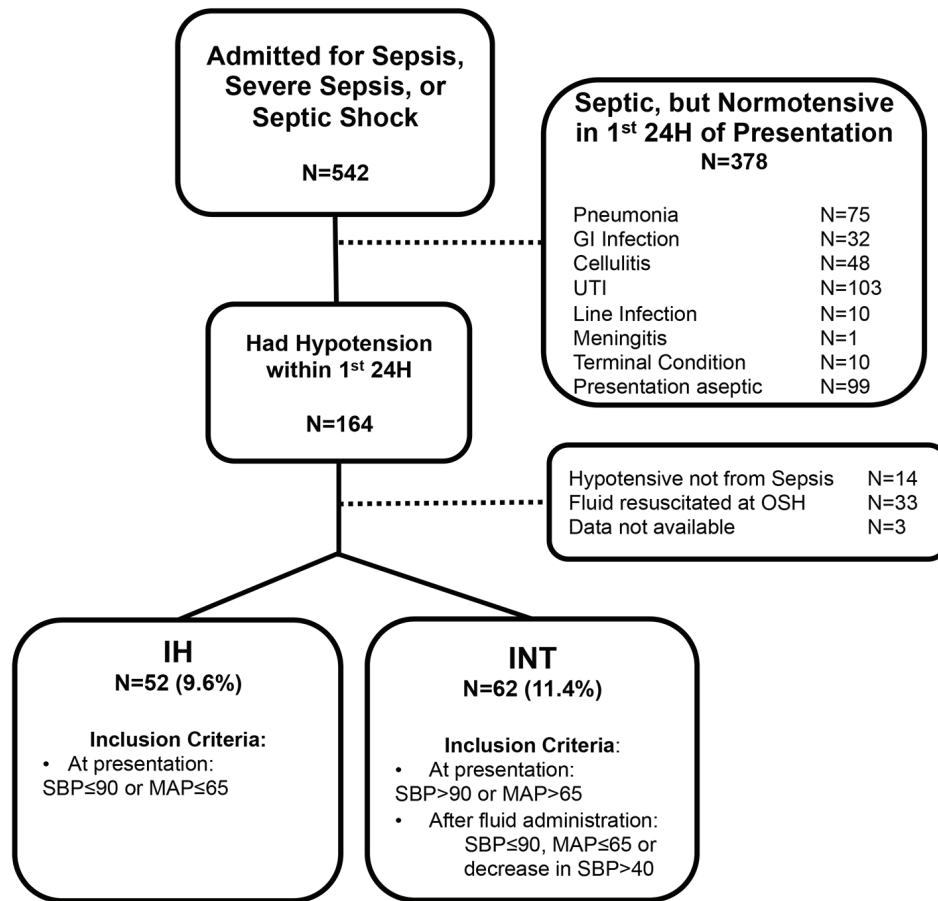


Figure 1. Retrospective cohort study design. H: hours; IH: initially hypotensive; INT: initially normotensive; OSH: outside hospital; SBP: systolic blood pressure; MAP: mean arterial pressure.

Affairs (VA) New York Harbor Healthcare System, an urban tertiary referral center. Data were from the electronic medical record (EMR) of all patients that were identified as having been admitted with the diagnosis of sepsis, severe sepsis, or septic shock in 2011 and 2012, (n = 542, Fig. 1). We excluded patients who 1) remained stable and had normotensive blood pressure during the initial 24 h of their hospitalization, 2) became hypotensive from etiologies other than sepsis or 3) had received significant sepsis treatment, specifically fluids or antibiotics, prior to hospital admission from other hospitals/nursing facilities and 4) did not have complete blood pressure data available. Study was approved by the hospital’s Institutional Review Board and granted a waiver of informed consent.

The remaining septic patients were identified as either cases of initial hypotension (IH) or initial normotension (INT). Patients with IH had systolic blood pressure (SBP) ≤ 90 mm Hg or mean arterial pressure (MAP) ≤ 65 mm Hg at the time of presentation. INT subjects presented with SBP > 90 mm Hg or MAP > 65 mm Hg but then developed hypotension in the first 24 h after hospitalization as defined by IH blood pressure parameters, or had a decrease in SBP more than 40 mm Hg from baseline, as consistent with Society of Critical Care Medicine/American College of Chest Physicians criteria for septic shock [1, 13-15].

We collected demographic data, chronic comorbidities, home medications, reason for hospital admission, length of stay, survival, laboratory data, and timing of sepsis treatment from their EMR. Respiratory failure was defined as requiring ventilator use; kidney failure was defined by a creatinine increase 1.5-fold from baseline; liver failure was defined by a bilirubin level greater than 1.2 mg/dL.

