Fever Burden in Patients With Subarachnoid Hemorrhage and the Increased Use of Antibiotics

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Background: Fever occurs in the majority of subarachnoid hemorrhage (SAH) patients. Nearly 50% of SAH patients have noninfectious fevers. Data are lacking describing the effects of fever burden in the SAH patient population. *Methods:* This was a single-center, retrospective observational cohort study in patients more or equal to 18 years of age with a diagnosis of nontraumatic SAH admitted to an ICU between January 1, 2010 and September 1, 2015. Exclusion criteria were SAH secondary to trauma or admission for more than 48 hours. Temperature measurements, demographic data, and other pertinent information were collected from Day 0 to Day 13. Daily fever burden was calculated for each patient by calculating an area under the curve. *Results:* A total of 194 subjects were included. The mean study period maximum temperature (Tmax) for all 194 patients was 40.8 ± 0.83°C. The mean overall fever burden for all 194 patients was 89.2 ± 99.59°C h more than 37°C. The overall fever burden peaked on day 5 and declined thereafter. Fever burden, Tmax, and length of stay in the hospital were all significantly associated with receipt of antibiotics. Only Tmax was associated with poor outcome. The 31 patients who had fever but no identified cause of infection received 1000 doses of antibiotics or 32.25 doses per patient. *Conclusion:* Fever is common in SAH patients and is associated with antibiotic use, infection, vasospasm, and poor outcome. Some SAH patients may receive antibiotics unnecessarily for noninfectious fever. Clinicians should consider using site-specific parameters related to infection rather than systemic symptoms such as fever to evaluate infection in SAH patients.
Key Words: Fever—fever burden—subarachnoid hemorrhage—antibiotics

Introduction

Fever is the most common medical complication after subarachnoid hemorrhage (SAH) and is estimated to occur in approximately 72% of SAH patients.[1,2] Fever likely occurs following SAH due to hypothalamic or brainstem irritation caused by an inflammatory response to the presence of subarachnoid blood.[3] Several patient characteristics have been identified as predictors of fever in SAH, including presence of intraventricular hemorrhage, poor Hunt-Hess grade, SAH sum score, large aneurysm size, and loss of consciousness at ictus.[3] Studies have suggested fever (defined as daily

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maximum temperature or Tmax) after SAH leads to worse outcomes, increased length of hospital stay, and a greater degree of disability at 3-month follow-up.[3,4]

One practical difficulty in treating fever in SAH patients is determining if the origin is infectious or noninfectious. Fever in a broad neurocritical care population is only attributed to infection in approximately 50% of patients, suggesting a large proportion of fevers are due to noninfectious or central causes.[5,6] Differentiating between infectious and noninfectious fevers in SAH patients can be difficult, as systemic inflammation and leukocytosis is often similarly prevalent in both groups,[6,7] Hocker et al studied the differentiation of noninfectious and infectious fevers in a broad neurocritical care population and found noninfectious fever was associated with onset of fever within the first 72 hours of admission, persistent fever, intraventricular hemorrhage, or tumor. Infectious fever was associated with higher percentage of neutrophils, positive cultures, and infiltrates on chest radiography.[6]

The contemporary emphasis on early intervention with appropriate antibiotics for patients with presumed sepsis may lead to a low threshold for clinicians to initiate broad spectrum antimicrobials at the onset of fever.[8] Empirical antimicrobials are often continued unnecessarily in cases of central fever. This prolonged use of antibiotics in the absence of infection can lead to microbial resistance, super infections such as *Clostridium difficile*, increased cost, and unnecessary lab tests.

While maximum temperature (Tmax) has been evaluated in neurocritical care, it is also apparent that persistent hyperthermia, even at nonfever thresholds, is deleterious in neurocritical care patients.[3,4] One method of depicting persistent hyperthermia is fever burden, or time and extent of temperature elevation.[4] Few data are available describing the association between fever burden and use of antibiotics. The aims of the current study are to (1) determine if fever burden after SAH is associated with antibiotic use, (2) identify patient characteristics which increase antibiotic use, (3) describe the frequency of inappropriate antibiotic use in central fever, and (4) evaluate the association of fever, fever burden, and outcomes.

