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Clinical and demographic factors associated with antipyretic use in gram-negative severe sepsis and septic shock

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Abstract

Background—Antipyretic therapy is commonly prescribed to patients with infection, but its impact on clinical outcomes has yielded mixed results. No data currently exist to characterize the use of antipyretic medications in patients with severe sepsis or septic shock.

Objective—We sought to identify clinical and demographic factors associated with antipyretic medication administration in severe sepsis and septic shock.

Methods—Single-center retrospective cohort study of all febrile patients ($T_{\max} \geq 38.3^{\circ}\text{C}$) at a 1,111-bed academic medical center with gram-negative severe sepsis or septic shock between January 2002 and February 2008. Patients were excluded for liver disease, acute brain injury, and allergy to acetaminophen. Generalized estimating equations were used to estimate the effect of clinical factors on treatment of patients with antipyretic medications.

Results—Although 76% of patients in this febrile cohort ($n = 241$) had an order for an antipyretic agent, only 42% received antipyretic therapy and 95% of antipyretic doses were acetaminophen. Variables associated with antipyretic treatment were temperature (OR 2.11/ $^{\circ}\text{C}$,

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1.53 – 2.89), time after sepsis diagnosis (OR 0.88/8 hrs, 0.82 – 0.95), surgery during hospitalization (OR 0.49, 0.31 – 0.80), death within 36 hours (OR 0.35, 0.15 – 0.85), and mechanical ventilation (OR 0.58, 0.34 – 0.98).

Conclusions—Most febrile episodes in patients with gram-negative severe sepsis or septic shock were not treated with antipyretic medications. Treatment factors predicted antipyretic therapy, but severity of illness factors, demographic factors, and location in the hospital did not.

Index keywords

fever; antipyretics; septic shock; sepsis; acetaminophen

Introduction

Antipyretic medications are commonly prescribed for hospitalized patients.^{1, 2} Despite the frequency of fever in human disease, however, very little is understood about the role of antipyretics in the treatment of fever with coexisting infection.³ Observational data suggest that fever may be important for immune function, and animal data corroborate those findings, suggesting reduced mortality in subjects allowed to mount a normal febrile response.^{4–12} Clinical trials exploring antipyretic therapy in the critically ill have yielded mixed results.^{13–17} Fever can increase the metabolic demands in critically ill patients by over 40% and can degrade left ventricular performance.^{18, 19} Febrile-range hyperthermia also increases lung injury in experimental models of pneumonia.^{20, 21} Some clinicians have suggested that certain patients may not tolerate the tachycardia, increased minute ventilation, and metabolic load of fever, and have proposed that these patients may benefit from antipyretic therapy.^{19, 22} Despite the controversy, no evidence-based guidelines for the treatment of fever in life-threatening illness exist.

Previous authors have described orders written for antipyretic therapy and doses administered, but no previous study has investigated clinical factors associated with antipyretic medication administration in febrile patients.^{1, 2} The objective of this study was to characterize clinical factors associated with antipyretic therapy in a cohort of hospitalized patients with gram-negative severe sepsis or septic shock.

Patients and Methods

Design

This study was a retrospective cohort study of febrile gram-negative bacteremic patients hospitalized at a 1,111-bed academic medical center between January 2002 and February 2008 (n=241). All included patients had fever ($T_{\text{max}} \geq 38.3^{\circ}\text{C}$) within 24 hours of blood culture, and met criteria for severe sepsis or septic shock by ICD-9 criteria as reported by Angus, et. al. and Martin, et. al.^{23, 24} The data set was restricted to gram-negative bacteria because of the presumed homogeneity in the cause of fever with gram-negative bacteremia (e.g., lipopolysaccharide release). Furthermore, gram-negative bacteremia is less likely to represent false positive contamination as may occur with gram-positive organisms. Patients who had simultaneous blood cultures which also grew gram-positive or fungal organisms were excluded.

