Fever Is Associated with Delayed Ventilator Liberation in Acute Lung Injury

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Abstract

Background: Acute lung injury (ALI) is characterized by inflammation, leukocyte activation, neutrophil recruitment, endothelial dysfunction, and epithelial injury, which are all affected by fever. Fever is common in the intensive care unit, but the relationship between fever and outcomes in ALI has not yet been studied. We evaluated the association of temperature dysregulation with time to ventilator liberation, ventilator-free days, and in-hospital mortality.

Methods: Analysis of a prospective cohort study, which recruited consecutive patients with ALI from 13 intensive care units at four hospitals in Baltimore, Maryland. The relationship of fever and hypothermia with ventilator liberation was assessed with a Cox proportional hazards model. We evaluated the association of temperature during the first 3 days after ALI with ventilator-free days, using multivariable linear regression models, and the

association with mortality was evaluated by robust Poisson regression.

Measurements and Main Results: Of 450 patients, only 12% were normothermic during the first 3 days after ALI onset. During the first week post-ALI, each additional day of fever resulted in a 33% reduction in the likelihood of successful ventilator liberation (95% confidence interval [CI] for adjusted hazard ratio, 0.57 to 0.78; $P < 0.001$). Hypothermia was independently associated with decreased ventilator-free days (hypothermia during each of the first 3 d: reduction of 5.58 d, 95% CI: -9.04 to -2.13; $P = 0.002$) and increased mortality (hypothermia during each of the first 3 d: relative risk, 1.68; 95% CI, 1.06 to 2.66; $P = 0.03$).

Conclusions: Fever and hypothermia are associated with worse clinical outcomes in ALI, with fever being independently associated with delayed ventilator liberation.

Keywords: respiratory distress syndrome, adult; fever; hypothermia; body temperature regulation; respiration, artificial

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Fever is common among the critically ill, occurring in at least half of patients admitted to the intensive care unit (ICU) (1, 2). Among patients with acute lung injury (ALI), fever (defined as temperature > 38°C) may be even more frequent (3). Fever is associated with worse clinical outcomes (4, 5). In animal models of sepsis, fever increases neutrophil-dependent lung injury (6), augments oxygen toxicity (7), and decreases survival in antibiotic-treated pneumonia (6) and peritonitis (7). Elevated temperatures reduce endothelial barrier function for macromolecules and neutrophils both *in vitro* and *in vivo* (8, 9).

Prior research has focused on the effect of reducing fever in septic shock. In a randomized trial evaluating intravenous ibuprofen therapy, reducing temperature resulted in lower oxygen consumption and lactate production, but not a reduction in the incidence or duration of shock, or an increase in survival (10). A randomized trial evaluating external cooling in febrile patients with septic shock found that reducing body temperature toward normal

resulted in a decreased vasopressor requirement, a higher rate of shock reversal, and reduced mortality at 14 days but not at later time points (11). However, little is known regarding fever and clinical outcomes in patients with ALI.

ALI is characterized by a high inflammatory state, leukocyte activation, neutrophil recruitment, endothelial barrier dysfunction, and epithelial injury (12, 13), all of which are affected by fever (6–8, 14). We hypothesized that fever augments lung injury, resulting in worse outcomes in ALI. We sought to evaluate the frequency of temperature dysregulation and its association with clinical outcomes, with the primary aim of evaluating the association of fever with ventilator liberation, and secondary aims of evaluating the association of temperature dysregulation (both fever and hypothermia) with in-hospital mortality, and fever with ventilator-free days (the composite outcome of mortality and duration of mechanical ventilation) in the first 28 days after ALI.