Materials and Methods

This was a single-center, retrospective observational cohort study in patients admitted to an adult intensive care unit (ICU) following aneurysmal SAH. The study protocol was approved by the institutions Medical Institutional Review Board. Patients with a diagnosis of spontaneous, nontraumatic SAH at the University of Kentucky Albert B Chandler Medical Center between January 1, 2010 and September 1, 2015 were screened for inclusion. Patients were identified from the Center for Clinical and Translational Enterprise Data Warehouse utilizing (ICD9) diagnosis code 430 (SAH). To meet inclusion criteria, patients had to be more than and equal to 18 years, admitted to an adult ICU, have a primary or admitting diagnosis of aneurysmal or nontraumatic SAH, and have at least 10 temperature measurements recorded. Patients were excluded if the SAH was secondary to trauma or arteriovenous malformation rupture or if admitted for less than 48 hours.

Demographic data and information about the severity of SAH were collected for each subject. Poor Hunt and Hess score and poor Fisher score were both defined as any score more than and equal to 3. Hourly temperature measurements were collected from Day 0 (the date of admission to ICU or date of SAH) through Day 13. A 14-day study period was chosen as this is the typical window for cerebral vasospasm. Daily measures for maximum temperature (Tmax), mean temperature, and fever burden were determined for each patient. Fever burden was calculated as area under the curve (AUC) to capture both time and extent of temperature more than and equal to 37°C. AUC was calculated for each patient using formulas derived from the trapezoidal method (Fig 1.). Fever was defined as a temperature more than 38.3°C.

The Center for Disease Control definitions for urinary tract infections, meningitis, pneumonia, and bacteremia were utilized to evaluate the presence of infection.[9] A physician independent from the medical team retrospectively reviewed the chest radiographs for all patients who received antibiotics and graded pneumonia risk as no pneumonia, possible, or probable pneumonia. Head CTs were also reviewed for each patient to accurately describe the Fisher score and identify the presence of intraventricular hemorrhage or cerebral edema. These additional reviews were performed to maintain consistency in diagnosing infection across the study periods, thus improving the validity of the study methods.

Continuous variables were tested for distribution by histogram visualization and with the Shapiro-Wilk test. Nonnormally distributed continuous variables are presented as median (IQR). Temperature, as a nonparametric variable, is presented as both median (IQR) and mean ± (SD) for better

Both T_1 and T_2 <37◦C: No AUC calculation, value is zero

Both T_1 and T_2 ≥37◦C:

$$\frac{1}{2}(x_2 - x_1)\{(T_1 - 37) + (T_2 - 38.3)\}$$

$T_1 \leq 37$◦C and $T_2 > 37$◦C:

$$\frac{1}{2}(T_2 - 37)\left\{(x_2 - x_1)(37 - T_1)\left(\frac{x_2 - x_1}{T_2 - T_1}\right)\right\}$$

$T_1 > 37$◦C and $T_2 \leq 37$◦C:

$$\frac{1}{2}(T_1 - 37)\left\{(x_2 - x_1)(37 - T_2)\left(\frac{x_2 - x_1}{T_2 - T_1}\right)\right\}$$

Figure 1. *Area under the curve (fever burden) equations.*

visualization. Continuous variables were analyzed using the Wilcoxon Rank-sum test in the bivariate analysis. Categorical variables are presented as frequencies and proportions and analyzed using the Pearson's chi-square or Fisher's Exact test as appropriate. Demographic variables, fever variables, and the primary outcomes (antibiotic use) were analyzed as appropriate per variable description.

Multivariate logistic regression models were created to assess the effects of independent variables on our primary outcome, receipt of antibiotics, and on our secondary outcome, neurologic outcome (via the modified Rankin Score [mRS]). All variables that displayed statistical significance in the bivariate analysis (< 0.05) were included for consideration into the final model. Two models were constructed to visualize the effect sizes of temperature AUC and Tmax on receipt of antibiotics and a poor neurologic outcome.

Multivariate linear regression was used to detect characteristics associated with fever burden. Known characteristics associated with fever in this patient population were included in the model such as infection, vasospasm, type of intervention, Hunt and Hess score, Fisher score, loss of consciousness, and seizure upon presentation. The models were tested for assumptions of logistic and linear regression as appropriate. Multicollinearity was assessed using variance inflation factor; normality of errors was assessed with the IQR test. We assessed model fit with the Hosmer-Lemeshow and likelihood ratio tests. Heteroscedasticity of residuals was assessed with the Breusch-Pagan/Cook-Weisberg test, and standardized robust errors were used to adjust for heteroscedasticity in the models as appropriate. All other assumptions were met. We removed independent variables that were not statistically significant and did not improve model fit comparisons according to the likelihood ratio test from the final models. Statistical analyses were done using Stata (version 14.2, Stata Corp, College Station, TX).

