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PGY 賴冠汝

Supervisor Dr. 陳欣伶

Association between timing of antibiotic administration and mortality from septic shock in patients treated with a quantitative resuscitation protocol*

Michael A. Puskarich, MD; Stephen Trzeciak, MD; Nathan I. Shapiro, MD; Ryan C. Arnold, MD; James M. Horton, MD; Jonathan R. Studnek, PhD; Jeffrey A. Kline, MD; Alan E. Jones, MD; on behalf of the Emergency Medicine Shock Research Network (EMSHOCKNET)

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Introduction

- The Surviving Sepsis Campaign international consensus guidelines recommend initiating broad-spectrum antibiotic coverage within the first hour of recognizing severe sepsis and septic shock

- Recent large cohort of 165 hospitals treating >15,000 patients with septic shock: only 68% received broad-spectrum antibiotics within 3 hrs of ED presentation.
- This study: to evaluate if the timing of antibiotic administration in relation to both triage time and time of shock recognition was associated with in-hospital mortality

Methods

- **Preplanned analysis**

  to assess the noninferiority of lactate clearance vs. central venous oxygen saturation

→as the protocol end point that evaluated the adequacy of oxygen delivery during ED-based early quantitative resuscitation of sepsis

- January 2007 to January 2009, at three urban U.S. emergency departments

◆>17 yrs
◆confirmed or suspected infection
◆≧2 systemic inflammatory response criteria
◆hypoperfusion evidenced by hypotension after fluid challenge or lactate ≧4 mmol/L.

lactate clearance

central venous oxygen saturation

Until all end points were achieved or a maximum of 6 hrs

- 6% (95% confidence interval, -3 to 14%) in-hospital mortality difference between the two study groups

→confirming the primary hypothesis of noninferiority between the two resuscitation end points

- all patients received broad-spectrum antibiotic coverage—As early as possible after sepsis recognition

- Primary outcome: in-hospital mortality
- Compared the outcomes of subjects who received an initial dose of antibiotics after compared with before each hourly increment up to a maximum of 6 hrs after ED triage.
- compared outcomes of patients receiving initial antibiotics after compared with before each hourly increment after shock recognition

◉ Shock recognition:

≧ 2 SIRS criteria

SBP < 90 mm Hg after a minimum of 20-mL/kg rapid volume challenge

or

blood lactate concentration of at least 4 mmol/L

- One infectious disease specialist reviewed the blood culture and clinical data from all subjects.

- *Staphylococcus epidermidis* and other coagulase(-) staphylococci were considered contaminants unless the patient had a pre-existing indwelling venous catheter.

Results

300 patients

291 patients

received a first dose of antibiotics after presentation to the hospital.

172 patients (59%) received the initial dose of antibiotics after recognition of shock.

9 patients

received antibiotics before hospital arrival

excluded from subsequent analysis

Table 1. Patient demographics and clinical characteristics

Variable (n = 291)	Value
Age, yrs (IQR)	62 (50–73)
Race (%)	
White	158 (54)
Black	101 (34)
Hispanic	27 (9)
Other	5 (2)
Sex, %	
Male	156 (53)
Female	135 (46)
Eligibility criteria (IQR)	
Temperature, °F	99 (97–101)
Heart rate, beats/min	102 (85–112)
Respiratory rate, breaths/min	22 (18–27)
White blood count, cells per mm^3	12.4 (7.7–17.5)
Systolic blood pressure, mm Hg	86 (77–98)
Lactate, mmol/L	3.3 (1.8–5.8)
Baseline laboratory values (IQR)	
Platelets per mm^3	214 (135–294)
Hemoglobin, mg/dL	11.4 (9.8–13.4)
Creatinine, mg/dL	1.7 (1.1–3.0)
Total bilirubin, mg/dL	1.0 (0.6–1.6)
HCO_3, mg/dL	21 (17–24)
International normalized ratio	1.3 (1.1–1.7)
Disease severity (IQR)[a]	
Simple Acute Physiology Score II	42 (30–55)
Sequential Organ Failure Assessment score	6 (4,9)
Mortality in Emergency Department Sepsis score	11 (8–14)