Methods

Study Design

We performed a secondary analysis of a prospective cohort study, the Improving Care of Acute Lung Injury Patients (ICAP) Study (15), which enrolled consecutive mechanically ventilated patients with ALI (16) between October 2004 and October 2007 from 13 ICUs in 4 hospitals in Baltimore, Maryland. Key study exclusion criteria were (1) life expectancy less than 6 months, (2) preexisting cognitive impairment or communication/language barriers, (3) no fixed address, (4) transfer to a study site with preexisting ALI greater than 24 hours in duration, (5) more than 5 days of mechanical ventilation before ALI, (6) more than 4 days between ALI onset and enrollment, (7) prior lung resection, and (8) a physician order for no escalation of ICU care at the time of study eligibility. The ICAP study excluded neurologic specialty ICUs at participating hospitals to exclude primary neurologic disease or head trauma (17). The institutional review

Table 1. Patient characteristics*

Variable	All Patients (n = 450) [†]	Patients Liberated from Mechanical Ventilation (n = 288)	Patients Not Liberated from Mechanical Ventilation [‡] (n = 162)	P Value [§]
Age, yr	51 (41–62)	49 (40–60)	55 (46–66)	<0.001
Male	252 (56%)	164 (57%)	88 (54%)	0.62
White race	257 (57%)	173 (60%)	84 (53%)	0.09
ICU type, surgical/trauma	80 (18%)	60 (21%)	20 (12%)	0.03
Days in ICU before ALI onset	1 (0–2)	1 (0–2)	1 (0–3)	0.06
Sepsis as ALI risk factor	317 (70%)	192 (67%)	125 (77%)	0.02
Charlson Comorbidity Index score	2 (1–4)	2 (1–4)	3 (1–4)	0.001
APACHE II score	26 (20–33)	24 (19–29)	29 (22–35)	<0.001
Hypothermia in the first 3 d after ALI onset	209 (46%)	112 (39%)	97 (60%)	<0.001
Fever in the first 3 d after ALI onset	279 (62%)	197 (68%)	82 (51%)	<0.001
ICU days of observation	10 (6–16)	10 (6–16)	10 (6–18)	0.79
Mean daily SOFA score	7.1 (4.6–10.6)	5.6 (4.1–8.0)	10.7 (7.2–14.3)	<0.001
Mean daily tidal volume, ml/kg PBW	6.5 (6.0–7.8)	6.5 (6.0–7.8)	6.4 (5.6–7.7)	0.37
Cumulative net fluid balance, L	7.9 (1.3–18.9)	4.1 (–0.6 to 12.6)	17.0 (7.6–27.3)	<0.001
Percentage of ICU study days septic	100 (80–100)	97 (78–100)	100 (86–100)	0.11
Hypothermic days	2 (0–5)	1 (0–3)	3 (1–7)	<0.001
Febrile days	4 (1–8)	5 (1–9)	3 (1–7)	0.004

Definition of abbreviations: ALI = acute lung injury; APACHE = Acute Physiology and Chronic Health Evaluation; ICU = intensive care unit; PBW = predicted body weight; SOFA = Sequential Organ Failure Assessment.

*Reported as n (%) or median (interquartile range).

[†]Excludes 8 patients who were missing any temperature measurements and 62 patients who either died (n = 53) or were liberated from ventilation (n = 9) within 3 days of ALI onset.

[‡]Includes date of extubation to comfort care (n = 6) or transfer to long-term acute care while receiving mechanical ventilation (n = 12).

[§]Comparing patients who were liberated from ventilation with those who died or were discharged while receiving mechanical ventilation, using the Fisher exact test, Wilcoxon rank-sum test, analysis of variance, or chi-square test, as appropriate.

^{||}Of 187 nonwhite patients, 179 (95.7%) were African American.

^{||}Hypothermia is defined as any site-adjusted temperature less than 36.0°C, and hyperthermia as any site-adjusted temperature equal to or greater than 38.0°C on a day without hypothermia.

boards of the University of Maryland (HP 40606) and Johns Hopkins University (NA 00041630) approved this research.