Results

Of the 403 patients initially identified, a total of 194 patients were included (Fig 2). Table 1 describes the baseline characteristics and bivariate analysis outcomes, stratified by group (received antibiotics or not). Of the 194 total patients, 42% (81/194) patients did not receive antibiotics during the study period, while 58% (113/194) did receive antibiotics. Patients included were primarily white (88%) and female (64%) with a median age of 54 (IQR 45-61). The median length of stay was 12 (IQR 8-22) days with a median ICU length of stay of 10 (IQR 5-16) days. The majority of patients were discharged alive 73% (Table 1). Twelve percent of patients died at more than 48 hours and 15% were discharged to a skilled nursing or long-

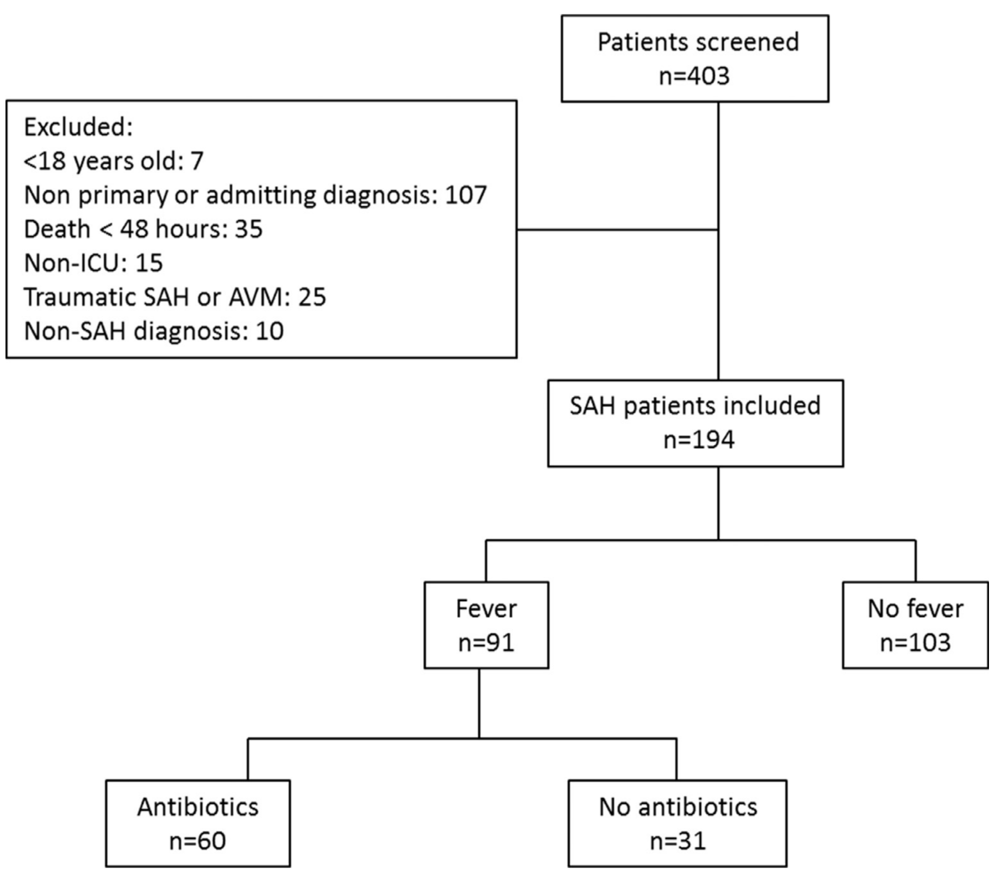

Figure 2. *Patient inclusion and categorization by presence of fever and receipt of antibiotics.*