Figure 1 shows the flow diagram of study participants. Patients were included from all inpatient hospital services (including emergency department, intensive care units, and ward beds). Patients were excluded for factors that might bias their likelihood of being treated with antipyretic medications at the time of sepsis diagnosis, including cirrhosis, elevation in hepatic enzymes (aspartate aminotransferase or alanine transaminase > 5 times normal or

total bilirubin > 3 times normal), acute brain injury (including traumatic brain injury, stroke, or intracerebral hemorrhage) diagnosed during hospitalization before diagnostic blood culture, and allergy to acetaminophen. Patients were removed for incomplete data only if the chart did not reflect a disposition or if insufficient information was available to apply exclusion criteria. For patients with more than one episode of severe sepsis with bacteremia during the study period, only the first occurrence was considered.

All medication orders and medication administration history were collected for drugs containing acetaminophen or ibuprofen between the index time and 72 hours after the index time. "Index time" was defined as the time at which a blood culture was collected that subsequently yielded a gram-negative organism. Temperatures, mechanical ventilation, vasopressor use, treatment in an intensive care unit (ICU) or emergency department (ED), and demographic factors (age, sex, skilled nursing facility residence, admission through ED) were gathered. Vasopressors were defined as norepinephrine, dopamine, or phenylephrine administered by continuous infusion (excluding agents typically used for their inotropic effects, including dobutamine, milrinone, and epinephrine). Features of the medical history, home medications, and other therapeutic interventions (including antibiotics, drotrecogin alfa, corticosteroids, immune suppressive medications, etc.) were also recorded. Inappropriate antibiotics were defined to be antimicrobial therapy that was either not initiated within 24 hours of index time or therapy to which in vitro sensitivity testing subsequently showed the pathogen to be resistant.

Each patient's hospital course for the 72 hours immediately following the index time was divided into sequential 8-hour time periods, and the maximum temperature ($T_{\max}$) attained over that period was recorded, defining the presence or absence of fever. Each time period was then evaluated for the presence of each of the clinical factors (i.e., mechanical ventilation, vasopressor use, ICU residence) at any point during that 8-hour period. Antipyretic orders and doses administered were recorded for the entire 72 hours, then were divided into the appropriate 8-hour time periods. Of the 2169 time periods included, no data were missing.

Fever was defined as temperature greater than or equal to 38.3°C as recommended by a consensus of the American College of Critical Care Medicine and the Infectious Diseases Society of America.²⁵ Modified APACHE-II scores were calculated at the index time because the authors were unable to assign accurately a Glasgow Coma Scale score to each patient, and not all patients had all laboratory values available at the time the culture was collected (most extreme values over 24 hours before and after index time were used).²⁶

The Washington University Human Research Protection Office approved this study protocol and granted a waiver of informed consent.

Statistical Methods

Generalized estimating equations (GEE) were used to assess the relationship of various factors with antipyretic exposure, because GEEs allow analysis using both independent (between patients) and repeated measures (within patient) data. Univariable analysis was initially performed using single predictor variables to assess significance of relationships. The subsequent multivariable GEE analysis incorporated factors found to be relevant in univariable analysis and calculated the adjusted odds ratios controlling for measured covariates.

The GEE model used a binomial probability distribution with a logit link function and an exchangeable correlation structure, similar to logistic regression. Predictor variables were included in a main effects explanatory model. All febrile episodes were included, none of

the included variables contained missing data, and each variable was tested for collinearity. Interaction variables with potential physiologic plausibility were placed in the model, but none were found to be independently significant, so they were removed from the final model. Data were analyzed using PASW Statistics 18.0® (IBM Corporation®, Somers, NY).

Results

Table 1 shows characteristics of patients included in the study group (n = 241 patients). Of the 801 doses of antipyretic medication administered for the entire study cohort, only 40 (5.0%) were ibuprofen. Each patient contributed a different number of febrile time periods, with 84 patients (34.9%) contributing a single time period, 127 (52.7%) contributing 2 – 5 time periods, and 30 (12.4%) contributing 6 or more time periods.

Administration of Antipyretic Therapy

Of the time periods where fever was observed (n = 673), a conditional order for acetaminophen or ibuprofen was present in 494 (73.4%). Antipyretic therapy was administered in only 283 febrile time periods (42.1% of time periods where fever was observed). Afebrile patients were treated with acetaminophen or ibuprofen in 281 of 1601 periods (17.6%). The likelihood of being treated with an antipyretic medication was unrelated to time of day or nursing shift (42.7% day shift, 39.0% evening shift, 44.9% night shift, p = 0.43). Univariable comparison is shown in Table 2 (p-values test the hypothesis that the parameter does not differ between the two groups).