Outcome Measurement

The primary outcome was time to successful ventilator liberation, defined as the number of days from ALI onset to extubation (for reasons other than terminal weaning) resulting in at least 48 continuous hours alive and free of mechanical ventilation. Our secondary outcomes were the number of days alive and liberated from the ventilator in the first 28 days after ALI onset ("ventilator-free days") (18) and in-hospital mortality.

Exposure Measurement

After ALI onset, temperature was abstracted daily from medical records based on available recordings at 6:00 A.M. and 6:00 P.M. (± 60 min) and daily maximum and minimum values. Temperatures were measured for clinical purposes from tympanic, axillary, oral, rectal, and bladder sites. Each measurement was adjusted by site, using standardized equations (19–21). We defined hypothermia as a daily, site-adjusted minimum temperature less than 36.0°C (4), and fever as a daily, site-adjusted maximum temperature of at least 38.0°C (22, 23). Extreme hyperthermia was defined as a site-adjusted temperature greater than 39.4°C . Because of the strong

association of hypothermia with increased mortality (4, 24) and our focus on hyperthermia, we classified patients both hypo- and hyperthermic in the same 24-hour period as hypothermic for that day.

Our primary exposure variables were the number of hypothermic and febrile days. In our primary analysis of the time to successful ventilator liberation, these days were counted for the entire duration of the patient's ICU stay. Fever is not a contraindication to extubation per the protocols of all study sites. In our secondary analyses of mortality and ventilator-free days, we evaluated the association of hypothermia and fever during only the first 3 days after ALI onset, based on animal models (6, 7), reflecting the likely time window for biological effect modification.

Covariate Measurement

We evaluated potential confounders in this analysis: patient demographics, ICU type (medical or surgical/trauma), duration of ICU stay before ALI onset, Charlson Comorbidity Index score (25), and Acute Physiology and Chronic Health Evaluation [APACHE] II score within the first 24 hours after ICU admission (26). We evaluated the following time-varying variables on a daily basis after ALI onset: Sequential Organ Failure Assessment (SOFA) score (27), tidal volume at 6:00 P.M. (in milliliters per kilogram predicted body

weight), net fluid balance, and sepsis status. Sepsis was defined consistent with consensus criteria: documented infection or suspected infection (as evidenced by use of antibiotics for other than a prophylactic indication), accompanied by two or more systemic inflammatory response syndrome criteria (28). These time-varying covariates were evaluated as a running mean (SOFA score, tidal volume), running cumulative total (net fluid balance), and running proportion of study days (sepsis status). All variables and modeling approaches were selected *a priori* on the basis of their expected relationship with the outcomes.

Statistical Analysis

All days of fever were assessed. To account for varying lengths of time receiving mechanical ventilation and the potential for the resultant immortal time bias (29), we used time-varying Cox proportional hazards regression analysis to assess time to ventilator liberation for Day 4 onward. We assumed that ventilator liberation and mortality occurred at the end of each 24-hour observation period. The Breslow method was used for tied observations (30). We excluded person-days with no recorded temperature measurement ($n = 126$, 1.5% of all observations) unless the outcome occurred during this period, in which case we carried forward the preceding day's exposure data. We assessed model

Figure 1. Temperature dysregulation after acute lung injury onset. Shown here are the number of eligible patients (i.e., alive, mechanically ventilated, with at least one daily temperature measurement) by day in the intensive care unit (ICU) after acute lung injury (ALI) onset. On each day, 13–31% of patients experienced at least one hypothermic episode ($<36.0^{\circ}\text{C}$), 36–49% of patients experienced at least one febrile episode ($\geq 38.0^{\circ}\text{C}$) without hypothermia, and 28–47% of patients remained normothermic throughout the 24-hour period. The proportion of hypothermic patients declined with time (Spearman's $\rho = -0.49$; $P < 0.001$), and the proportion of febrile patients rose correspondingly (Spearman's $\rho = 0.41$; $P < 0.001$), whereas the proportion of normothermic patients did not vary significantly with time (Spearman's $\rho = 0.14$; $P = 0.17$).

specification using the link test, multicollinearity using uncentered variance inflation factors, and the proportional hazards assumption using rank-scaled Schoenfeld residuals.