Table 1. *Baseline characteristics and outcomes*

Variable	Did not receive antibiotics (N = 81)	Received antibiotics (N = 113)	Total (N = 194)	*P* value
Gender				
Female	49/81 (60%)	75/113(66%)	124/194 (64%)	.401
Male	32/81 (40%)	38/113 (34%)	70/194 (36%)	
Race				
White	70/81 (86%)	100/113 (89%)	170/194 (88%)	.487
Black	9/81 (11%)	8/113 (7%)	17/ 194 (9%)	
Other	2/81 (3%)	5/113 (4%)	7/194 (3%)	
Age median (IQR)	53 (45-63)	54 (46-61)	54 (45-61)	.934
Fever present	14/93 (18%)	79/93 (70%)	93/194 (48%)	<.0001
Daily Tmax median (IQR)	37.61 (37.3-38.2)	38.8 (38.2-39.2)	38.3 (37.6-39)	<.00001
Total AUC >37 median (IQR)	7.17 (1.41-29.27)	120.19 (39.88- 206.94)	46.83 (6.82-154.78)	<.00001
Total AUC >37 mean (SD)	26.52 (42.22)	134.07 (104.48)	89.17 (99.59)	<.00001
Median temperature	36.8 (36.72-37)	37.4 (36.95- 37.68)	37.02 (36.78-37.51)	<.00001
Mean (SD) temperature	36.89 (0.30)	37.36 (0.44)	37.16 (0.45)	<.00001
Anti-pyretic use	72/81 (89%)	105/113 (93%)	177/194 (91%)	.327
Hunt and Hess median (IQR)	2 (2-3)	3 (2-4)	2 (2-3)	<.0001
HH 1-2	60/81 (74%)	48/113(42%)	108/194 (56%)	
HH 3-4	21/81 (26%)	65/113(58%)	86/194 (44%)	
Fisher median (IQR)	3 (2-3)	3(3-4)	3 (2-3)	.002
Fisher (1-2) (1)	33/81 (42%)	21/113 (19%)	54/194 (27.8%)	
Fisher (3-4) (0)	47/81 (58%)	92/113 (81 %)	139/194 (71.2%)	
Vasospasm present	18/81 (25%)	52/113 (46%)	70/194 (36%)	.001
Intraventricular Hemorrhage Present	28/81 (35%)	54/113 (48%)	82/ 194 (42%)	.077
Intraparenchymal Hemorrhage Present	14/81 (17%)	37/113 (33%)	51/ 194 (26%)	.016
Cerebral Edema Present	29/81 (36%)	59/113 (52%)	88/194 (45%)	.024
Seizure at SAH onset	4/81 (5%)	12/113 (11%)	16/194 (8%)	.156
Loss of consciousness at SAH onset	18/81 (22%))	43/113 (38%)	61/194(31%)	.019
Aneurysm Coiled	35/81 (43%)	70/113 (62%)	105/194 (54%)	.023
mRS* median (IQR)	2 (1-5)	4 (3-5)	4 (1-5)	.002
mRS 0-3	42/74 (57%)	37/110 (34%)	79/194 (43%)	
mRS 4-6	32/74 (43%)	73/110 (66%)	105/194 (57%)	
LOS median (IQR)	9 (5-13)	18 (10-26)	12 (8-22)	<.00001
ICU LOS median (IQR)	8 (4-11)	14 (8-20)	10 (5-16)	<.00001
Discharge Status				
Alive, Routine	66/81 (81%)	75/113 (66%)	141/194 (73%)	.007
Long Term Care/SNF	12/81 (15%)	17/113 (15%)	29/194 (15%)	
Death >48 hours	3/81 (4%)	21/113 (19%)	24/194 (12%)	
Antibiotic days	0	12 (6.5-18)	3.5 (0-15)	<.00001

Table 1 (*Continued*)

Variable	Did not receive antibiotics (N = 81)	Received antibiotics (N = 113)	Total (N = 194)	*P* value
Number of antibiotic doses	0	32 (12-50)	6.5 (0-35)	<.00001
Positive cultures	1/81 (1%)	49/113(43%)	50/194 (26%)	<.0001
Documented sites of infection	0/81 (0%)	63/113 (56%)	63/195 (32%)	<.0001
			Bacteremia 9	
			Endocarditis 4	
			CNS infection 2	
			Pneumonia 37	
			GU/ Urinary Tract Infection 19	
			Skin and Soft Tissue 1	

*Only patients with adequate documentation were included. N = 184.

term care facility. The median mRS score at discharge was 4 (IQR 1-5) (Table 1).

Fever burden, Tmax, and length of stay in the hospital were all significantly associated with receipt of antibiotics. Increasing fever burden (AUC) by 1 unit was statistically significantly associated with a 2.1% increase in the odds of receiving antibiotics, (OR 1.021; 95% CI 1.014-1.029, $P < .00001$). For every 1 degree increase in Tmax, the odds of receiving antibiotics increased 4-fold, (OR 4.291; 95% CI 2.324-7.924, $P < .0001$). For each additional day spent in the hospital, the odds of receiving antibiotics increased by 6% (OR 1.064; 95% CI 1.015-1.115, $P = .01$). Clinical factors or interventions such as vasospasm, coiling or clipping of aneurysm, Hunt and Hess score, Fisher score, loss of consciousness, cerebral edema, and length of hospital stay did not change the overall model fit according to the likelihood ratio test and were not associated with increased antibiotic use, therefore these variables were removed from the final antibiotic use model.