Figure 2 shows the proportion of patients being administered an antipyretic drug for fever stratified by magnitude of fever, with 50% of fevers being treated at 38.9 °C. Patients with fever greater than 39.3°C were less likely to receive an antipyretic medication than those with fevers of a lesser magnitude. Figure 3 shows the relationship between treatment with antipyretic medication and time since diagnosis of sepsis. Patients are most likely to receive antipyretic therapy shortly after initial diagnosis.

Multivariable Analysis

An explanatory logistic regression model was constructed using GEEs to determine the influence of underlying factors on administration of antipyretic medications in febrile patients. Factors associated with administration of antipyretic medications were temperature magnitude, time after diagnosis of sepsis, surgery during hospitalization, death in the subsequent 36 hours, and mechanical ventilation (Table 3). The effect magnitude is given by the adjusted odds ratio. For instance, the odds of receiving an antipyretic medication increase by more than twice (OR 2.11) for each degree increase in the T_{max} , when corrected for the other covariates in the model. Temperature was included as a linear variable despite the apparent nonlinearity of the probability (Figure 2) because so few cases of very high fevers were included, and stratifying maximum temperature into categories did not change the parameter significance.

Discussion

This analysis intended to describe current antipyretic therapy practice in patients with severe sepsis and septic shock and to identify patterns in patients who are treated with antipyretic medications. One of the interesting findings is that there is wide practice variability in which patients are treated, and little of that variability is explained by the measured patient or provider factors. Those factors which are predictive seem to have little correlation with physiologically plausible theories upon which some recommend fever therapy.^{19, 22} Such

variability in prescribing and administration is likely a reflection of the absence of strong evidence-based guidelines with which to guide decision making about fever treatment in sepsis. If antipyretic therapy were shown definitively to affect sepsis outcomes, however, most would agree that wide practice variation is undesirable.

Data conflict on the potential protective role of fever in severe human infections.^{13–15} Clearly, failure to mount fever is a marker for worse clinical outcomes, but whether therapeutically attenuating fever has a similar effect is unclear.^{27–29} Furthermore, understanding clinicians' choices in treating patients with fever may lend new insight to factors that play a role in the unique risk-benefit tradeoff for a therapy of uncertain utility.

For this series, patient data were divided into 8-hour time periods for the analysis. Isaacs, et. al. reported on the practice patterns of clinicians ordering antipyretic medication, and in their series, 94% of “as needed” orders specified a time period for re-dosing of 6 hours or less.¹ Further, nurses often work in 8–12 hour shifts, and nurses are the primary decision maker for whether a febrile episode is treated with an antipyretic for a given patient. Body temperature for patients on a general ward is measured at a minimum of every 8 hours. We intended to identify a time period small enough to associate an antipyretic dose with a particular febrile episode, with a temperature being measured during each time period, giving adequate time for a fever to be recognized and treated with an order allowing the nursing staff to do so.

Although only 42% of patients with fever were treated with an antipyretic drug during the study period, that factor was not strictly a function of the fever magnitude. Surprisingly, patients with very high fevers were less likely to receive antipyretic therapy than those with less extreme temperatures. This factor may be a reflection of exclusion criteria, where patients with contraindications to acetaminophen dosing were only excluded at the time culture was drawn, which may have included some patients in our analysis that subsequently developed liver dysfunction after the first 24 hours. This finding could also reflect that patients who manifest very high temperatures have already proven to be refractory to antipyretic therapy, and subsequent therapy was deemed futile. Four of the 14 patients (29%) with sustained (in more than 2 time periods) fevers over 40°C were administered an antipyretic during their first episode of fever, but not during subsequent similarly extreme fever episodes.

There were a number of patients (17.6%) who received an antipyretic drug when they had no fever. These medication doses were likely given for another indication, such as pain or other perceived discomfort. From these data, one could also conclude that some of the doses of antipyretic medications given to febrile patients were for other indications than fever, which would suggest that even fewer cases of fever are being treated.

