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MAJOR ARTICLE

Association of Daily Body Temperature, White Blood Cell Count, and C-reactive Protein With Mortality and Persistent Bacteremia in Patients With *Staphylococcus Aureus* Bacteremia: A Post Hoc Analysis of the CAMERA2 Randomized Clinical Trial

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Introduction. Classification of patients with *Staphylococcus aureus* bacteremia as complicated versus uncomplicated is based on a combination of clinical and microbiologic variables. Whether daily body temperature and common laboratory tests such as C-reactive protein (CRP) and white blood cell (WBC) can improve risk stratification algorithms is unclear.

Methods. We conducted a post hoc secondary analysis of the CAMERA2 trial, which enrolled hospitalized adult patients with methicillin-resistant *S aureus* bacteremia and prospectively collected daily body temperature and peripheral blood WBC and CRP. We evaluated the prognostic relevance of each parameter by calculating crude and adjusted odds ratios for 90-day all-cause mortality comparing patients with the abnormal parameter of interest versus those with normal parameters on each day of illness.

Results. A total of 345 patients were included in this analysis, of whom 63 (18.3%) died within 90 days. Fever (body temperature ≥38.0 °C) was associated with increased odds of 90-day mortality from day 4 and onwards. Fever later in the illness course was associated with higher adjusted odds of mortality (8.78; 95% confidence interval, 2.78–27.7 on day 7 vs adjusted odds ratio 3.70; 95% CI, 1.58–8.67 on day 4). In contrast, CRP and abnormal WBC count did not demonstrate a consistent or temporal association with mortality.

Conclusions. Persistent fever after 72 hours is associated with increased mortality in patients with methicillin-resistant *S aureus* bacteremia, supporting recommendations that this should be kept as a criterion for classifying patients as either "high-risk" or "complicated." Within this dataset, there was limited additional predictive value in WBC or CRP.

Keywords. c-reactive protein; MRSA; risk stratification; staphylococcus aureus bacteremia; white blood cell.

Staphylococcus aureus bacteremia (SAB) is associated with significant morbidity and mortality and is one of the most common conditions encountered in the practice of infectious diseases worldwide [1–3]. One key decision point in the management of SAB is the classification of patients into those with "complicated" SAB versus "uncomplicated" SAB, with guidelines from the Infectious Diseases Society of America recommending 2 weeks of therapy for uncomplicated SAB and 4–6 weeks of therapy for complicated SAB [4, 5]. However, there is no clear consensus as to the definition of complicated SAB, with guidelines using different combinations of variables, including positive follow-up blood cultures after 48 hours, persistent fever >72 hours, presence of prosthetic implants, community-acquired infection, hemodialysis dependency, and skin examination findings [4–8].

However, this approach of using risk factors to define complicated SAB may have low to moderate predictive value and may overcall the diagnosis of complicated SAB, resulting in unnecessary overtreatment of some patients [9]. Some

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investigators have recently called for a move away from this dichotomy of complicated versus uncomplicated, and instead suggest a risk stratification algorithm to guide advanced diagnostic tests, with subsequent individualization of therapy based on the results of those diagnostic tests [10]. Readily available clinical parameters may be able to inform some of these risk stratification algorithms.

In this exploratory post hoc analysis of the CAMERA2 trial, we aimed to explore the associations between daily body temperature, C-reactive protein (CRP), white blood cell (WBC) count, and clinical outcomes of persistent bacteremia and mortality. Such quantification can inform whether these variables should be used in risk stratification algorithms.

METHODS

Study Population

The methods and results of the CAMERA2 trial have been previously reported [11]. In brief, the CAMERA2 trial enrolled hospitalized patients aged 18 years or older with monomicrobial methicillin-resistant *S aureus* (MRSA) bacteremia, defined as having a positive blood culture for MRSA. Patients were randomized 1:1 to standard therapy (vancomycin or daptomycin based on treating clinician preference) or combination therapy (standard therapy plus an intravenous β-lactam [flucloxacillin, cloxacillin, or cefazolin]). The trial primary endpoint was a composite of (1) all-cause mortality, (2) persistent bacteremia at study day 5, (3) microbiological relapse, and (4) microbiological treatment failure, assessed at 90 days. The study was terminated early because of safety due to increased acute kidney injury in the combination therapy group. There was no significant difference in the primary composite endpoint.