Of the 194 patients included, 93 (48%) patients had fever. The mean Tmax for all patients for the entire study period (the single highest temperature recorded for each patient) was 40.8 ± 0.83°C. The mean overall fever burden for all 194 patients was 89.2 ± 99.59°C h more than 37°C. The mean daily fever burden peaked on day 5 and declined thereafter (Fig 3). In the multivariate linear regression model infection, the presence of infection, vasospasm, clipping/coiling of the aneurysm, a poor Hunt and Hess score, a poor Fisher score, loss of consciousness, and seizure at the time of the SAH were included in the final model (Table 2). Holding the presence all other variables constant, the presence of infection was associated with a mean increase in 60 units of fever burden, (coefficient 60.84; 95% CI 28.60-93.09, $P < .0001$). Holding the other variables constant, patients who had a coiled aneurysm had a mean increase in AUC by 30 points, (coefficient 30.74; 95% CI 4.28-57.20, $P = .023$). A poor Fisher score and loss of consciousness on admission were also both statistically significantly with increasing fever burden. For the model testing associations between Tmax and the same variable list, only infection, poor Hunt and Hess score and a poor Fisher score on admission were associated with increased Tmax, while holding other variables constant (Table 3). Therefore, infection, endovascular coiling of the aneurysm, poor Fisher score and loss of consciousness on admission were all associated with increased fever burden. Similarly, infection, poor Hunt and Hess score, and poor Fisher score were all associated with increased Tmax.

Of the 194 patients included, 133 (68.6%) received antibiotics for either confirmed infection or prophylaxis. Twenty patients (15%) received single doses of antibiotics for prophylaxis around insertion of extraventricular devices or lumbar drains. The remaining 113 patients received treatment-dose antibiotics for presumed infection. Only 63 of 194 (32.5%) of patients had infection (Table 1). Forty-five patients were determined to have noninfectious fever, yet 31 of these