Table 2. Source of infection

Source	No. of Patients (%)
Pneumonia	99 (34.0)
Urinary tract infection	71 (24.4)
Intra-abdominal	49 (16.8)
Skin and soft tissue	23 (7.9)
Indwelling intravascular catheter	11 (3.8)
Surgical wound	7 (2.4)
Endocarditis	4 (1.4)
Meningitis	3 (1.0)
Septic arthritis	2 (0.7)
Tuberculosis	1 (0.3)
Ear, nose, throat	1 (0.3)
Toxic shock syndrome	1 (0.3)
Unknown	40 (13.8)
Two or more sources	21 (7.2)

Overall mortality: 55 of 291 (18.9%)

Table 3. Organisms isolated from the blood

	No. of Patients
Gram-positive organisms	
Staphylococcus aureus	21
Methicillin-sensitive	11
Methicillin-resistant	10
Coagulase-negative *staphylococcus*	1
Streptococcus pneumoniae	7
Other streptococcus species	9
Enterococcus species	8
Peptostreptococcus	1
Bacillus cereus	1
Clostridium perfringens	2
Diphtheroids	2
Micrococcus	1
Lactobacillus	1
Gram-negative organisms	
Escherichia coli	17
Klebsiella species	7
Proteus species	7
Serratia marcescens	4
Pseudomonas species	2
Enterobacter species	2
Vibrio vulnificus	1
Acinetobacter species	1
Morganella species	1
Citrobacter species	1
Yeast/fungi	
Candida species	3
Positive blood cultures	100 (34.4%)

Mortality rate	
blood culture (+) septic shock	26/100 (26.0%)
blood culture (-) septic shock	29/191 (15.2%)

P=0.03

100 B/C (+) patients

➢91 received antibiotics in the ED to which the causative organism was susceptible.

➢7 received broad-spectrum ABx, the causative organism was resistant

➢2 fungemia, untreated in ED

Mortality rate	
appropriate antibiotics	23/91 (25.3%)
inappropriate antibiotics	3/9 (33.3%)

P=0.69

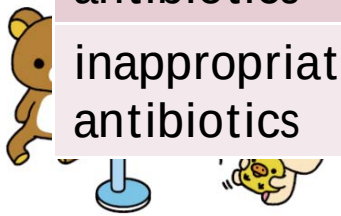


Table 4. Inhospital mortality: Triage to initial antibiotics

Time to Antibiotics	Number of Patients	Mortality (%)	Difference (%)	Odds Ratio[a]	95% Confidence Interval	Adjusted Odds Ratio[a]	95% Confidence Interval
≤1 hr	65	16.9	2.6	1.18	0.57–2.46	1.81	0.74–4.44
>1 hr	226	19.5					
≤2 hrs	155	21.3	−5.1	0.71	0.39–1.30	1.07	0.54–2.16
>2 hrs	136	16.2					
≤3 hrs	223	20.6	−7.4	0.59	0.27–1.27	0.66	0.27–1.63
>3 hrs	68	13.2					
≤4 hrs	255	20.4	−12.1	0.35	0.10–1.20	0.39	0.08–1.90
>4 hrs	36	8.3					
≤5 hrs	274	19.7	−13.8	0.25	0.03–1.96	0.69	0.07–6.86
>5 hrs	17	5.9					
≤6 hrs	281	19.6	−19.6	—	—	—	—
>6 hrs	10	0					

