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MAJOR ARTICLE

Interleukin (IL)-1β and IL-10 Host Responses in Patients With *Staphylococcus aureus* Bacteremia Determined by Antimicrobial Therapy

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Background. Patient interleukin (IL)-1β and IL-10 responses early in *Staphylococcus aureus* bacteremia (SaB) are associated with bacteremia duration and mortality. We hypothesized that these responses vary depending on antimicrobial therapy, with particular interest in whether the superiority of β-lactams links to key cytokine pathways.

Methods. Three medical centers included 59 patients with SaB (47 methicillin-resistant *S. aureus* [MRSA], 12 methicillin-sensitive *S. aureus* [MSSA]) from 2015–2017. In the first 48 hours, patients were treated with either a β-lactam (n = 24), including oxacillin, cefazolin, or ceftaroline, or a glyco-/lipopeptide (n = 35), that is, vancomycin or daptomycin. Patient sera from days 1, 3, and 7 were assayed for IL-1β and IL-10 by enzyme-linked immunosorbent assay and compared using the Mann-Whitney U test.

Results. On presentation, IL-10 was elevated in mortality (P = .008) and persistent bacteremia (P = .034), while no difference occurred in IL-1β. Regarding treatment groups, IL-1β and IL-10 were similar prior to receiving antibiotic. Patients treated with β-lactam had higher IL-1β on days 3 (median +5.6 pg/mL; P = .007) and 7 (+10.9 pg/mL; P = .016). Ex vivo, addition of the IL-1 receptor antagonist anakinra to whole blood reduced staphylococcal killing, supporting an IL-1β functional significance in SaB clearance. β-lactam–treated patients had sharper declines in IL-10 than vancomycin or daptomycin –treated patients over 7 days.

Conclusions. These data underscore the importance of β-lactams for SaB, including consideration that the adjunctive role of β-lactams for MRSA in select patients helps elicit favorable host cytokine responses.

Keywords. cytokines; vancomycin; daptomycin; β-lactam; bacteremia.

Staphylococcus aureus is a leading cause of both community- and hospital-acquired bacteremia in the United States, with an estimated annual incidence of 15–40 cases per 100 000 individuals [1]. Despite diagnostic and therapeutic advances, mortality rates for patients with *S. aureus* bacteremia (SaB) remain as high as 15%–20% or even higher in patients with methicillin-resistant *S. aureus* (MRSA) infection [2, 3]. The sources of SaB are diverse, including skin and soft tissue infections, catheter-associated infections, prosthetic joint infections, and endocarditis, among others. Patient outcomes vary greatly depending on the source and spread of infection. Current treatment guidelines recommend the use of vancomycin or daptomycin to treat MRSA and a β-lactam, such as intravenous nafcillin, oxacillin, or cefazolin, to treat methicillin-sensitive *S. aureus* (MSSA) infection [4]. Recent studies demonstrate that the addition of anti-staphylococcal β-lactams nafcillin/oxacillin/cefazolin to vancomycin or daptomycin therapy can reduce the duration of MRSA bacteremia [5, 6]. Similarly, use of ceftaroline combined with vancomycin or daptomycin shortens bacteremia and may reduce mortality in high-risk patients [5, 7].

Various cytokine responses have recently been linked to the severity of SaB infection. A robust interleukin (IL)-1β response, evidenced by elevated serum IL-1β concentrations at clinical presentation, is important for SaB clearance, wherein a failure of this response predisposes prolonged bacteremia (>4 days) [8, 9]. *Staphylococcus aureus* strains with reduced vancomycin susceptibility display attenuated virulence, greater intracellular persistence, and delayed bacteremia clearance linked to dampened proinflammatory cytokine production [10, 11]. Additional studies identified high intravascular *S. aureus* burden driving peptidoglycan-mediated IL-10 elevation as an independent risk factor for mortality [8, 12]. These select cytokine biomarkers, among others, may be valuable for identifying those patients at greatest risk for disease complications and guiding optimal antibiotic therapy [13].