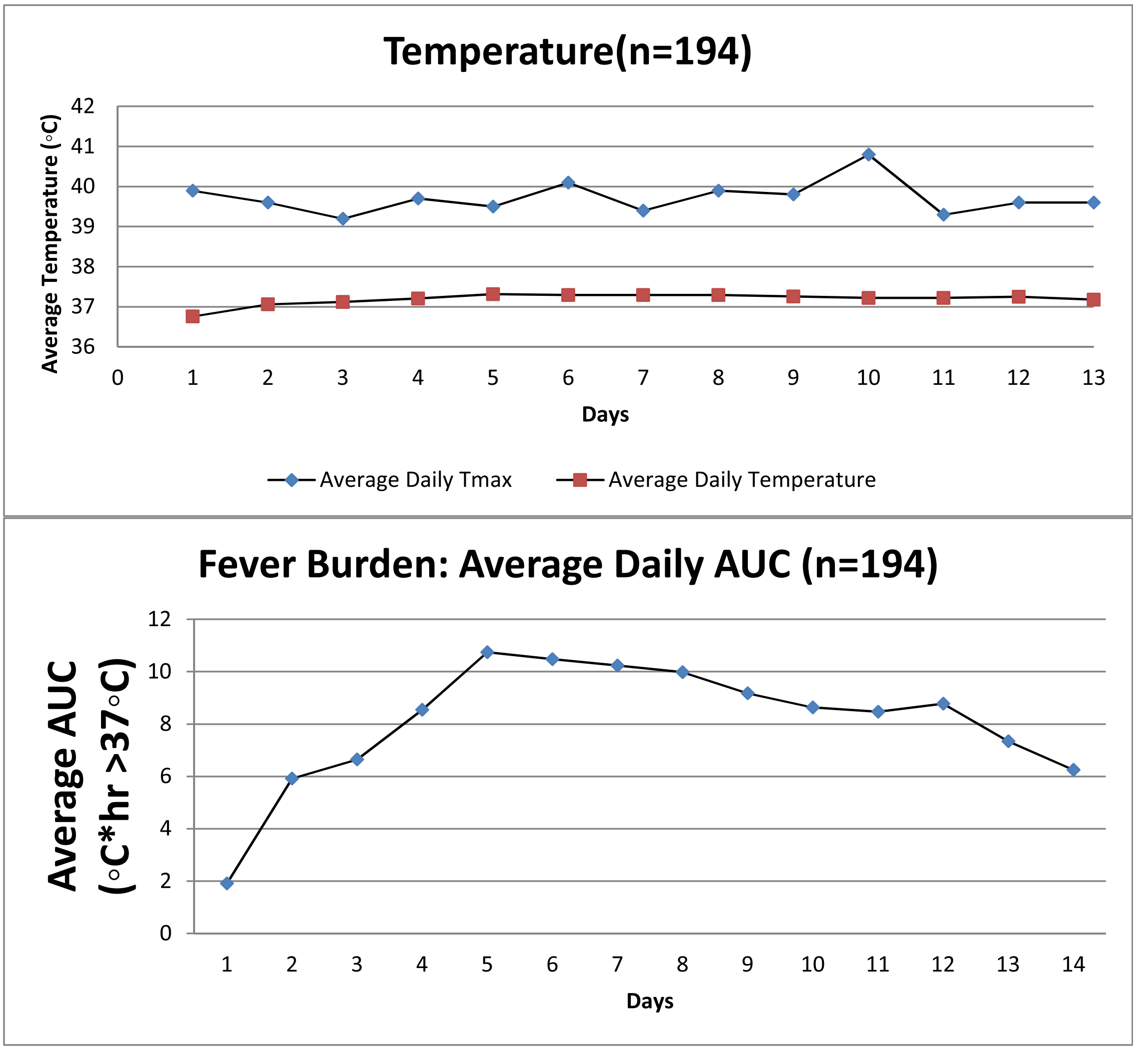

Figure 3. *Average Tmax, average daily temperature, and fever burden.*

patients received antibiotics (69%). Eighty-six patients had no fever, yet 19 patients with no fever and no documented source of infection were treated with antibiotics (Table 6). Both Tmax and fever burden were associated with receipt of antibiotics (Table 4). The 31 patients who had fever but no identified cause of infection received 1000 doses of antibiotics or 32.25 doses per patient. The cost of these unnecessary doses of antibiotics using wholesale acquisition cost in April of 2017 for the most common dose of each antibiotic totaled $10,828.39. Of the studied patients, only 2 had *Clostridium difficile*. Both of these patients were on antimicrobials for a culture positive infection. Antipyretic use was common in this

Table 2. *Multivariate linear regression of characteristics associated with fever burden*

Characteristics associated with fever burden (AUC)			overall $P < .00001$ R^2 .32	
Variable	Coefficient	$P>\|t\|$	95% confidence interval	
Infection	60.84469	<.0001*	28.60418	93.0852
Vasospasm	18.3458	.221	−11.14569	47.83728
Intervention				
1. Coiled	30.73749	.023*	4.27516	57.19982
2. Other	10.7167	.522	−22.25392	43.68733
Hunt and Hess (poor 3-5)	26.33003	.116	−6.561253	59.22131
Fisher Score (poor 3-4)	30.41402	.026*	3.707855	57.12018
LOC	37.79257	.028*	4.128952	71.4562
Seizure	−35.28574	.221	−92.02535	21.45387

*Statistically significant <.05.

Table 3. *Multivariate linear regression of characteristics associated with Tmax*

Characteristic associated with increased Tmax			overall $P < .00001$, R^2.36	
Variable	Coefficient	$P>$|t|	95% confidence interval	
Infection	.4832955	<.0001*	.242259	.7243313
Vasospasm	.1812452	.084	−.0245539	.3870443
Intervention				
1. Coiled	.201373	.066	−.0130968	.4158428
2. Other	.2183434	.173	−.0967537	.5334405
Hunt and Hess (poor 3-5)	.3219527	.012*	.0706438	.5732615
Fisher Score (poor 3-4)	.3915278	.001*	.1565607	.6264948
LOC	.1439599	.227	−.0905447	.3784646
Seizure	−.3296722	.051	−.6607994	.001455

*Statistically significant at $P<.05$.