The median time from triage to initial antibiotic administration was 115 mins

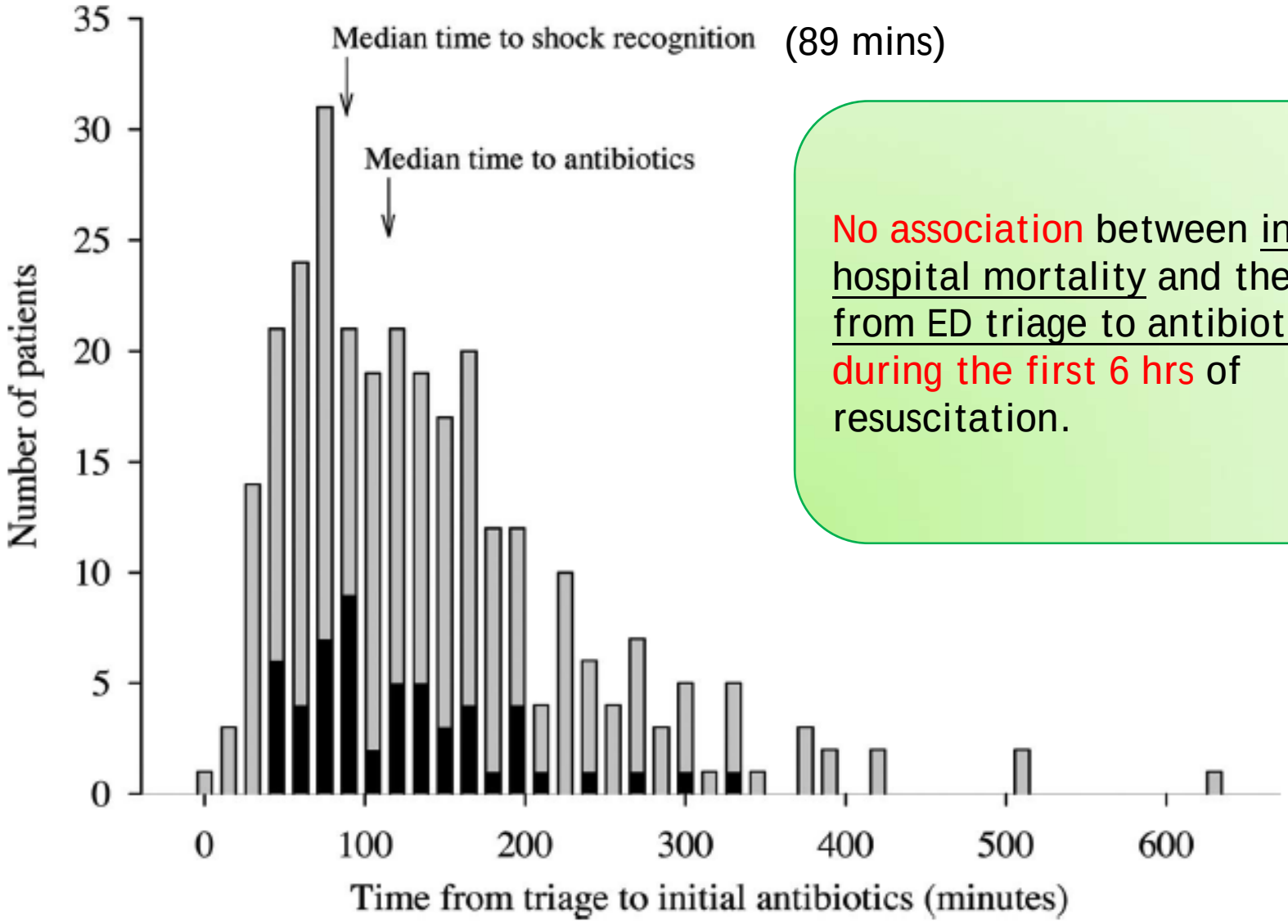


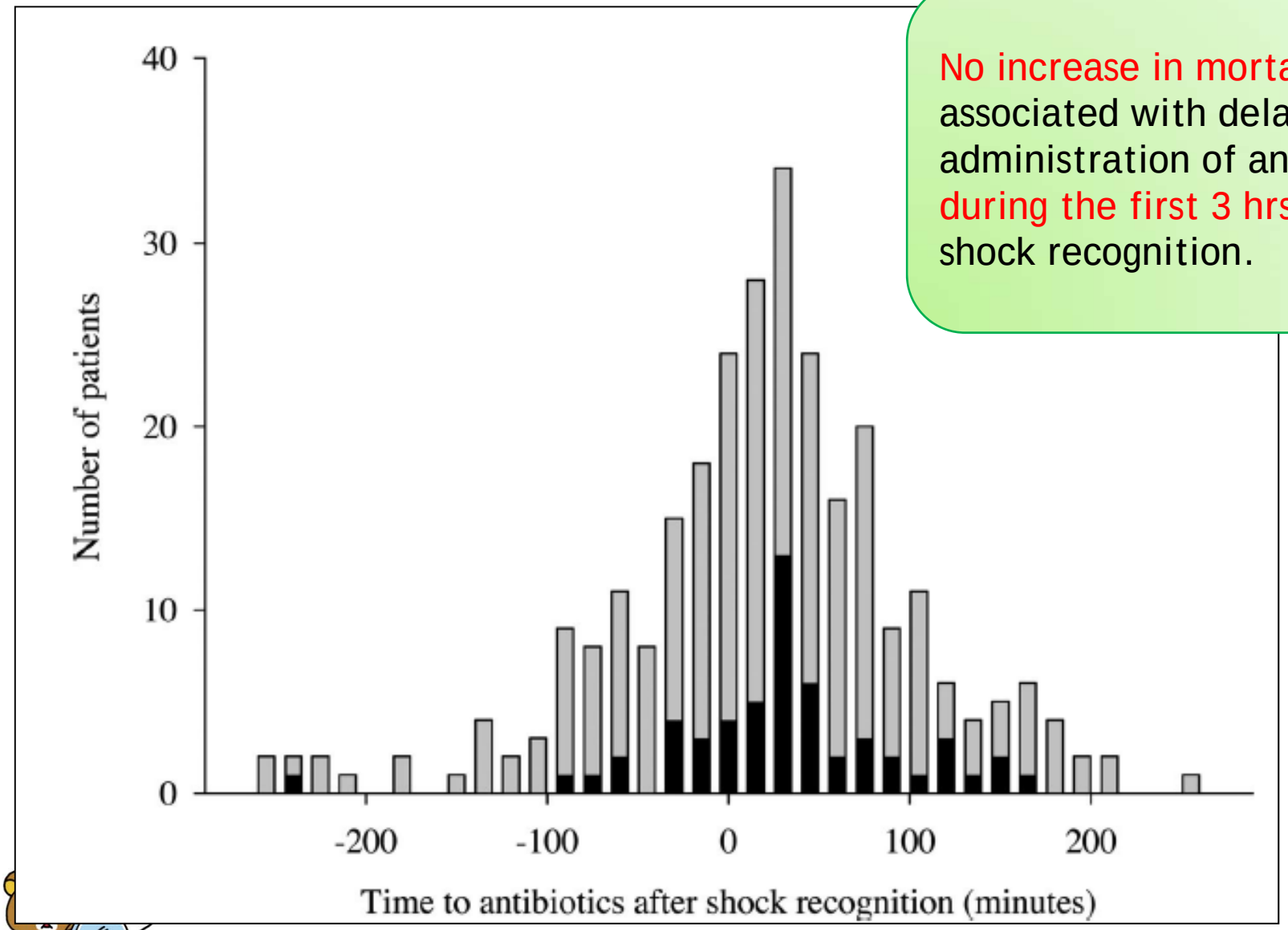
Figure 1. Graphic depiction of the time from triage to initial antibiotics in the entire cohort stratified by final hospital outcome. Gray bars represent patients who survived the hospitalization and black bars represent patients who died in the hospital.

No association between in-hospital mortality and the time from ED triage to antibiotics during the first 6 hrs of resuscitation.

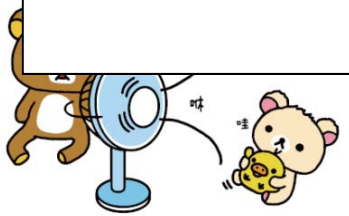
Table 5. Inhospital mortality: Shock recognition to initial antibiotics

Time to Antibiotics	Number of Patients	Mortality (%)	Difference (%)	Odds Ratio[a]	95% Confidence Interval	Adjusted Odds Ratio[a]	95% Confidence Interval
Before shock recognition	119	11.8	12	2.35	1.12–4.53	2.59	1.17–5.74
After shock recognition	172	23.8					
≤1 hr	101	25.8	−4.7	1.29	0.63–2.67	0.93	0.41–2.12
>1 hr	71	21.1					
≤2 hrs	145	24.1	−1.9	1.11	0.42–2.98	0.69	0.21–2.22
>2 hrs	27	22.2					
≤3 hrs	164	23.8	1.2	0.94	0.18–4.82	0.84	0.13–5.52
>3 hrs	8	25.0					

[a]Odds of death with increasing delays in antibiotic administration.



No increase in mortality associated with delay to administration of antibiotics during the first 3 hrs after shock recognition.



Discussion

- No association between time from triage to initial antibiotic administration and hospital mortality
- However, our data suggest an increased risk of death if antibiotics are delayed until after the recognition of shock.
- Once a patient meets the consensus definition for shock, no association between subsequent hourly delays in antibiotic administration and mortality.