For this secondary post hoc analysis, we included the primary analysis population in the main CAMERA2 report (n = 345, after excluding 4 patients found to be ineligible post-randomization and 7 patients lost to follow-up).

Data Collection and Curation

Data were prospectively collected in the CAMERA2 trial using standardized baseline and daily case report forms. In the original trial, study day 1 was the day of randomization, which was up to 72 hours after the timing of index blood culture collection. The highest body temperature observed on each day was recorded from study days 1 through 7. Peripheral blood WBC and CRP were collected per protocol on study days 2, 5, and 7. Blood cultures were collected on study days 2 and 5 and every 48 hours thereafter while remaining positive. Results of any additional blood cultures collected by managing clinicians were also recorded. All blood cultures and routine laboratory tests were processed at each site per the local laboratory's usual procedures. For this analysis, to align the time course of all patients to a common reference point, we used the index positive blood culture collection date as the reference day 0 of illness and determined the day of illness of each temperature, WBC, CRP, and blood culture observation accordingly. As enrollment and randomization could occur at any time within 72 hours of the index positive blood culture (ie, day of illness 1, 2, or 3), this resulted in a spread of data observations from days 1 to 9 of illness for each data field. We defined fever as body temperature ≥38 °C, a normal WBC as a value ≥4 and ≤11 $\times 10^9$/L, and a high CRP as a value ≥50 mg/L [12, 13].

Handling of Missing Data

Missing blood culture results were imputed as follows: any missing day that was in between 2 positive days was imputed as positive (eg, if blood cultures on days 2 and 5 were positive, days 3 and 4 were imputed as positive), and any missing day that was in between 2 negative days was imputed as negative (eg, if days 4 and 6 were negative, day 5 was imputed as negative). Missing days in between a positive and negative culture (or vice versa) were not imputed and treated as missing. Missing temperature, WBC, and CRP data were not imputed and treated as missing. A complete case approach was used for all analyses, only including available observations (after imputation of blood culture results).

Statistical Analyses

To describe the daily clinical course of body temperature, WBC, and CRP in the first 9 days of illness, we calculated the mean and 95% confidence interval (CI) of each parameter on each day, for the entire cohort, and stratified by (1) those still bacteremic versus those no longer bacteremic and (2) those who died within 90 days versus those who did not. To evaluate the prognostic relevance of each parameter on mortality, we calculated odds ratios (ORs) with 95% CIs for each day of illness using logistic regression models with 90-day all-cause mortality as the dependent outcome variable and the parameter of interest (fever vs no fever, abnormal WBC vs normal WBC, and high CRP vs low CRP in separate models) as the independent variable. As the relationship between these parameters and mortality may be confounded by multiple confounders such as age, sex, comorbidity, and immune status [14, 15], we also calculated corresponding adjusted ORs by including age (as a continuous variable), sex, immunosuppression status, and Charlson comorbidity index as covariates in each model. We also included the assigned treatment group in the CAMERA-2 trial (combination therapy vs standard therapy). The crude and adjusted ORs for each parameter were summarized in modified forest plots presenting the OR for mortality on each day of illness. We also varied the outcome by conducting the same analyses for 14-day and 42-day all-cause mortality, which were both prospectively collected secondary outcomes in the CAMERA2 trial. Last, to explore the effect of relative CRP decline instead of absolute CRP values, we determined if patients achieved a CRP decline to ≤50% and ≤25% from peak

CRP per day and used this (achieving CRP decline target vs not achieving CRP decline target) instead of a binary CRP cutoff of ≥50 mg/L versus <50 mg/L in the models.

RESULTS

Study Population and Outcomes of Interest

A total of 345 patients were included in this analysis; baseline characteristics are summarized in Supplementary Table 1. Mean age was 62.3 years (standard deviation 17.6), and 119 (34.5%) were female. Twenty-six (7.5%), 44 (12.8%), and 63 (18.3%) patients died within 14, 42, and 90 days, respectively. A total of 30.5% (90 of 302) and 21.3% (67 of 314) patients were still bacteremic at days 3 and 4 of illness, respectively (Supplementary Figure 1A). Patients in the combination therapy arm had faster clearance of bacteremia (Supplementary Figure 1B), whereas those who died within 90 days had a slower clearance of bacteremia (Supplementary Figure 1C). The numbers of patients with available observations on each day of illness for temperature, CRP, and WBC are summarized in Supplementary Figure 2. There was a high proportion of missing data on day 1 of illness as most patients were only enrolled in the CAMERA2 trial from day 2 of illness onwards.