We evaluated bivariable associations using Spearman's rho (ρ) for correlations, the Wilcoxon rank-sum test for continuous variables across categories, and Fisher's exact test for categorical variables. We assessed the association of fever on Days 1–3 with the number of ventilator-free days out of the subsequent 28 days, using analysis of variance and simple linear regression to evaluate unadjusted associations, and multivariable linear regression for adjusted associations. We assessed regression models with the link test and plotting residuals against predicted values, influence using DFBETA statistics and Cook's distance, and multicollinearity

using variance inflation factors (31). Because mortality was a common outcome (rendering odds ratios difficult to interpret), we used robust Poisson regression to estimate the relative risk (RR) of exposures and confounders with mortality (32).

We defined statistical significance as a two-sided P value less than 0.05. All analyses were conducted using STATA 11.0 (Stata Corporation, College Station, TX).

Results

Of 520 participants in the prospective cohort study, 70 patients were excluded: 8 (1.5%) because of no temperature measurements before death or ICU discharge, 53 (10.2%) because of death within the first 3 days, and 9 (1.7%) because of ventilation liberation in the first 3 days

after ALI onset. Patient characteristics are shown in Table 1. At ICU admission, 8 (1.5%) patients carried any central nervous system diagnosis.

Temperature abnormalities were common in the first 3 days after ALI onset (Figure 1 and Table 1). During these first 3 days, 65% (293 of 450) of patients had one or more febrile days, and 80% (361 of 450) were febrile at any point during their ICU stay. At least 39% of patients were febrile on any given day of observation. During the first 3 days after ALI onset, 46% (209 of 450) of patients had at least one hypothermic day; these decreased over time. Only 12% of patients remained normothermic during their first 3 days after ALI onset. The proportion of patient days with sepsis receiving antibiotics was similar across temperatures. Among febrile days, 85% were septic and receiving antibiotics;

Table 2. Time-varying predictors of time to liberation from mechanical ventilation

Variable	Adjusted Hazard Ratio of Successful Ventilator Liberation*			
	Days 4–7		Days 8–21	
	HR (95% CI)	P Value [†]	HR (95% CI)	P Value [†]
Age, per 5 yr	0.92 (0.85, 0.99)	0.03	0.95 (0.90, 1.00)	0.07
Sex, male	1.58 (0.94, 2.63)	0.08	1.67 (1.19, 2.33)	0.003
Race, white [‡]	0.87 (0.53, 1.43)	0.59	0.91 (0.64, 1.27)	0.57
ICU type, surgical/trauma	1.10 (0.55, 2.19)	0.79	1.24 (0.81, 1.89)	0.32
Time in ICU before ALI onset, per day	1.00 (0.88, 1.13)	0.94	0.91 (0.82, 0.99)	0.04
ALI risk factor, pneumonia/sepsis	1.12 (0.64, 1.98)	0.69	1.07 (0.73, 1.59)	0.72
Charlson Comorbidity Index, per point	0.94 (0.85, 1.04)	0.24	1.01 (0.94, 1.08)	0.81
APACHE II score, per 5 points	1.00 (0.84, 1.20)	0.97	0.93 (0.83, 1.05)	0.24
Hypothermic days, per day [§]	0.80 (0.66, 0.98)	0.03	0.93 (0.86, 1.01)	0.11
Febrile days, per day [§]	0.67 (0.57, 0.78)	<0.001	0.92 (0.87, 0.97)	0.001
Mean SOFA score				
<5.0	1.0 (ref)		1.0 (ref)	
5–9.99	0.61 (0.35, 1.06)	0.08	0.60 (0.42, 0.87)	0.007
≥10	0.33 (0.14, 0.77)	0.01	0.40 (0.22, 0.74)	0.004
Mean tidal volume, ml/kg IBW				
≤6.0	1.0 (ref)		1.0 (ref)	
6.01–7.99	1.35 (0.76, 2.37)	0.30	1.14 (0.78, 1.67)	0.50
≥8.0	1.30 (0.67, 2.52)	0.44	1.87 (1.23, 2.84)	0.003
Cumulative fluid balance, L				
<2.0	1.0 (ref)		1.0 (ref)	
2.0–9.99	0.61 (0.37, 1.01)	0.06	0.63 (0.43, 0.93)	0.02
≥10.0	0.37 (0.17, 0.82)	0.01	0.40 (0.27, 0.61)	<0.001
Proportion of days septic				
0.81–1.0	1.0 (ref)		1.0 (ref)	
≤0.8	1.21 (0.68, 2.16)	0.51	1.24 (0.83, 1.86)	0.30