Ultimately, the treatment of fever is an individualized clinical decision. Many febrile patients have orders for antipyretic agents, but a large percentage of those with orders do not receive therapy for a given febrile episode. Physiologically, some patients may have clinical factors that favor antipyretic treatment based on evidence of shock, tissue hypoperfusion, or risk factors for myocardial ischemia. Some of these factors may drive clinicians to seek to attenuate tachycardia or other physiologic sequelae, such as increased CO₂ production, by administering antipyretics. The metabolic load of fever is significant, and patients expected to withstand the demands may benefit from forgoing antipyretic treatment.^{15, 19, 30} If there is benefit to treating fever, that benefit is probably realized early when patients are most unstable, which could explain the shift toward early treatment after the diagnosis of sepsis.

The negative association between mechanical ventilation and antipyretic therapy is notable, because mechanical ventilation is likely a surrogate not only for respiratory failure, but also

for sedation. Sedated patients seem less uncomfortable, and they are less likely to receive antipyretic therapy. Those patients with respiratory failure could be thought to have more metabolic load which might justify more aggressive antipyretic therapy, but that is not the relationship that is observed. Despite the relationship with mechanical ventilation, no such relationship exists with vasopressor use, which does not necessarily alter the perception of discomfort.

Surgical patients seem significantly less likely to receive antipyretic medications than nonsurgical patients. This finding corroborates a previous observation that antipyretic therapy is associated with the admitting service.¹ We did not specifically control for admitting service in our analysis, so we suspect that the surgical finding is actually a practice variation. There seems to be a trend in our institution whereby surgical patients are less likely to receive antipyretic medications for fever, although there does not seem to be a clear physiologic basis for this observation. We do not have data on which patients were fasting secondary to postoperative ileus, but this could be one explanation for the difference between surgical and nonsurgical patients (note that this study was performed prior to the availability of intravenous acetaminophen). Notably, most neurosurgical patients would have been excluded from our analysis.

Another interesting finding was the strong association between treatment with an antipyretic drug and death. It is impossible to know from this retrospective cohort whether end-of-life care does not include antipyretic therapy or whether antipyretic therapy decreases mortality. It is possible that patients with massive cytokine release exhibit factors that make them less likely to receive antipyretic therapy not adjusted by other covariates in the multivariable model. The number of patients who died within 36 hours of antipyretic therapy was small ($n = 28$) relative to the size of the entire cohort.

The last factor that seems to influence the likelihood of being treated is the time since diagnosis of severe sepsis or septic shock. As expected, the likelihood of therapy decreases as the acute phase of illness resolves. If there are benefits to antipyretic therapy, those benefits may be early in shock attenuation and reversal of respiratory failure. Figure 3 shows that not only does the rate of antipyretic administration fall over the first 32 hours, but that rate begins to climb again later. As some patients improve, patients who are persistently febrile may be “sicker” in the opinion of treating clinicians, and thus may be given antipyretic therapy for treatment of their shock. Many of these critically ill patients were treated during the entire time period, but because more patients were included in the 8–32 hour period who were febrile but less ill, the rate of treatment appears to be lower.

One of the nonsignificant trends that deserves comment is the association between male sex and antipyretic therapy. This finding contradicts an earlier report that male sex was associated with an increased risk for an order for antipyretic therapy in univariable analysis, although the association was nonsignificant in multivariable logistic regression.¹ Intuitively, it does not make sense that this single demographic factor influences the probability of being treated for fever even though the effect size seems modest (adjusted OR 0.66, $p = 0.052$). There have been reports that female sex is protective in various inflammatory states, so it is possible that fewer females required treatment for their fever because clinical evidence of life-threatening inflammation (i.e., severe shock, organ failure, respiratory failure) was absent.^{31–33} This is an interesting finding that should be explored in other controlled analyses as a factor potentially confounding analysis, and the effect of therapy should be explored in subgroup analysis in prospective clinical trials.

One of the findings of this analysis is that specific administrative and demographic factors do not influence the likelihood to be treated with antipyretic medications. Patients in the

intensive care unit may have more actual interventions and more personalized nursing staff, but critical care does not predict the likelihood for fever therapy. That observation is especially interesting because it likely means that the clinical decisions leading to antipyretic administration by nurses in the intensive care are similar to those made by nurses on wards and in the emergency department.