Statistical analysis

SPSS 21 (IBM, Armonk, NY) was used for database management and statistics. Data were analyzed by Student’s *t*-test and Pearson Chi-square test where appropriate. A two-sided P-value less than 0.05 was considered significant. We used logistic regression to examine clinical biomarkers that were predictive of the dichotomous outcome of being INT or IH. Variables identified as potential confounders and those with a P-value ≤ 0.05 in univariate analysis were included in the multivariate logistic regression model. Over-fitting was limited by excluding variables with inadequate prevalence and assessed by the Hosmer-Lemeshow goodness-of-fit. The model discrimination was evaluated using the receiver operating characteristic area under the curve (ROC-AUC).

Table 1. Demographics

	IH	INT	P*
Number of subjects	52	62	
Age, years*	79 (12)	75 (11)	0.124
Gender, male [†]	52 (100)	61 (98)	0.362
Race [†]			0.013
Caucasian	27 (52)	46 (74)	
African American and other	25 (48)	16 (26)	
Outpatient setting [†]			0.619
Home	36 (69)	44 (71)	
Nursing Home	16 (31)	17 (27)	
Undomiciled	0 (0)	1 (2)	
Days of illness prior to presentation*	3 (3)	3 (3)	0.207
BMI, kg/m ² *	24 (5)	27 (6)	0.010

BMI: body mass index. *Value expressed as mean (SD). [†]Value expressed as N (%). *Significance assessed by Student's *t*-test or Pearson's Chi-square test as applicable.

Results

Demographic characteristics of cohort

Retrospective case cohort design of patients with sepsis in 2011 - 2012 based on inclusion/exclusion criteria is shown in Figure 1. Among a total of 542 patients who were admitted for sepsis, we identified 52 (9.6%) patients with IH and 62 (11.4%) patients with INT. Demographics of the INT and IH groups are described in Table 1.

The two groups were not significantly different in age, gender, days of illness prior to presentation, or pre-hospitalization setting. They were significantly different in regards to race and BMI. INT patients were more likely to be Caucasian and had higher BMI. INT patients were also more likely to be on alpha-blockers and chronic steroids. They were also not significantly different in comorbidities, or most home medications (Table 2).

Clinical presentation and source of infection

At presentation, mean heart rate and temperature were significantly higher in the INT group (Table 3).

The average blood pressure of the IH group was significantly lower (81/46, MAP: 57 mm Hg), compared to the INT group (121/71, MAP: 88 mm Hg). Over the next 24 h, laboratory values were obtained and the most abnormal values were recorded (Table 3). Patients in IH and INT groups had similar white blood cell counts, hemodynamic stability, and serum sodium values. The IH group had significantly higher levels of serum creatinine compared to INT, but this may be a reflection of the higher prevalence of end-stage renal disease (ESRD) in the IH group compared to INT (Table 2) as incidence of acute renal failure was not different. Mean bicarbonate serum level

Table 2. Past Medical History

	IH	INT	P [†]
Comorbid conditions*			
Cancer	18 (35)	21 (34)	0.933
DM	16 (31)	24 (39)	0.376
ESRD	11 (21)	6 (10)	0.087
Heart disease	22 (42)	31 (50)	0.412
Neurologic disease	11 (21)	15 (24)	0.700
Home medications*			
ACE/ARB	22 (42)	27 (44)	0.834
α-blocker	12 (23)	25 (40)	0.050
Aspirin	20 (39)	28 (45)	0.525
β-blocker	26 (50)	25 (40)	0.301
Ca ²⁺ channel blocker	12 (23)	13 (21)	0.786
Chronic Steroid	3 (6)	11 (18)	0.045
Diuretics	20 (39)	20 (32)	0.489
Statin	18 (35)	28 (45)	0.253

DM: diabetes mellitus; ESRD: end-stage renal disease; ACE/ARB: angiotensin converting enzyme inhibitor/angiotensin receptor blocker. Heart disease: coronary artery disease, congestive heart failure, and arrhythmia; neurologic disease: dementia, Parkinson's disease, seizure, cerebral vascular aneurysm, and multiple sclerosis. *Value expressed as N (%). [†]Significance assessed by Pearson's Chi-square test.

was also higher in INT patients, although both expressed average levels within the normal range (Table 3). The INT patients were also more likely to be septic from pneumonia compared to other sources of infection, whereas IH patients more likely had positive, gram positive cultures from specimens other than blood or urine (Table 4).