Definition of abbreviations: ALI = acute lung injury; APACHE = Acute Physiology and Chronic Health Evaluation; CI = confidence interval; HR = hazard ratio; IBW = ideal body weight; ICU = intensive care unit; SOFA = Sequential Organ Failure Assessment.

*Defined as liberation from mechanical ventilation for a minimum of 48 consecutive hours after extubation. HR < 1 signifies reduced HR of successful liberation.

[†]Analysis performed by time-varying Cox proportional hazards regression.

[‡]Of 187 nonwhite patients, 179 (95.7%) were African American.

[§]Hypothermia is defined as any site-adjusted temperature less than 36.0°C, and hyperthermia as any site-adjusted temperature equal to or greater than 38.0°C on a day without hypothermia.

^{||}Measured in running/cumulative manner from the date of ALI onset to the date of measurement.

for normothermic days, this proportion was 81%; and on hypothermic days, 83%. The proportion of patients receiving one or more doses of steroids was similar among afebrile and ever-febrile patients (66 vs. 72%; $P = 0.248$).

The number of ICU days with fever was strongly associated with delayed ventilator liberation (Table 2). Each preceding febrile day reduced the likelihood of ventilator liberation on Days 4–7 by 33% (hazard ratio [HR], 0.67; 95% confidence interval [CI], 0.57 to 0.78; $P < 0.001$). Overall, the hazard ratio was not proportional over time ($P < 0.001$ for linearity of scaled Schoenfeld residuals) but was within the strata evaluated ($P = 0.62$ for Days 4–7, $P = 0.68$ for Days 8–21). The association was weaker during Weeks 2–3 after ALI onset (HR, 0.92 per febrile day; 95% CI, 0.87 to 0.97; $P = 0.001$), and not detectable beyond 21 days (HR, 1.04; 95% CI, 0.98 to 1.10; $P = 0.18$). Cumulative mean SOFA score and cumulative net fluid balance were also consistent, significant predictors of delayed ventilator liberation, as were older age and number of hypothermic days.

At 3 days post-ALI, the strongest independent predictors of increased ventilator-free days were lower APACHE II scores and fewer hypothermic days (Table 3). A dose-response relationship existed between the number of hypothermic days and ventilator-free days. The mean (SE) number of ventilator-free days was 11.5 (0.6) for patients with no hypothermic episodes, 9.6 (1.0) with one hypothermic day, 7.0 (1.1) with two hypothermic days, and 5.6 (1.2) with three hypothermic days. After adjustment for covariates, patients with one or more days of extreme hyperthermia after ALI onset had significantly fewer ventilator-free days (–2.50 d; 95% CI, –4.72 to –0.28; $P = 0.03$) as did patients febrile for all 3 days (–2.56 d; 95% CI, –5.41 to 0.28; $P = 0.08$), although not meeting the traditional definition of significance. A post-hoc analysis of the association between hyperthermia during the first 7 days and oxygenation index using a random-effects linear regression model was not significant (log coefficient for hyperthermia, 0.030; SE, ± 0.0034 ; $P = 0.37$).