- **Kumar et al:** administration of ABx within the first hour of documented hypotension was associated with a survival rate of 79.9%.
- Each hour of delay in antimicrobial administration over the ensuing 6 hrs was associated with an average decrease in survival of 7.6%.

What's the difference?

- Kumar et al study included all ICU patients, and the overall reported mortality rate was 56%. The subjects had a higher severity of illness
- Those patients presented from a variety of settings and likely received various methods of initial resuscitation.
- All of the patients in the current study underwent the same early recognition and aggressive treatment protocol, likely resulting in more uniform screening and initial resuscitative efforts

- **Gaieski et al**: emphasizes appropriateness of antibiotic administration in their conclusions.
- Measure the effect of an antibiotic with activity against the causative organism

→ accurately performing this measurement in a clinical setting, particularly the ED, is nearly impossible.

- High rate of B/C(-) septic shock:

→ Appropriateness in these cases is relegated to "broad spectrum"

- For those >1 B/C (+) with different organisms

→ subjective decisions as to the causative organism must be made

- This study incorporated appropriateness of antibiotics in our multivariate model. These adjusted results were nearly identical to unadjusted results.

The strength of this study

- Prospectively studied the timing of antibiotic administration to ED patients with septic shock.
- Standardized, prescribed early recognition and resuscitation protocol
- 75% of patients receiving initial antibiotics within 3 hrs and 97% within 6 hrs of triage.

Limitation

- These results may not be generalizable to hospitals without such protocols

- Vast majority of patients received antibiotics within 3 hrs of triage, relatively small numbers of patients in subsequent time points → wide CI, difficult to draw definitive conclusions.

- It is impossible in most cases to identify the exact time of onset of septic shock, the timing of antibiotics in relation to onset of shock can often not be ascertained.
- given the design of our study, this study only draw conclusions regarding associations and not causation.

Conclusion

- failed to demonstrate an association between timing of antibiotic administration from ED triage and hospital mortality.
- A delay in antibiotics until after shock recognition was associated with increased mortality
- if antibiotics are administered after shock recognition, there is no increase in mortality with hourly delays.

Hypertensive heart failure: patient characteristics, treatment, and outcomes☆

Frank Peacock MD[a,*], Alpesh Amin MD[b], Christopher B. Granger MD[c], Charles V. Pollack Jr MD[d], Phillip Levy MD[e], Richard Nowak MD[f], Kurt Kleinschmidt MD[g], Joe Varon MD[h], Allison Wyman[i], Joel M. Gore MD[i]
For the Stat Investigators

[a]*The Cleveland Clinic, Cleveland, OH, USA*
[b]*UCIMC, Orange, CA, USA*
[c]*Duke Clinical Research Institute, Durham, NC, USA*
[d]*Pennsylvania Hospital, Philadelphia, PA, USA*
[e]*Wayne State University, Detroit, MI, USA*
[f]*Henry Ford Health System, Detroit, MI, USA*
[g]*UT Southwestern Medical Center, Dallas, TX, USA*
[h]*The University of Texas Health Science Center, Houston, TX, USA*
[i]*Center for Outcomes Research, UMass Medical School, Worcester, MA, USA*

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Introduction

- Hypertensive crisis:
- ~1% of patients with long-term hypertension will experience a crisis in their lifetime.
- If untreated, the 1-year mortality of uncontrolled hypertension is high, and in patients presenting with crises, the 5-year death rate is 26%.

- Heart failure:
- ~1.1 million annual US ED visits for HF, 80% require hospitalization.
- Once hospitalized, the in-hospital HF mortality rate is 2% to 20% .
- After discharge, 11% die within 30 days, 44% require re-hospitalization within 6 months, and 33% do not survive 1 year
- ED presentation for acute pulmonary edema has a particularly poor prognosis; 12% die during their admission and > 40% within 1 year

Hypertension vs. Heart failure

- 3% to 73% of all patients presenting with AHF have a history of hypertension, which is more prevalent in preserved systolic function
- > 60% of patients with AHF have normal or elevated BP, and some report they have a lower mortality than patients with lower BP
- Hypertensive emergencies presenting as AHF have been poorly described

- **This study:**

  to describe the characteristics, treatment, and outcomes of patients presenting with severe hypertension complicated by AHF

Methods

- Studying the Treatment of Acute HyperTension (STAT) registry
- In US, multicenter, observational, cross-sectional survey of the management practices and outcomes for patients with acute, severe hypertension receiving parenteral antihypertensive therapy

- Eligible patients:

  > 18 years, presenting to the hospital with acute, severe hypertension and receiving treatment in a nonoperative, critical care setting.