Temperature Trends and Association With Mortality

Mean peak temperature on each day of illness for the entire cohort is shown in Figure 1*A*, and numbers and proportion of patients with persistent fever, per day, is shown in Supplementary Table 2. Stratified by presence of ongoing bacteremia, those who were still bacteremic had persistently higher temperatures compared to those not bacteremic throughout the first 9 days of illness (Figure 1*B*). In contrast, there was minimal separation in temperature comparing survivors and nonsurvivors, with nonsurvivors having a slightly higher mean peak temperature from day 4 and onwards (Figure 1*C*). Age was negatively associated with temperature, with older patients having lower peak temperatures throughout the entire course of illness, particularly in the first 3 days of illness (Supplementary Figures 3, 4).

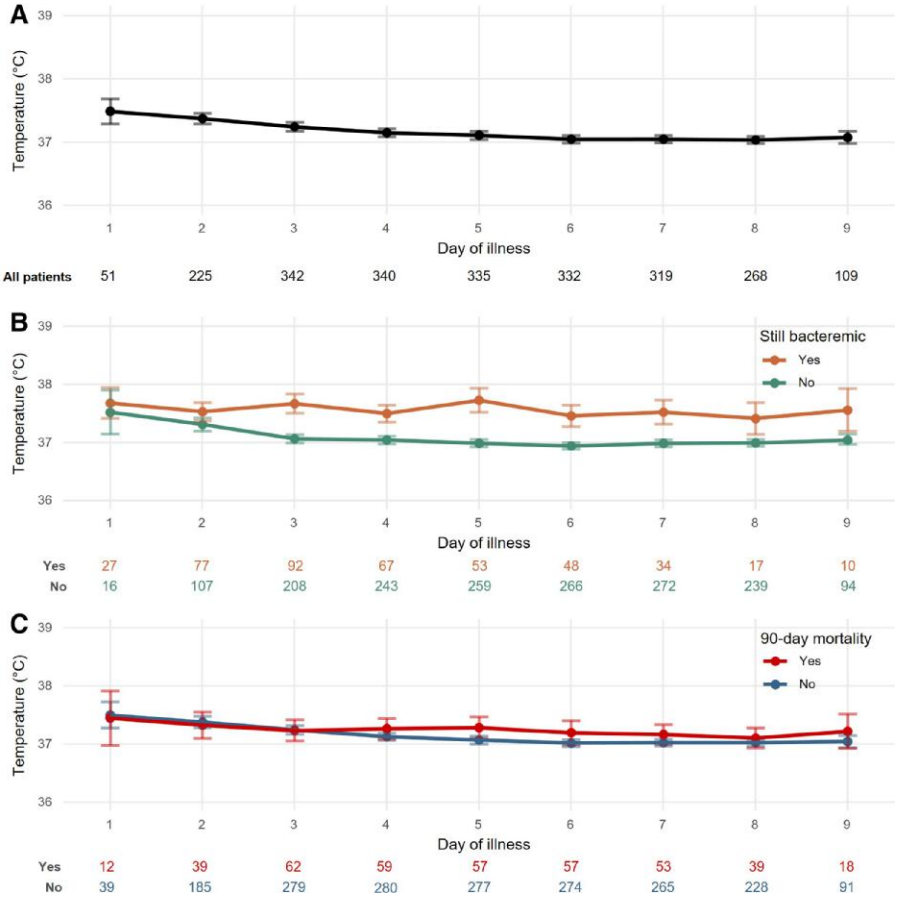


Figure 1. Mean temperature on each day of illness, for all patients (*A*) and stratified by presence of persistent bacteremia (*B*) and 90-d mortality (*C*). Points depict mean values for each day of illness for each subgroup, whereas error bars depict the 95% confidence interval around the mean. Corresponding numbers below each graph show the number of patients with available observations per subgroup for each day (eg, on day 8 there were 239 patients who were no longer bacteremic with available temperature readings and 17 patients who were still bacteremic on day 8 and had available temperature readings).