Table 4. *Characteristics associated with increased antibiotic administration*

Model 1. Characteristic associated with increased antibiotic administration overall model $P < .00001$, R^2.29				Model 2. Characteristic associated with increased antibiotic administration overall model $P< .00001$, R^2.28			
	Odds ratio	$P >$ |z|	95% CI		Odds ratio	$P >$ |z|	95% CI
AUC 37	1.021	<.0001*	1.014- 1.029	Tmax	4.291	<.0001*	2.324-7.924
				Length of stay	1.064	.010*	1.015-1.115

*Statistically significant.

population. Of the 194 patients included, 177 patients received at least 1 dose of an acetaminophen-containing product or an NSAID. The mean number of doses of antipyretics in the study period was 24.4 ± 21.1 doses per patient.

mRS was worse in patients with fever. A logistic regression model assessing characteristics associated with a poor outcome (mRS 4-6) was performed for both fever burden and Tmax. Only Tmax and a poor Hunt and Hess score were associated with a poor outcome OR 1.87; 95% CI 1.22-2.89, $P = .004$) and (OR 3.23; 95% CI 1.64-6.36, $P = .001$), respectively (Table 5). Fever burden was not significantly associated with neurologic outcome.

Discussion

The present study aimed to determine if fever burden was associated with an increased use of antibiotics in patients with SAH. Previous studies have characterized fever in terms of daily maximum temperature, but fever burden may better express hyperthermia in the cases of a low-grade temperature for a longer period of time while still including 1 abrupt increase in temperature. For example, if a patient had a fever burden of 24°C h more than 37°C over the course of a 24-hour period, the patient would have a mean increase in temperature above 37°C of 1°C each hour. This incorporates an element of time exposure to hyperthermia, rather than solely focusing on the highest values of the day. The current study sought to determine if fever burden was more predictive of antibiotic use and infection than Tmax. In fact, our data suggested that both Tmax and fever burden were associated with the receipt of antibiotics and the presence of infection. However, Tmax had a stronger association with receipt of antibiotics. Thus, while both measures may be helpful to predict receipt of antibiotics, Tmax may be the better predictor (and is practically more accessible to clinicians).

The demographics, rates of mortality, ICU length of stay, and neurologic outcomes of our population were

Table 5. *Logistic regression characteristics associated with poor outcomes (mRS 3-6)*

Model 1. Factors associated with a poor outcome mRS (3-6) overall $P< .00001$, R^2.10				Model 2. Factors associated with a poor outcome mRS (3-6) overall $P< .00001$, R^2.12			
	Odds ratio	$P >$ |z|	95% CI		Odds ratio	$P >$ |z|	95% CI
AUC 37	1.003	.138	.999-1.006	Tmax	1.87	.004*	1.216-2.892
HH score bad	3.849681	<.0001*	1.981-7.479	HH score bad	3.232	.001*	1.641-6.364

*Statistically significant.

Table 6. *Analysis of patients without documented infection*

Analysis of patients without documented infection (N = 131)				
	Did not receive abx	Received abx	Total	*P* value
Central fever (45)	14/45 (18%)	31/45 (62%)	45/131 (34%)	$P < .0001$*
No fever	67/86 (78%)	19/86 (22%)	86/131 (65%)	

*Patients with central fever are 8 times more likely to receive abx than those without central fever ($P < .0001$).

similar to previously reported data.[3] The incidence of fever in this study, 48%, was much lower than the previously reported (72%).[2] This could be explained by the consistent use of antipyretics and other strategies for temperature control. Of the 194 patients included, 177 patients received at least 1 dose of an acetaminophen containing product or an NSAID. The use of cooling techniques was not collected in this study, but integration of external cooling techniques into our institutional practice is common due to existing data regarding the harmful effects of hyperthermia.

Previous studies investigating fever after SAH and outcomes have used Tmax to describe this relationship.[4] Exposure to hyperthermia has consistently been associated with poor outcome, more functional disability, and increased cognitive impairment.[3] Our initial hypothesis was that fever burden may more accurately portray consistent exposure to hyperthermia because it incorporates both duration and extent of fever as opposed to singular extreme instances. However, the current study demonstrated that a 1 degree increase in Tmax increased the likelihood of poor neurologic outcome while increases in fever burden did not. This suggests that perhaps the exposure to singular instance of high temperature is more predictive of outcomes than overall exposure to hyperthermia.