- **Severe hypertension:**

  SBP> 180 mmHg and/or DBP> 110mmHg

- **Exclusion criteria**
- received hypertension therapy during the peripartum period
- had a primary neurologic etiology for their presentation
- had therapy delayed longer than 24 hours
- were treated with “comfort care measures” only

- **Parenteral antihypertensives:**

  Patients must have received >1 antihypertensive bolus or have received a continuous antihypertensive infusion within 24 hours of hospitalization.

- **Acute HF:**
  - pulmonary edema on x-ray
  - BNP > 500 or NTproBNP > 900 pg/mL in those with a serum creatinine level $\leqq$2.5 mg/dL

End-organ damage:

- Hypertension-associated emergencies occurring or worsening during the short-term hospitalization or considered new

- Encephalopathy
- Any myocardial infarction, unstable angina with dynamic ST changes
- Renal insufficiency
- Microangiopathic hemolytic anemia
- Aortic dissection

- patients presenting with any type of acute stroke or intracranial bleeding (including ophthalmologic) were excluded, unless this occurred after hospitalization

Result

1199 STAT registry patients:

- median age was 57 years
- 48% were women
- 62% were African American.
- Most had a prior hypertension (92%)
- 33% had a prior hospitalization for hypertension

Table 1 Demographics of AHF vs non-HF STAT patients

25.2%

	AHF (n = 302)	Non-HF (n = 897)	*P*
Age, mean (SD)	59 (15)	57 (16)	.06
Male sex, n (%)	156 (52)	463 (52)	.99
Race, n (%)			<.0001
White	49 (16)	281 (31)	
Black	226 (75)	522 (58)	
Other	21 (7.0)	72 (8.0)	
Cardiac history, n (%)	195 (65)	361 (40)	<.0001
Myocardial infarction	56 (19)	121 (13)	.032
Congestive HF	153 (51)	156 (17)	<.0001
Hospitalization for HF	47 (16)	42 (4.7)	<.0001
Ejection fraction, median (interquartile range)	50 (39, 55)	55 (50, 60)	<.0001
Diabetes, n (%)	133 (44)	322 (36)	.013
Chronic obstructive pulmonary disease, n (%)	52 (17)	80 (8.9)	<.0001
Prior hypertension hospitalization, n (%)	136 (45)	261 (29)	<.0001
History of hypertension, n (%)	286 (95)	816 (91)	.040
Chronic kidney disease, n (%)	147 (49)	299 (33)	<.0001
Dialysis dependent, n (%)	62 (21)	104 (12)	<.0001
Admission laboratory examinations			
BNP, pg/mL (median [interquartile range])	1020.0 (603.0, 2226.0)	231.1 (94.0, 495.0)	<.0001
NTpro-BNP, pg/mL (median [interquartile range])	3351.0 (1882.0, 5406.0)	7519.5 (230.6, 9999.9)	.60
Troponin T	0.04 (0.03, 0.10)	0.07 (0.03, 0.12)	.28
Troponin I	0.08 (0.04, 0.19)	0.06 (0.03, 0.15)	.015
Creatinine level, mg/dL (median [interquartile range])	1.9 (1.2, 4.5)	1.2 (1.0, 2.5)	<.0001

Mean SBP	210±26	205±23	P=0.008
Mean DBP	117±24	111±23	P<0.0001

Table 2 Resource use

	AHF (n = 302), n (%)	Non-HF (n = 897), n (%)	*P*
ICU admission	152 (50)	308 (34)	<.0001
Hospital length of stay, d (median [interquartile range])	4 (3, 8)	4 (2, 7)	.012
Cardiac catheterization	24 (8.0)	83 (9.3)	.49
Dialysis	59 (20)	84 (9.4)	<.0001
Dialysis dependent at discharge	44 (15)	61 (6.8)	<.0001
Arterial line	47 (16)	133 (15)	.76
Mechanical ventilation	38 (13)	90 (10)	.21
Bilevel positive airway ventilation	22 (7.3)	9 (1.0)	<.0001
Chest x-ray	297 (98)	757 (84)	<.0001
Admission electrocardiogram	297 (98)	804 (90)	<.0001
Atrial fibrillation	20 (6.6)	34 (3.8)	.040
Left ventricular hypertrophy	108 (36)	235 (26)	.002