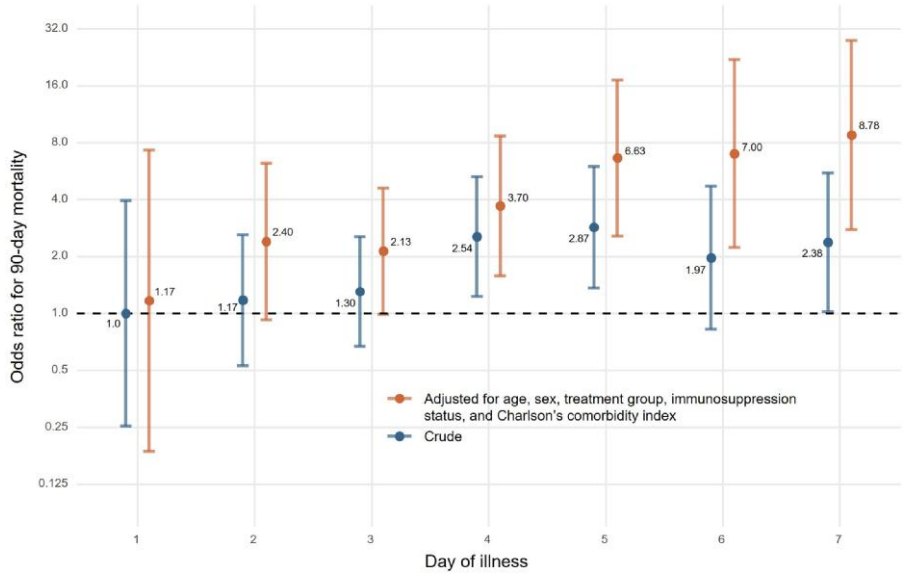


Figure 2. Crude and adjusted odds ratios for 90-day all-cause mortality comparing patients with fever to patients without fever, for each day of illness. Points reflect the crude or odds ratio while error bars reflect the 95% confidence interval. Blue points and bars show the crude odds ratio while orange points and bars show the adjusted odds ratio after adjustment for age, sex, treatment group, immunosuppression status, and Charlson comorbidity index. Annotated numbers beside each point shows the point effect estimate of the odd ratio.

Comparing patients with fever to patients without fever, fever was not associated with an increased odds of 90-day mortality on day 1 but was associated with increased odds of 90-day mortality from day 4 and onwards (Figure 2). A similar pattern was observed after adjusting for age, sex, and immunosuppression status. Fever later in the illness course was associated with higher adjusted odds of mortality (adjusted OR 8.78; 95% CI, 2.78–27.7 on day 7 vs adjusted OR 3.70; 95% CI, 1.58–8.67 on day 4). Similar trends were observed with outcomes of 14-day and 42-day all-cause mortality (Supplementary Figure 5).

C-reactive Protein Trends and Association With Mortality

Mean CRP for the entire cohort showed a gradual decline over the first 9 days of illness (Supplementary Figure 6A). Similar to temperature, the subgroup with persistent bacteremia had a consistently higher mean CRP compared to those without persistent bacteremia (Supplementary Figure 6B). Comparing survivors and nonsurvivors, nonsurvivors had a lower mean CRP in the first 2 days of illness compared to survivors. However, survivors showed a rapid decline of CRP, with mean CRP dropping from 192 mg/L on day 2 to 115 mg/L on day 4 (Supplementary Figure 6C). In contrast, nonsurvivors, though starting with a lower CRP, had a more static trend without the same reduction in mean CRP (Supplementary Figure 6C).

We also analyzed relative CRP declines instead of absolute CRP values, using target thresholds of a CRP decline to ≤50% or ≤25% of peak value. More than half of patients with available observations achieved a CRP decline to ≤50% of peak value by day 5 of illness, whereas the target of a decline to ≤25% peak value was only met by more than half of the cohort by day 8 of illness (Supplementary Figure 7). Stratified by 90-day all-cause mortality, there was minimal separation at days 3 and 4, but a lower proportion of nonsurvivors met each CRP target from day 5 onwards.