Of the 450 patients evaluated, 288 (64%) were liberated from mechanical ventilation whereas 162 (36%) either died in hospital or were discharged to long-term care without being liberated ($n = 12$). In

unadjusted analysis, any hypothermia during the first 3 days after ALI onset was associated with increased mortality or ventilator nonliberation (112 of 288 [39%] vs. 97 of 162 [60%]; $P < 0.001$). The number of total hypothermic days was higher in patients who died (median, 1 [interquartile range, IQR], 0 to 3; vs. median, 3 [IQR, 1 to 7]; $P < 0.001$). In unadjusted analysis, fever was associated with reduced mortality (197 of 288 [68%] vs. 82 of 162 [51%]; $P < 0.001$); more febrile days occurred among survivors (median, 5 [IQR, 1 to 9]) versus those who died (median, 3 [IQR, 1 to 7]; $P = 0.004$). Age, comorbidity, severity of illness, positive fluid balance, sepsis as a primary ALI risk factor, and proportion of ICU days with sepsis were associated with increased mortality in the unadjusted model. In adjusted analysis (Table 4), hypothermia continued to be associated with increased mortality. Compared with those with no days of hypothermia, one hypothermic day

was associated with an RR of death of 1.29 (95% CI, 0.87 to 1.92; $P = 0.20$), two hypothermic days with an RR of 1.69 (95% CI, 1.13 to 2.52; $P = 0.01$), and 3 days with an RR of 1.68 (95% CI, 1.06–2.66; $P = 0.03$). Febrile days were not associated with increased mortality in the multivariable model. Age and ICU days before ALI onset were also risk factors for death in the adjusted analysis.

Discussion

We found that fever and hypothermia were common among patients with ALI, accounting for a substantial majority of ICU days. During the first week post-ALI, each additional febrile day was associated with a 33% reduction in successful ventilator liberation, with this effect attenuated in subsequent weeks. At 3 days post-ALI, both a single day with either hypothermia or extreme hyperthermia was associated with

Table 3. Predictors of 28-day ventilator-free days at 3 days after acute lung injury

Variable	Absolute Change in Number of Ventilator-Free Days			
	Crude Analysis		Multivariable Analysis	
	HR (95% CI)	P Value*	HR (95% CI)	P Value†
Age, per 5 yr	–0.27 (–0.56, 0.01)	0.06	–0.32 (–0.61, –0.03)	0.03
Sex, male	0.62 (–1.17, 2.41)	0.50	0.57 (–1.15, 2.29)	0.52
Race, white‡	0.75 (–1.04, 2.55)	0.41	0.62 (–1.16, 2.39)	0.50
ICU type, surgical/ trauma	2.95 (0.65, 5.26)	0.01	1.43 (–0.94, 3.79)	0.24
Time in ICU before ALI onset, per day	–0.52 (–0.94, –0.10)	0.02	–0.71 (–1.13, –0.30)	0.001
ALI risk factor, pneumonia/sepsis	–1.74 (–3.69, 0.20)	0.08	0.13 (–1.86, 2.11)	0.90
Charlson Comorbidity Index, per point	–0.38 (–0.74, –0.03)	0.03	0.02 (–0.34, 0.39)	0.89
APACHE II score, per 5 points	–1.47 (–1.97, –0.96)	<0.001	–1.32 (–1.87, –0.78)	<0.001
Hypothermic days§				
0	0.0 (ref)		0.0 (ref)	
1	–2.50 (–3.00, –2.00)	<0.001	–2.60 (–5.03, –0.17)	0.04
2	–2.28 (–2.87, –1.68)	<0.001	–4.65 (–7.55, –1.76)	0.002
3	–4.09 (–4.75, –3.42)	<0.001	–5.58 (–9.04, –2.13)	0.002
Febrile days§				
0	0.0 (ref)		0.0 (ref)	
1	1.51 (0.94, 2.07)	<0.001	0.72 (–1.72, 3.17)	0.56
2	1.64 (1.06, 2.23)	<0.001	–1.59 (–4.35, 1.17)	0.26
3	1.42 (0.90, 1.93)	<0.001	–2.56 (–5.41, 0.28)	0.08

Definition of abbreviations: ALI = acute lung injury; APACHE = Acute Physiology and Chronic Health Evaluation; CI = confidence interval; HR = hazard ratio; ICU = intensive care unit.