Table 3 Medications before admission to hospital and within 24 hours of admission

Medication received	Medications before admission (oral)			Medications within 24 h of admission (intravenous or per os)		
	AHF, n (%)	Non-HF, n (%)	*P*	AHF, n (%)	Non-HF, n (%)	*P*
ACEI or ARB	149 (49)	339 (38)	<.001	169 (56)	380 (42)	<.0001
β-Blocker	165 (55)	409 (46)	.007	217 (72)	765 (85)	<.0001
Calcium channel blocker	91 (30)	227 (25)	.10	132 (44)	345 (38)	.11
α-Blocker	10 (3.3)	25 (2.8)	.64	17 (5.6)	29 (3.2)	.061
Hydralazine	33 (11)	59 (6.6)	.014	145 (48)	376 (42)	.06
Diuretic	128 (42)	224 (25)	<.0001	167 (55)	214 (24)	<.0001
Clonidine	50 (17)	144 (16)	.84	68 (23)	209 (23)	.78
Minoxidil	14 (4.6)	32 (3.6)	.40	12 (4.0)	18 (2.0)	.06
Other antihypertensives	8 (2.7)	29 (3.2)	.61	9 (3.0)	36 (4.0)	.41
Nitrates	52 (17)	84 (9.4)	<.001	170 (56)	293 (33)	<.0001

In hypertensive HF patients, BP control was not rapidly achieved.

- At 1 hour, only 29% of HF patients had a systolic BP < 160 mm Hg
- by 6 hours, 74% still had SBP >140 mm Hg.

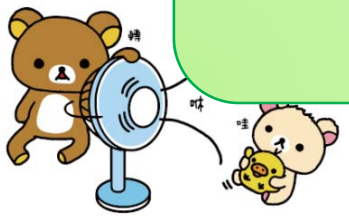

Table 4 Clinical outcomes

	New/worse end-organ damage [a]			No end-organ damage		
	AHF, n = 153	Non-HF, n = 373	*P*	AHF, n = 149	Non-HF, n = 524	*P*
ICU admission, n (%)	88 (58)	183 (49)	.08	64 (43)	125 (24)	<.0001
Median length of stay (interquartile range)	5 (3, 10)	5 (3, 9)	.27	3 (2, 6)	3 (1, 5)	.11
In-hospital death, n (%)	9 (5.9)	22 (5.9)	.99	2 (1.3)	4 (0.8)	.62 [b]
90-day hospitalization, n (%)	59 (45)	126 (39)	.22	68 (48)	158 (33)	.002
Postdischarge death, n (%)	5 (3.7)	15 (4.6)	.68	6 (4.3)	16 (3.3)	.60 [b]

[a] Excluding acute pulmonary edema.
[b] Fisher exact test used due to small cell values.

Among the population with end-organ damage, HF had little impact on outcomes.

Table 5 Predictors of readmission

	Readmitted (n = 127)	Not readmitted (n = 147)	*P*
Blood urea nitrogen, median (interquartile range)			
Admitting	28.0 (18.0, 45.0)	22.0 (17.0, 36.0)	.06
Discharge	29.0 (21.0, 44.0)	25.0 (19.0, 37.0)	.049
Creatinine level, median (interquartile range)			
Admitting	2.1 (1.3, 5.6)	1.6 (1.2, 2.9)	.023
Peak	2.5 (1.5, 6.7)	2.0 (1.4, 3.8)	.031
Discharge	2.3 (1.4, 4.8)	1.7 (1.1, 3.2)	.009
Troponin I, median (interquartile range)			
Admitting	0.09 (0.04, 0.20)	0.08 (0.03, 0.17)	.46
Peak	0.10 (0.05, 0.25)	0.10 (0.05, 0.29)	.80
BNP, median (interquartile range)			
Admitting	1326.5 (796.8, 3105.5)	840.5 (507.0, 1536.0)	<.001
Discharge	1169.5 (622.0, 2453.0)	522.0 (282.0, 1197.0)	.002
NTpro-BNP, median (interquartile range)			
Admitting	2766.7 (1402.0, 4426.0)	3331.8 (1904.5, 6205.0)	.44
Discharge	641.1 (641.1, 641.1)	2015.0 (167.0, 2611.2)	.77