In contrast to temperature, daily CRP did not demonstrate a consistent or time-dependent association with mortality, whether using a fixed cutoff threshold value of 50 mg/L (Figure 3*A*), a relative threshold of decline to ≤50% from peak (Figure 3*B*), or a relative threshold of decline to ≤25% from peak (Figure 3*C*). However, repeating CRP at day 6 or 7 of illness may provide some prognostic information since a more rapid CRP decline was associated with lower odds of 90-day mortality. Combining CRP and temperature variables did not further improve the prognostic ability compared to temperature alone (Supplementary Figure 8), though this was limited by the smaller sample size of patients with both available observations.

WBC Count Trends and Association With Mortality

In contrast to temperature and CRP, WBC count trends were fairly static, with mean WBC count fluctuating between 10.8 to 12.6 $\times 10^9$/L throughout the first 9 days of illness (Supplementary Figure 9A). Mean WBC count was also consistently higher in the subgroups of patients with persistent bacteremia (vs those without) (Supplementary Figure 9B) and nonsurvivors (vs survivors) (Supplementary Figure 9C),

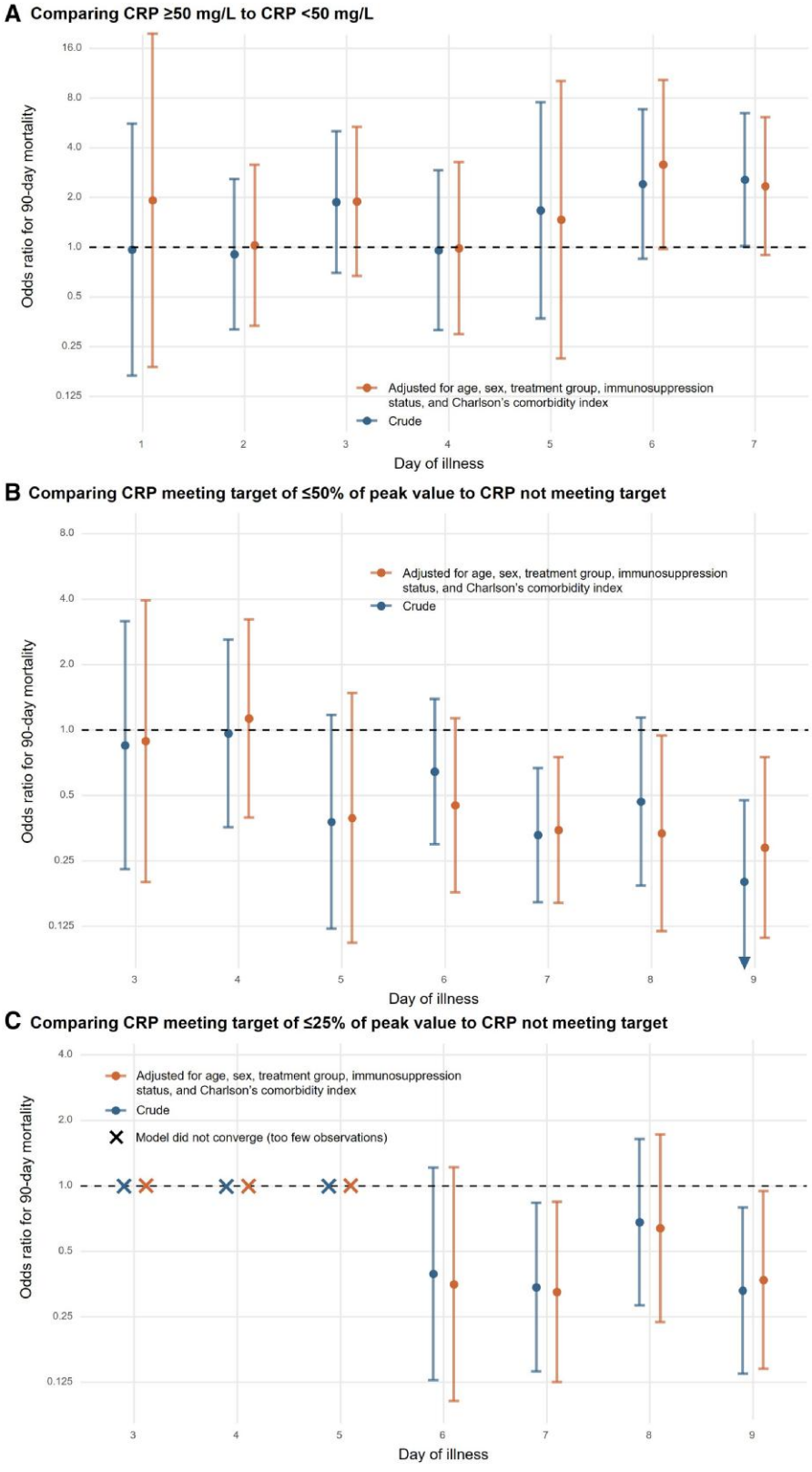