Treatment and measures of outcome

INT and IH groups did not differ in treatment protocols for their sepsis (Table 4). Of interest, both groups received antibiotics within 3 h, but INT patients developed hypotension to an average of 79/48 mm Hg (MAP: 59 mm Hg) at 3 h and 18 min. INT and IH patients also received similar fluid volumes over the first 24 h, and had similar vasopressor and ventilator requirements. Other measures of the severity of illness were studied in the population (Table 5). The INT and IH groups had similar end-organ dysfunction, length of stay, and mortality at 28 days or 1 year. INT patients had a mean APACHE II score of 18, compared to IH patients with mean 20 (P = 0.07).

Association between development of INT and clinical biomarkers

A logistic regression model to predict INT was created and adjusted for race, source of infection, BMI, and age (Table

Table 3. Clinical Parameters at Presentation

	IH	INT	P*
HR, per minute	81 (22)	97 (25)	0.001
RR, per minute	20 (4)	20 (5)	0.275
BP, mm Hg			
Systolic	81 (10)	120 (16)	< 0.001
Diastolic	46 (9)	71 (14)	< 0.001
MAP	57 (7)	88 (12)	< 0.001
Temperature, °F	98.8 (2)	100.4 (2)	< 0.001
APACHE II lab values within 24 h			
CBC			
WBC, × 10 ³ /μL	17 (10)	14 (8)	0.054
Hct, %	33 (6)	34 (7)	0.470
Platelet, × 10 ³ /μL	230 (140)	211 (92)	0.383
Chemistries			
Sodium, mEq/L	141 (7)	139 (5)	0.057
Potassium, mEq/L	5.7 (6)	4.7 (0.9)	178
CO ₂ , mmol/L	22 (7)	25 (6)	0.037
Creatinine, mg/dL	3.9 (3)	2.2 (1)	< 0.001
Liver function test			
AST, U/L	117 (320)	93 (190)	0.616
ALT, U/L	107 (321)	63 (127)	0.327
Bilirubin, mg/dL	1.6 (4.2)	1.0 (0.8)	0.215
Lactate, mmol/L	3 (3)	3 (2)	0.476

HR: heart rate; RR: respiration rate; BP: blood pressure; MAP: mean arterial pressure; CBC: complete blood count; WBC: white blood count; Hct: hematocrit; AST: aspartate transaminase; ALT: alanine transaminase. All available values reported in mean (SD). *Calculated by Student's *t*-test.

6). Source of sepsis was coded as a dichotomous variable of pneumonia versus other sources to prevent over-fitting. Potential biomarkers were individually tested as crude variables for ability to predict INT as an outcome, and then incorporated into a final multivariable model in stepwise regression.

Outpatient alpha-blocker use was very predictive of being in the INT group and increased odds 302% (Table 6). An increase of 1 °F in temperature increased odds by 36% of being in the INT group. Of interest, race was also a significant predictor of INT. Caucasians were 323% more likely of presenting in the INT group. ROC curve analysis had AUC of 0.815 (95% CI: 0.736 - 0.894) and demonstrated good predictive ability (Supplementary Fig. 1, www.jocmr.org). The final model was robust and did not suffer from over-fitting, with Hosmer-Lemeshow Chi-square of 9.67 (*P* = 0.289). Sensitivity of the model was 75.0%, and specificity was 77.4%.

Discussion

The major findings of our retrospective study include that the presentation of INT is at least as common as IH subgroup.

The INT patients differed from the IH patients in that they had increased sympathetic-adrenergic tone manifested by higher heart rate and body temperature, higher BMI, race, higher rate of pneumonia as the source of sepsis, and more frequent alpha-blocker and chronic steroid use as outpatient medications. We further identified that being Caucasian, on an alpha-blocker, and having a higher temperature increased the odds of declining further to septic shock.

Phenotyping the subgroup of patients that present with sepsis and further decline to shock has been the focus of recent studies. Similar to our findings, the proportion of septic patients who developed shock between 4 and 48 h after admission was more than half in this recently published work [11]. The great majority of these patients developed shock within 24 h, and pneumonia was a common source of infection. Variables associated with progression to shock included female gender, coronary artery disease, bacteremia and elevated lactate [11].