*Unadjusted comparisons performed by analysis of variance and simple linear regression.

†Adjusted analysis performed by multivariable linear regression.

‡Of 187 nonwhite patients, 179 (95.7%) were African American.

§Hypothermia is defined as any site-adjusted temperature less than 36.0°C, and hyperthermia as any site-adjusted temperature equal to or greater than 38.0°C on a day without hypothermia.

Table 4. Multivariable predictors of in-hospital mortality at 3 days after acute lung injury

Variable	Relative Risk of Death (95% CI)*	P Value*
Age, per 5 yr	1.07 (1.03, 1.12)	0.001
Male	1.00 (0.78, 1.29)	0.97
White race†	0.87 (0.67, 1.13)	0.29
ICU type, surgical/trauma	0.80 (0.52, 1.24)	0.32
Days in ICU before ALI onset, per day	1.09 (1.04, 1.15)	0.001
Sepsis as ALI risk factor	1.21 (0.88, 1.65)	0.24
Charlson Comorbidity Index, per point	0.99 (0.94, 1.04)	0.65
APACHE II score, per 5 points	1.17 (1.08, 1.26)	<0.001
Hypothermic days‡		
0	1.0 (ref)	
1	1.29 (0.87, 1.92)	0.20
2	1.69 (1.13, 2.52)	0.01
3	1.68 (1.06, 2.66)	0.03
Febrile days		
0	1.0 (ref)	
1	0.81 (0.58, 1.13)	0.22
2	0.97 (0.62, 1.51)	0.88
3	0.81 (0.48, 1.37)	0.43

Definition of abbreviations: ALI = acute lung injury; APACHE = Acute Physiology and Chronic Health Evaluation; CI = confidence interval; ICU = intensive care unit.

*Estimated by Poisson regression with robust variance estimator.

†Of 187 nonwhite patients, 179 (95.7%) were African American.

‡Hypothermia is defined as any site-adjusted temperature less than 36.0°C, and hyperthermia as any site-adjusted temperature equal to or greater than 38.0°C on a day without hypothermia.

decreased ventilator-free days. The number of hypothermic days was a risk for in-hospital mortality.

Only 17% of the patients with ALI in this cohort did not develop fever during their ICU stay. Fever may worsen lung injury by increasing neutrophil extravasation and vascular permeability via effects on the endothelium (8, 9) and increasing epithelial injury (6, 14, 33). Because ALI is often neutrophil-dependent (34), fever may result in worsened pulmonary outcomes, including delayed liberation from mechanical ventilation. Although the biological persistence of fever suggests that its benefits usually outweigh its harm in the natural setting (35), in the modern ICU setting this may not be the case. In animal models of sepsis not receiving appropriate antimicrobial therapy, the febrile response was associated with improved survival (36, 37). However, in the presence of antibiotics and other exogenous therapeutic interventions, the harms of the febrile response may outweigh its benefits. In antibiotic-treated *Klebsiella pneumoniae* pneumonia, normothermic mice had increased survival and less lung injury compared with mice with febrile-range hyperthermia (6, 38). Thus, fever

control may be an important target for intervention in ALI.