To date, correlations of serum IL-1β and IL-10 levels to clinical outcome in SaB have been limited to serum cytokine values obtained at the time of clinical presentation, prior to initiation of antimicrobial therapy. This study was performed to evaluate host responses for these cytokines during the first 7 days

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of antimicrobial therapy. Specifically, we hypothesized that favorable clinical data corresponding to β-lactam therapy in SaB may be based, at least in part, on the ability of this drug class to promote a more vigorous immunostimulatory IL-1β response and/or an attenuation of the dysregulated immunosuppressive IL-10 response.

METHODS

Fifty-nine patients aged ≥18 years with SaB were identified retrospectively from 3 medical centers: UW Health (Madison, WI), Sharp Memorial Hospital (San Diego, CA), and Sharp Grossmont Hospital (La Mesa, CA). These patients included consecutive patients from a randomized clinical trial (ClinicalTrials.gov: NCT02660346) of daptomycin plus ceftaroline vs standard of care [5] and an ongoing *S. aureus* bacteria immune response biorepository study at the University of Wisconsin–Madison. Each institution ascertained health-sciences institutional review board protocol approval prior to study initiation [5, 8]. Patients had diverse sources of infection, including endovascular, extravascular, and catheter-related infections. All patients had complicated bacteremia as previously defined [4, 14]. Of these patients, 47 were infected with MRSA and 12 with MSSA.

Patients were selected and divided into 2 groups based on their initial treatment within 48 hours of clinical presentation. Patients in the glyco/lipopeptide group (n = 35) were treated with either vancomycin or daptomycin alone as the current standard of care for MRSA bacteremia. Patients in the β-lactam group (n = 24) were treated with oxacillin, nafcillin, cefazolin, or ceftaroline. Patients with MSSA bacteremia primarily received oxacillin, nafcillin, or cefazolin as the main treatment within 48 hours of presentation per standard protocol at each institution. Ceftaroline was used as part of a combination randomized study with daptomycin for MRSA, which was initiated on day 1 of patient presentation [5]. β-lactam–treated patients may have also received a glyco/lipopeptide at some point during their therapy, but β-lactam therapy was never discontinued. Conversely, patients in the glyco/lipopeptide group only received vancomycin or daptomycin throughout their entire course and never received a β-lactam at any point during therapy. Patient demographics and clinical characteristics for the 2 groups were compared using the *t* test or Mann-Whitney *U* test for continuous variables depending on Gaussian distribution and the Fisher exact test for categorical variables. Statistical analysis was performed in Stata version 15 (Stata Corp LP).

Serum samples were obtained from patients with SaB on day 1 of presentation prior to treatment initiation and then on day 3 and day 7 of treatment. Sera were stored at −80°C until the time of analysis. IL-1β and IL-10 quantitative sandwich enzyme-linked immunoassays were performed on each collected sample in duplicate. The manufacturer's (R&D Systems) recommended protocol was followed, and the absorbance was measured at 450 nm. IL-1β and IL-10 concentrations for patients in the 2 treatment groups were compared using the Mann-Whitney U test in Prism (GraphPad Software, LLC). Significance was defined as $P < .05$.

For ex vivo whole blood studies, a single colony of MRSA TCH1516 was grown overnight to stationary phase in 5 mL Todd Hewitt (TH) broth, washed once in 5 mL phosphate-buffered saline (PBS), and resuspended to an optical density 600 nm wavelength (OD600) absorbency of 0.4 in PBS. Whole blood was collected in hirudin-containing tubes from 3 healthy donors. Blood for each condition was placed in a 2-mL siliconized Eppendorf tube and treated with carrier control (1.8 mg disodium EDTA, 82.2 sodium chloride, 19.3 mg sodium citrate, and 10.5 mg polysorbate 80 in 10 mL water, filtered with a 0.2-μm filter) or with 2500 ng/mL IL-1 receptor antagonist anakinra for 30 minutes at 37°C with rotation. The anakinra concentration tested represents steady state concentrations achieved in plasma with 1–3 mg/kg recommended doses [15]. After preincubation, MRSA was added to a final inoculum of 1×10^6 colony forming units (CFU)/mL and incubated with rotation at 37°C for 2 hours. Samples were transferred to a 96-well round-bottom plate and sonicated in triplicate twice for 3 seconds with a 3-second pause in between. Each sample was then serially diluted, plated on TH agar plates, and incubated at 37°C overnight; bacterial CFUs were enumerated. Differences in bacterial counts obtained with anakinra vs without anakinra in blood killing assays from the 6 individual blood donors were evaluated using the Mann-Whitney *U* test.