Our study similarly sought to identify risk factors for progression to septic shock and suggest mechanisms that may contribute to vascular decompensation in INT patients. It could be argued that the INT patients were at an earlier point

Table 4. Sepsis Source and Treatment

	IH	INT	P [‡]
Source of infection [†]			
Cellulitis	3 (6)	9 (15)	0.130
GI	12 (23)	9 (15)	0.240
Line infection	3 (6)	1 (2)	0.230
Pneumonia	5 (10)	15 (24)	0.042
Urinary tract	25 (48)	22 (36)	0.174
Unclear source	6 (12)	7 (11)	0.967
Positive culture [†]			
Blood	12 (23)	16 (26)	0.736
Urine	19 (37)	17 (27)	0.297
Others	14 (27)	4 (7)	0.003
Gram stain [†]			
Gram positive	18 (35)	9 (15)	0.012
Gram negative	23 (44)	21 (34)	0.258
Time to hypotension, H:min*	-	3:18	-
Time to antibiotics, H:min*	2:21 (1:48)	2:52 (2:47)	0.268
Amount of fluid in 24 h, L*	3.9 (2)	4.3 (2)	0.217
Required vasopressor [†]	12 (23)	13 (21)	0.786
Mortality [†]			
28 days	14 (27)	15 (24)	0.739
1 year	28 (54)	31 (50)	0.682

GI: gastrointestinal; H: hours; min: minutes. *Value expressed as mean (SD). †Value expressed as N (%). ‡Significance assessed by Student's t-test or Chi-square test as applicable.

of their sepsis trajectory, and became acutely hypotensive as their disease progressed during the early hospital course. This hypothesis is supported by the findings that INT patients have fewer positive cultures and fewer isolates of gram-positive organisms than IH patients. However, number of days of illness prior to presentation did not differ significantly between the two groups. Additionally, INT patients' APACHE II scores trended lower than those of the IH patients (P < 0.07), and would have differed more had APACHE II scores been taken

Table 5. Indices of Severity of Illness

	IH	INT	P [‡]
Charlson comorbidity index*	7 (2)	7 (2)	0.795
APACHE II*	20 (5)	18 (5)	0.070
Organ dysfunction [†]			
Respiratory	7 (14)	8 (13)	0.930
Kidney	35 (67)	38 (61)	0.505
Liver	11 (22)	19 (31)	0.277
Length of stay, days*			
ICU	15 (13)	17 (26)	0.149
Hospital	8 (6)	8 (6)	0.960

*Value expressed as mean (SD). †Value expressed as N (%). ‡Significance assessed by Student's t-test or Chi-square test as applicable.

at presentation before INT patients became hypotensive, rather than at 24 h. Moreover, less severity of illness at presentation would suggest better outcomes in the INT subgroup compared to the IH subgroup, given prior studies showing that early treatment with fluid resuscitation and antibiotics improve survival [7, 8-10].

Fluid resuscitation could have contributed to the transition from a hemodynamically compensated circulation in the INT patients to a full-blown septic shock state. Fluid resuscitation is a mainstay of treatment for septic shock to maintain pressure in the central circulation [9]. However, it does not treat the main pathophysiology of distributive shock and, when given excessively, it could potentially compromise the microcirculation due to worsening interstitial edema [16, 17]. The fluid expansion as supportive therapy (FEAST) trial questioned the role of fluid resuscitation in sepsis, showing higher mortality in fluid-resuscitated African children with sepsis than in non-resuscitated controls [6]. The *post hoc* analysis, based on presenting symptoms and predominant terminal clinical events, showed that cardiovascular collapse was the major cause of death after rapid fluid resuscitation rather than fluid overload [18]. A possible explanation is that rapid restoration of circulatory volume via fluid resuscitation has unintended consequences, including the interruption of the compensatory, sympathetic, and innate response to hypovolemia [17, 19]. This compensatory response

Table 6. Logistic Regression Model Predictive of INT

Covariates	Crude*	P	Adjusted*	P
α-Blocker	2.25 (0.991 - 5.118)	0.053	3.02 (1.09 - 8.36)	0.033
Caucasian	2.66 (1.21 - 5.85)	0.015	3.23 (1.23 - 8.50)	0.018
Temperature	1.37 (1.15 - 1.64)	0.001	1.36 (1.11 - 1.67)	0.003
Age	0.98 (0.94 - 1.01)	0.124	0.97 (0.93 - 1.01)	0.188
BMI	1.09 (1.02 - 1.17)	0.014	1.08 (0.99 - 1.17)	0.071
Pneumonia	2.74 (0.92 - 8.22)	0.072	2.70 (0.80 - 9.15)	0.110
AUC			0.815 (0.736 - 0.894)	