Limitations

The greatest limitation for this cohort study is the retrospective nature of the data collection. As such, we are limited to times of medication administration as documented in the medical record and temperatures as recorded. It is possible that some doses are recorded at a time later than actually administered, but this is a recognized factor in retrospective research.

Another limitation is the inability to ascertain the indication for administration of antipyretic drugs. There is no mechanism to verify that antipyretic medications are actually administered for fever, but the rate of antipyretic medication administration in afebrile time periods was only 17.6%, so most doses were presumably given in response to fever. Although previous investigators have reviewed medical records to try to find this information, they noted that such data was rarely included in medical notes, which agrees with our practice experience.¹

In order to identify a cohort of patients with no biases influencing the administration of antipyretics, we excluded certain groups that either had an indication (e.g., brain injury) or a contraindication (e.g., liver disease, allergy to acetaminophen) to antipyretics for fever control. Those exclusions, while valid, may limit the external validity, and patient populations that contain these excluded patients are likely to have higher or lower incidence of antipyretic administration. Another limitation is the single-center design of our study, but the authors think it is reasonable to suspect that providers in other institutions likely use similar factors to affect their decision to treat with antipyretics as those in our institution.

Finally, factors that may influence the administration of antipyretic medications are broad. We only investigated several potential factors, but others likely exist and are not contained in our data set. For instance, the admitting service caring for patients was not explored rigorously, but has been shown previously to have significant impact on the likelihood of antipyretic medications being ordered. As such, only measured covariates were included in our regression model, and other unmeasured covariates undoubtedly still exist.

Conclusion

In this cohort of 241 patients, 673 (31.0%) time periods represented fever, and clinical factors seemed to influence which patients received antipyretic therapy. Demographic, administrative, and severity of illness markers do not seem to impact likelihood of therapy. Although this series sheds light on some factors that clinicians use to determine the necessity of antipyretic therapy, it does not answer the ultimate question of which patients, if any, benefit from antipyretics. Further studies are needed to demonstrate the effect of antipyretics on clinically relevant outcomes in severe sepsis and septic shock.

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Figure 1. Patient flow diagram

Figure 2. Proportion of patients treated with antipyretic medication by fever threshold

The rate of treatment with antipyretic medications depends on the clinician's definition of fever. Although fever is defined as 38.3°C, practitioners may have different treatment thresholds. The graph shows the rate of antipyretic treatment based on treatment threshold (95% confidence interval), including all febrile time periods ($n = 673$). Each patient may be represented in more than one time period.

Figure 3. Patients treated with antipyretic medication by time since diagnosis of severe sepsis or septic shock

The rate of treatment with antipyretic medications varies based on the time since diagnosis with infection. As the time increases, the rate of therapy falls over the first 32 hours, then rises again. White bars represent the rate of treatment, and black bars represent the portion of the cohort that is febrile (95% confidence interval). All time periods ($n = 2169$) are included in this analysis, and each patient may be represented in more than one time period.

Table 1**Patient characteristics**

Factor	Summary (n = 241)
Mean age, y (SD)	57.1 (16.1)
Male, no. (%)	125 (52)
Transplant (solid organ or bone marrow), no. (%)	31 (13)
End-stage renal disease, no. (%)	24 (10)
Mean modified APACHE-II (SD)	24.1 (6.9)
Drotrecogin alfa during hospitalization, no. (%)	18 (8)
Median days from admission to diagnostic culture (IQR)	4.6 (0.4 – 13.3)
Inappropriate antibiotics, no. (%)	63 (26)
Diagnostic blood culture within 12 hours of admission, no. (%)	101 (42)
Neutropenia (ANC<1000 PMNs/ μ L), no. (%)	35 (15)
Mean systolic blood pressure at time of blood culture (SD), mmHg	83.4 (24.2)
Pneumonia, no. (%)	114 (47)
<i>Pseudomonas</i> , no. (%)	45 (19)
Home corticosteroid or immune suppressive medications, no. (%)	54 (22)
Admitted to ICU during study period, no. (%)	179 (74)
New dialysis during hospitalization, no. (%)	27 (11)
Surgery during hospitalization, no. (%)	67 (28)
Median time from index to discharge, d (IQR)	10 (6–19)
Mechanical ventilation during study period, no. (%)	114 (47)
Vasopressor infusion during study period, no. (%)	105 (44)
Mortality, no. (%)	79 (33)