Readmission			
	HF	non-HF	
30 days	26%	21%	P =0.1013
90 days	46%	35%	P = .001

Table 6 Blood pressure control over time among HF patients

	Composite outcome (mechanical ventilation, ICU admission, hospital length of stay ≥7 d, death at 30 d)		
	Yes (n = 195), n (%)	No (n = 107), n (%)	*P*
Systolic BP has been <120 within 1 h	9 (4.6)	2 (1.9)	.34[a]
Systolic BP has been <120 within 2 h	18 (9.2)	4 (3.7)	.08
Systolic BP has been <120 within 3 h	22 (11)	6 (5.6)	.10
Systolic BP has been <120 within 6 h	32 (16)	8 (7.5)	.029
Systolic BP has been <120 within 12 h	45 (23)	10 (9.4)	.003

Lowering the BP < 120 mm Hg was associated with increased adverse events within 6 hours vs those with higher BPs (7.5% vs 16%; P = .029)

Lowering the BP to 140 or 160 mm Hg had no relationship adverse outcomes, regardless of timing.

Table 7 Components of composite outcome

Variable	AHF, n (%)	Non-HF, n (%)	*P*
Mechanical ventilation	38 (13)	90 (10)	.21
ICU admission	152 (50)	308 (34)	<.0001
Length of stay ≥7 d	93 (31)	234 (26)	.11
In-hospital death	11 (3.6)	26 (2.9)	.52
Death at 30 d	3 (1.0)	12 (1.3)	.77[a]

[a] Fisher exact test used due to the small cell values.

Discussion

- Prior reports : initial presenting hypertension is a low-risk predictor of adverse outcomes

→ This study found that hypertensive HF patients have significant in-hospital mortality, commonly require ICU admission, frequently have prolonged hospitalization, and have a high likelihood of readmission.

- The difference may due to selecting for a population with greater illness severity.

Patient characteristics

- hypertensive HF patients were more often African American
- Despite 75% of our hypertensive HF population were African Americans, only 11% were taking hydralazine and 17% were on nitrates.
- A general trend of poor adoption of this medication combination in African Americans.

- significant proportion of hypertensive HF patients had an initially elevated creatinine level
- Other HF analyses have demonstrated that as little as 0.2-mg/dL creatinine increase is associated with increased mortality
- hypertensive HF patients were twice as likely to require dialysis than non-HF
- Renal preservation may be an appropriate target for future management strategies.

Resource use

- hypertensive patients with AHF require more resource use than many previously published HF analyses
- ICU admissions ↑ , hospital course >1 week ↑
- 7-fold higher use of BiPAP in AHF, but mechanical ventilation rates similar to non-HF

→ Noninvasive airway support can avoid mechanical ventilation in decompensated HF. But this database cannot evaluate its impact on the rate of mechanical ventilation

Blood pressure control and outcome

- As previous data suggest:

  rapid BP reduction for patients with acute pulmonary edema is associated with improved outcomes

- This study:

  early excessive declines of BP were associated with increases in the adverse composite outcome

Patients whose SBP was decreased <120 mm Hg within 6 hours had a rate of composite adverse events more than double that of those whose BP stayed >120 mm Hg

Limitations

- As a retrospective registry, causality cannot be determined
- This study defined the diagnosis of HF as pulmonary edema on chest x-ray or elevated natriuretic peptides in the absence of renal failure. → select for a cohort of patients with greater severity of illness than a clinically derived diagnosis

Conclusions

- Acute HF patients with severe hypertension were similar to the non-HF acute hypertension cohort in age and sex but more commonly had a history of hypertension, renal insufficiency, and African American heritage.

- Excess resource use was required for a substantial proportion of AHF patients, as demonstrated by high rates of ICU admission, prolonged hospitalizations, and frequent 90-day readmissions.

- accurate BP control is critical, as declines below 120 mm Hg were associated with increased adverse event rates.

- Future prospective trials are needed to determine the best therapy, timing, and BP target for patients presenting with hypertension and AHF

THANK YOU