AUC: area under the curve. *Values expressed as odds ratio (95% CI). Hosmer-Lemeshow of adjusted final model: Chi-square 9.67, df = 8, P = 0.289.

distinguished the INT patients from the IH patients. The INT patients presented in a relatively hyperadrenergic state, maintaining blood pressure along with higher heart rate and body temperature. In this scenario, fluid bolus given early in sepsis management results in the rapid conversion from vasoconstriction to vasodilation by disseminating a localized and contained focus of cytokines from infected tissue to the systemic circulation. In this regard, we observed significantly more instances of pneumonia in the INT subgroup compared to the IH subgroup. Among the 20 patients with pneumonia overall, 15 were in the INT subgroup. This observation supports the hypothesis that the transition from normotension to septic shock may involve fluid-driven dissemination of cytokines, or other cell derived mediators, from a localized site of infection with a rich vascular supply, like the pulmonary microcirculation, to the systemic circulation. Although the INT subgroup did receive more fluid volume than the initial septic shock subgroup during the first 24 h (4.3 L vs. 3.9 L), the difference did not reach statistical significance.

An alternative explanation for hypotension during treatment of early sepsis may be the presence of a Jarisch-Herxheimer reaction following the administration of antibiotics [20, 21]. Time to initiation of first antibiotics was similar in both groups. Interestingly, antibiotic administration occurred before the recognition of hypotension in the INT subgroup (2 h 52 m vs. 3 h 18 m). Also, the INT group had relatively more gram-negative isolates than the septic shock subgroup. These observations suggest that antibiotics could contribute to the onset of septic shock via a Jarisch-Herxheimer reaction by lysing bacteria with the subsequent release of endotoxin. This question warrants further study.

We found two other differences between the INT and IH subgroups that may have affected their hemodynamic state at presentation. Although the Charlson comorbidity index was the same for both subgroups, INT patients were taking alpha-blockers as outpatients significantly more frequently than IH patients. Chronic alpha-blocker therapy may result in peripheral adrenergic receptor up-regulation and contribute to hyper-adrenergic compensation. Therefore, patients taking alpha-blockers may be more susceptible to acute decompensation after interruption of their hyper-adrenergic, compensatory response, as may occur after fluid resuscitation. Also, INT patients were more frequently on chronic steroid therapy prior to presentation, another factor that may have affected their ability to sustain a compensated hemodynamic state.

Limitations of our study include its retrospective design. Observed variables that are associated with the INT presentation cannot be regarded as causal. Also, the Veterans Affairs medical center has predominantly male patients with a potentially greater fraction of patients on alpha-blocker therapy, possibly limiting the generalizability of our findings. Finally, both INT and IH groups had similar mortality at 28 days and 1 year, similar organ failures, and similar ICU and hospital lengths of stay for both patient subgroups.

In summary, we found that the two presentations of septic shock, INT and IH, occur with equal frequency. Patient-specific variables may discriminate between these presentations. Although INT patients seem to have less severity of illness based on hemodynamic stability at presentation, we found no

differences in important clinical outcomes between the two subgroups. However, because the INT group provides a point of origin, or time zero, for progression into septic shock, further study of this group may provide clarification of the pathophysiology and mechanisms of septic shock.

Key messages

In our population, 46% of patients who present with sepsis progress to septic shock.

Being Caucasian or on an alpha-blocker increased the odds of progressing to septic shock independently at least three-fold.

Each 1 °F increase above the mean of the cohort increased odds of progressing to shock 36%.

Timing of antibiotic initiation, amount of fluid resuscitation in first 24 h, vasopressor use, and mortality at 28 days did not increase odds of progression to shock.

Author Contributions

YIL, RLS and AN participated in study conception and design; YIL, RLS and AN were the primary investigators; YIL, RLS and AN were responsible for data collection; YIL, RLS and AN were responsible for data validation; YIL, EJC, SK and AN participated in data analysis; YIL, SK and AN undertook the statistical analysis. All authors participated in data interpretation, writing and revision of the report and approval of the final version. No individuals contributing to data collection, analysis, writing or editing assistance, and review of manuscript have been omitted.

Guarantor Statement

AN has full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis, including and especially any adverse effects.

The funding agencies did not participate in the study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

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Conflicts of Interest

No conflicts of interest exist for any of the authors.

Abbreviations

DM: diabetes mellitus; ESRD: end-stage renal disease; EMR: electronic medical record; FEAST: fluid expansion as supportive therapy; IH: initial hypotension; INT: initial normotension; MAP: mean arterial pressure; SBP: systolic blood pressure; VA: veterans administration

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