Figure 3. Crude and adjusted odds ratios for 90-day all-cause mortality using different CRP interpretation criteria, for each day of illness. Points reflect the crude or odds ratio while error bars reflect the 95% confidence interval. Blue points and bars show the crude odds ratio while orange points and bars show the adjusted odds ratio after adjustment for age, sex, treatment group, immunosuppression status, and Charlson comorbidity index. Arrow points indicate that the limit of the confidence interval extends beyond the range of the y-axis. The X-symbol indicates that the model for that day did not converge (due to insufficient data points). CRP = C-reactive protein.

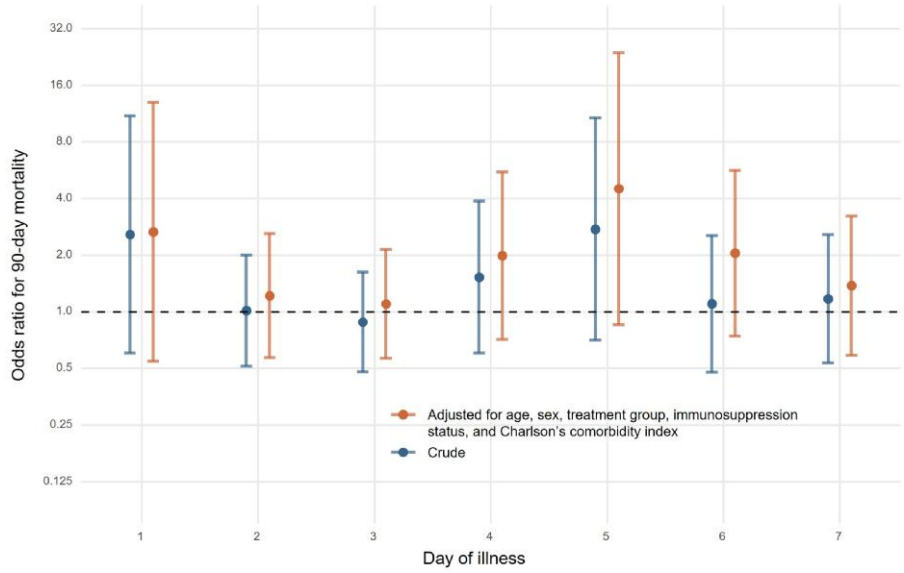


Figure 4. Crude and adjusted odds ratios for 90-day all-cause mortality, comparing patients with abnormal WBC count versus those with normal WBC count. Points reflect the crude or odds ratio while error bars reflect the 95% confidence interval. Blue points and bars show the crude odds ratio while orange points and bars show the adjusted odds ratio after adjustment for age, sex, treatment group, immunosuppression status, and Charlson comorbidity index. WBC = white blood cell.

although this distinction was smaller compared to the distinction seen in temperature and CRP trends. Abnormal WBC count was also not consistently associated with increased odds of 90-day all-cause mortality and showed a variable direction of effect depending on the day of illness (Figure 4).