In both septic (4) and nonseptic patients (5), observational studies have associated fever with increased mortality. Cooling patients in the ICU provides physiologic benefit, reducing metabolic requirements (38, 39). In a randomized clinical trial, Bernard and colleagues (10) evaluated the effect of intravenous ibuprofen on 455 septic patients. Patients receiving ibuprofen had lower levels of prostacyclin and thromboxane, and reduced oxygen consumption and lactate production, although clinical outcomes were not impacted. Schortgen and colleagues randomized 200 patients with septic shock to external cooling versus no external cooling. Patients receiving external cooling were more likely to reduce their vasopressor dose by 50% or have shock reversal, and also had a reduction in short-term (14-d) mortality, although ICU and hospital mortality did not differ (11). Neither trial demonstrated worse outcomes with temperature control interventions, in contrast to observational data associating antipyretic use with increased mortality (5).

We found that in patients with ALI, hypothermia is associated with increased

mortality, decreased ventilator-free days, and delayed ventilator liberation. Although fever is a complex physiologic response (40), hypothermia is likely to result from dysregulation of the thermoregulatory system and is more likely to have harmful effects in a wide range of clinical states (41, 42). Early correction of anesthesia-induced hypothermia in septic animal models improves outcomes (43). In humans, observational studies have shown that hypothermia independently predicts hospital mortality in the setting of sepsis (44), injury (45), and cardiac surgery (46). In the ICU, hypothermic patients with sepsis have higher levels of tumor necrosis factor- α and IL-6 (24) as well as a higher incidence of multiorgan dysfunction (47). Mortality is markedly increased in this group compared with patients mounting fevers (1, 4, 24, 48).

In evaluating a large, prospective cohort of patients with ALI and using time-dependent regression modeling, this study seeks to improve our understanding of the association of fever duration and outcomes, consistent with a call to action (49). Because each day on the ventilator may provide an additional day to be febrile, the “longevity” associated with each febrile day may introduce the immortal time bias (50). Treating fever as a time-dependent variable controls for this potential bias (29). In addition, we adjusted for known confounders, such as age, severity of illness, comorbidities, ALI risk factor, and cumulative net fluid balance. As an observational study, however, several potential limitations should be considered. Although we found an association between fever and duration of mechanical ventilation, a causal link cannot be established. Sepsis is a common cause of both fever and ALI (51). The proportion of antibiotic-treated days was similar across temperature categories, making it unlikely that our findings were due to imbalances in antibiotic use by exposure group. Source control, timing, and appropriateness of antibiotics were not assessed and, although unlikely, the possibility of differential treatment and confounding exists. Prior data evaluating the oxygenation index has focused on its predictive value for mortality and its impact on acute lung injury severity classification (52–56). We found no association between temperature and oxygenation index in our post-hoc analysis. Our findings regarding ventilator

liberation, and its association with temperature, may be independent of any association with oxygenation index. Antipyretic use was not assessed in this study. Although ibuprofen has not been shown to affect mortality (10) and acetaminophen is an ineffective antipyretic (57), the possibility exists that these medications may modify the pulmonary response to fever. Because our study focused on the pulmonary effects of temperature dysregulation, these data may not be extrapolatable to other organ systems or to other patient populations.

Given our findings in patients with ALI that fever is associated with delayed ventilator liberation and hypothermia with increased mortality, physicians may wish to consider clinical implementation of temperature control in the ICU. Two

randomized clinical trials have shown physiologic improvement with fever control (10, 11), with no harm evident. Given this potential benefit, on top of a large body of data in animal models, aggressive fever control should be considered in the supportive care of patients with ALI. Similarly, as hypothermia is associated with high mortality (1, 4, 24, 48) (as well as animal data), studies evaluating patient warming or other means of thermoregulation are needed in this population.

Conclusions

Both fever and hypothermia are common in patients with ALI, and are associated with delayed ventilator liberation. Each day of fever during the first week after ALI onset

is associated with a 33% increase in time to ventilator liberation, and patients with persistent fever may have reduced ventilator-free days. The duration of hypothermia is associated with increased mortality, decreased ventilator-free days, and delayed ventilator liberation. ■

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