This study also suggests that infection is not the only etiology of fever in this patient population. The extent of fever burden was associated with the presence of infection, as well as the severity of SAH and vasospasm. While a causal relationship between fever burden and vasospasm cannot be confirmed, this study does show an association between the 2. Notably, the rise and decline of fever burden appears to mirror the pattern of the risk of vasospasm after SAH. This emphasizes the importance of closely monitoring of the body temperature in SAH patients, as cerebral vasospasm still contributes substantially to morbidity and mortality after SAH.[10]

The clinical conundrum with fever in the SAH patient population is determining if the origin is infectious or noninfectious. With the contemporary emphasis on early initiation of antimicrobials in septic patients and the immunocompromised nature of SAH patients, some clinicians may err on the side of aggressive treatment with broad spectrum antibiotics at the onset of fever.[8,11] Fever, however, is poorly correlated with receiving antibiotics for infection, as evidenced by the present study. Clinicians should note that fever may not be a good marker for infection in SAH patients and that site-specific diagnostic criteria (ie, cultures, chest radiographs, urinalysis, etc) should be more heavily weighted. Our data suggests that Tmax is the better variable to predict receipt of antibiotics. This is somewhat expected as, clinicians are more likely to pursue potential sources of infection in response to a single elevated temperature rather than a low-grade fever.

The rates of infection in our study were lower than previously published studies: only 32%, compared to previously reported 50% infection rates in a broad neurocritical care population.[5,6] The lower rates of infection in this study could be attributed to less surgical wounds and less mechanical ventilation in patients with SAH compared with other neurosurgical patients. Additionally, rates of infection may have been underestimated given the retrospective nature of the study and inability to capture some culture negative infections.

In the present study, fever was overtreated with antibiotics due to presumed infection in some patients. Additionally, many patients without fever, positive cultures, or chest x ray findings suggestive of pneumonia were treated with antibiotics. Due to the retrospective nature of this study, it is hard to definitively say why these patients received antibiotics. The most likely reason for the antibiotics would be for prophylaxis reasons that were not evident or documented, known contamination (wound, EVD site) that was not documented, or for empiric treatment of infection despite having no obvious source. Indiscriminant use of antibiotics can lead to microbial resistance, superinfections including *Clostridium difficile* infections, increased cost, and unnecessary lab tests. Although we only observed 2 cases of *Clostridium difficile* and both of these patients were being treated for culture positive infection, this study is likely underpowered to detect this difference. Increased costs were observed in the cohort of patients receiving unnecessary antimicrobials. Patients received a total of 1000 unindicated doses of antibiotics that equated with $10,828.39. The actual cost of overtreating these patients is likely underestimated as the cost of labor for preparing and administering antibiotics and cost of unnecessary laboratory tests is not included. Clinicians should weigh the costs (financial and otherwise) when considering whether to start antimicrobial agents in patients with SAH who have fever in the absence of other signs and symptoms of infection.

Several limitations of our study deserve mention. First, many of our patients were routinely treated with acetaminophen for temperature more than 38.3°C and cooling measures such as surface cooling blankets with gel pads or forced air cooling with temperature modulating controls and cold wraps around extremities. Because all patients were routinely treated with standard antipyretic and cooling methods, our study essentially reflects the impact of treatment-refractory fever on outcome, rather than purely untreated fever. Another limitation is the retrospective nature of the study. All of the data collected relied on the documentation in the electronic medical record. The data collected were validated, but missing documentation was difficult to ascertain retrospectively. Additionally, we used every temperature recorded, independent of the site from which it was taken. Temperatures taken consistently taken from the same site could have less variation. Bladder, rectal, or esophageal temperatures may be more reflective of core and brain temperature than axial or tympanic measurements.[12,13] Because all recorded temperatures were utilized, some patients had more temperatures recorded than others which could slightly change their fever burden. A continuously monitored method of recording temperature might have been even more informative and might have yielded more accurate associations with outcome and calculations of fever burden. Lastly, culture-negative infection could have been underestimated due to the retrospective nature of the study. It is often difficult to assess situations when the use of antibiotics resulted in de-effervescence despite no positive cultures and limited other data to suggest an infection was present.

Conclusion

Fever is common in SAH patients and is associated with antibiotic use, infection, the incidence of vasospasm, and poor outcome. While fever burden was associated with increased receipt of antibiotics, Tmax was a better predictor for receipt of antibiotics and neurologic outcome after SAH. The amount of blood in the brain and the development of vasospasm are also associated with fever and may confound the clinician's assessment of the presence of infection. SAH patients may inappropriately receive antibiotics for noninfectious fever resulting in unnecessary expenditures and potentially harmful side effects. Other indicators of infection should be taken into consideration to determine origin of fever following spontaneous SAH. Further studies need to be done to better identify markers of infection in the fever-prone SAH patient population.

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Disclosures

None.

Declaration of Competing Interest

There are no conflicts of interest to declare.

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