DISCUSSION

In this post hoc analysis of the CAMERA2 trial, we reviewed trends of 3 common parameters used in the daily clinical assessment of patients with MRSA bacteremia. We found that fever was consistently associated with both persistent bacteremia and mortality, especially after 3 days. Temperature is readily assessable in any resource setting, and persistent fever provides an early indicator for clinicians to consider further diagnostic or therapeutic interventions. The cutoff of >72 hours to define persistent fever was based on the seminal paper by Fowler and colleagues in a prospective cohort of 724 patients with SAB from 1994 to 1999 [5], but there have been limited data validating this in other cohorts. Our data support this threshold and support guidelines recommending that persistent fever lasting >72 hours be included as a criterion for complicated MRSA bacteremia [4, 10]. In contrast, in another recently published study, van der Vaart and colleagues examined the utility of various risk factors to predict complicated SAB (defined as infection-related mortality, metastatic or locally complicated infection, embolic stroke, or relapse within 90 days) in a prospective cohort of 490 patients, and found that persistent fever was not significantly associated with having complicated SAB (unadjusted OR 1.2; 95% CI, 0.6–2.1; positive predictive value 63%; 95% CI, 48.7–75.7) [9]. One potential explanation is the difference in outcome between our study and their study—fever may be predictive of mortality alone but may not be a reliable indicator of complicated bacteremia. More data across multiple diverse cohorts are required to better delineate the prognostic significance of persistent fever in patients with SAB.

In our study, CRP and WBC count were both less reliable than temperature in their associations with persistent bacteremia or mortality. There does not appear to be value in repeating CRP and WBC early in the illness course, and in particular no value in daily measurements [16]. However, a comparison of peak CRP with the value 7 days following index blood culture may have some prognostic significance, which requires further study.

Mölkänen and colleagues evaluated in a prospective multicenter cohort different absolute thresholds and relative percentage changes of CRP and found that both could predict mortality or deep infection in patients with SAB, although further validation in other settings is required [17]. Blot and colleagues explored either baseline WBC count or change in WBC in the first 4 days in a prospective cohort of 574 patients with SAB and did not identify any significant associations with 12-week mortality [18]. Beyond routinely available biomarkers, the use of novel biomarkers such as interleukin-17a may be more specific in prognosticating risk or identifying patients with complicated SAB [19, 20]; however, further research is required before deploying these in routine clinical use.

There are several limitations to our study. First, this was a post hoc analysis that used data from a randomized controlled

trial, whose data collection protocol was not designed to answer the questions we asked in this analysis. Although temperature was measured daily, and CRP and WBC were measured systematically on days 2, 5, and 7, these timings were aligned to the study randomization date rather than the fixed point of date of onset of bacteremia. As such, there were variable numbers of available observations on different days. We thus avoided overinterpretation of any findings limited to specific days, but instead interpreted the overall trend of means and ORs/adjusted ORs for each parameter. However, because the date of enrollment into the trial relative to bacteremia onset date (day 1, 2, or 3) is likely to be random, the spread of different numbers of observations over different days is unlikely to have resulted in significant selection bias. Second, we were limited in the sample size of our cohort and thus could only explore associations between individual parameters (and a single combination of temperature and CRP) and the outcomes of interest. Further research should explore the combination of multiple parameters to determine if our current classification algorithms used in the management of SAB could be improved. Third, data on complications such as metastatic infections (eg, delayed endocarditis) were not available, and hence we could not determine a "gold standard" of complicated infection to calculate the performance characteristics (eg, sensitivity, specificity, positive/negative predictive values) of each parameter for identifying complicated SAB. Last, the CAMERA2 cohort was restricted to MRSA and thus caution should be taken before extrapolation of our findings to methicillin-sensitive *S aureus*. As vancomycin may be inferior to beta-lactam treatment for SAB, dynamics of these clinical variables may be different comparing MRSA and methicillin-sensitive *S aureus* due to differences in treatment. Relatedly, generalizability may be an issue since RCT patient populations may be systematically different (eg, lower mortality, different comorbidity profile) from the general population of patients, especially in the context of SAB [21, 22]. Patients enrolled in clinical trials are often younger than those not enrolled, and this may be especially important because we observed that age was negatively associated with temperature in our cohort.

CONCLUSION

Persistent fever >72 hours is associated with persistent bacteremia and increased mortality in patients with MRSA bacteremia, supporting recommendations that this should be kept as a criterion for classifying patients as either "high-risk" or "complicated." In contrast, the utility of serial WBC or CRP measurements in the management of SAB is unclear and requires further research.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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Potential Conflicts of interest: None declared.

Data Sharing Statement: The raw data used to generate these figures and analyses may be shared with other researchers on reasonable request by contacting the corresponding author.

Patient consent statement: The CAMERA2 trial was approved by the institutional review board at each participating site, and informed consent from patients or agreement from their substitute decision makers was obtained before participation. Because this study was a secondary analysis of previously collected data, reconsent of participants was not required.

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