Abbreviations: y, years; SD, standard deviation; no., number of patients meeting criterion; APACHE-II, Acute Physiology and Chronic Health Evaluation tool, 2nd revision; IQR, interquartile range; ANC, absolute neutrophil count; PMN, polymorphonuclear leukocytes; mmHg, millimeters of mercury; ICU, intensive care unit; d, days

Table 2

Univariable analysis of covariates stratified by antipyretic therapy (GEE univariable analysis)

Predictor	No antipyretic n = 390	Antipyretic n = 283	p
Mean age, y (SD)	55.0 (16.4)	54.4 (16.6)	0.669
Male, no. (%)	222 (57)	119 (42)	0.005
Mean modified APACHE-II (SD)	23.6 (7.3)	23.1 (6.3)	0.304
End-stage renal disease, no. (%)	34 (9)	15 (5)	0.196
Home corticosteroid or immune suppressive, no. (%)	68 (18)	57 (20)	0.477
Home HMG-CoA reductase inhibitor, no. (%)	34 (9)	38 (13)	0.084
Median T _{max} , °C (IQR)	38.8 (38.5 – 39.2)	39.1 (38.7 – 39.5)	< 0.001
Time period (8h) after diagnosis (IQR)	3 (2 – 6)	2 (1 – 5)	< 0.001
Mechanical ventilation, no. (%)	223 (57)	107 (38)	< 0.001
Vasopressor infusion, no. (%)	147 (38)	65 (23)	0.001
ICU residence, no. (%)	311 (80)	200 (71)	0.006
ED residence, no. (%)	16 (4)	9 (3)	0.556
Median time before diagnostic blood culture, d (IQR)	5.7 (1.3 – 15.3)	5.8 (0.8 – 13.1)	0.487
Diagnostic blood culture within 12 hours of admission, no. (%)	150 (39)	117 (41)	0.742
Surgery during hospitalization, no. (%)	147 (38)	55 (19)	< 0.001
Pneumonia, no. (%)	199 (51)	118 (42)	0.064
Acute renal failure, dialysis-requiring, no. (%)	52 (13)	29 (10)	0.357
Appropriate antibiotics, no. (%)	266 (68)	202 (71)	0.338
Death within 36 hours, no. (%)	37 (10)	8 (3)	0.005
In-hospital mortality, no. (%)	142 (36)	88 (31)	0.252

Abbreviations: GEE, generalized estimating equations; y, years; SD, standard deviation; no., number of patients meeting criterion; APACHE-II, Acute Physiology and Chronic Health Evaluation tool, 2nd revision; T_{max}, maximum temperature over 8-hour period; 8h, 8-hour time period; IQR, interquartile range; ICU, intensive care unit; ED, emergency department; d, days

Table 3

Multivariable binary logistic model (GEE multivariable analysis)

Predictor	Adjusted Odds Ratio (CI)	<i>p</i>
T _{max} (per °C)	2.11 (1.53 – 2.89)	< 0.001
Time after diagnosis (per 8 hours)	0.88 (0.82 – 0.95)	0.002
Surgery during hospitalization	0.49 (0.31 – 0.80)	0.004
Death within 36 hours	0.35 (0.15 – 0.85)	0.020
Mechanical ventilation	0.58 (0.34 – 0.98)	0.042
Male sex	0.66 (0.44 – 1.00)	0.052
Vasopressor administration	0.65 (0.40 – 1.06)	0.085
End-stage renal disease	0.59 (0.31 – 1.13)	0.113
Home HMG-CoA reductase inhibitor	1.35 (0.82 – 2.22)	0.242
Pneumonia	0.91 (0.59 – 1.41)	0.684
Home corticosteroid or immune suppressive	1.09 (0.69 – 1.71)	0.725
Intensive care unit residence	0.97 (0.58 – 1.61)	0.897

Abbreviations: GEE, generalized estimating equations; T_{max}, maximum temperature over 8-hour period; C, Celsius