RESULTS

Baseline patient and infection characteristics are displayed in Table 1. Patients who received β-lactam antibiotics (n = 24) did not differ significantly in terms of age, sex, comorbid conditions, source of infection, intensive care unit admission, or vancomycin susceptibility compared to those treated with glyco/lipopeptides only (n = 35). Though not statistically significant, we note that more patients in the β-lactam group had endovascular sources, while more in the glyco/lipopeptide group had a catheter-associated source of bacteremia. Also, the β-lactam group trended toward higher white blood cell counts at presentation ($P = .073$), but other inflammation or disease severity metrics including C-reactive protein and Pitt bacteremia score were comparable between the 2 groups. More patients in the glyco/lipopeptide group had MRSA ($P = .012$), but still more than half of the patients who received β-lactams had MRSA. Hospital length of stay was 1.5 days shorter on average in the β-lactam group ($P = .442$).

Table 2 displays the antibiotic treatments initiated within 48 hours of patient presentation. The majority of patients in the

Table 1. Patient Demographics and Infection Characteristics

Variable[a]	Glyco/Lipopeptide n = 35	β-Lactam n = 24	*P* Value[b]
Age, years	61.1 ± 3.1	60.4 ± 2.9	.891
Male	23 (34)	15 (62.5)	>.999
Source	…	…	>.138
Endovascular	10 (28.6)	9 (37.5)	…
Secondary	21 (60)	15 (62.5)	…
Catheter	4 (11.4)	0	…
Methicillin-resistant *Staphylococcus aureus*	33 (94.2)	14 (58.3)	.012
Serum creatinine at presentation, mg/dL	1.8 ± 0.3	1.9 ± 0.5	.900
Complicated bacteremia[c]	35 (100)	24 (100)	>.999
White blood cell count at presentation, 10^3 cells/μL	15.3 ± 1.3	19.4 ± 1.9	.073
Platelet count at presentation, 10^3 cells/μL	230.4 ± 23.4	249.9 ± 41.8	.665
C-reactive protein at presentation,[d] mg/L	122.0 [15.0–340.6]	124.9 [10–304.5]	.765
Vancomycin minimum inhibitory concentration, mg/L	1.0	1.0	.396
Pitt bacteremia score[d]	1 [0–8]	1 [0–8]	.808
Comorbidities	…	…	>.530
Diabetes mellitus	16 (45.7)	10 (41.7)	…
Liver disease	9 (25.7)	4 (16.7)	…
Immunocompromised	2 (5.7)	2 (8.3)	…
End-stage renal disease	6 (17.1)	3 (12.5)	…
Patient location at index culture	…	…	…
Intensive care unit	3 (8.5)	3 (12.5)	.679
Hospital length of stay, days	12.4 ± 1.4	10.9 ± 0.8	.442
Duration of bacteremia, days[c]	2 [1–11]	2 [1–9]	…
In-hospital mortality	6 (17.1)	3 (12.5)	…

[a] Data are presented as mean ± standard deviation for continuous variables and n (%) for categorical variables unless otherwise noted.

[b] The *t* test, Mann-Whitney *U* test, or Fisher exact test was used for analysis for the appropriate data type.

[c] Defined as patients with positive blood culture results who do not meet the following criteria for uncomplicated bacteremia: exclusion of endocarditis, no implanted prostheses, follow-up blood cultures performed on specimens obtained 2–4 days after the initial set that do not grow *Staphylococcus aureus*, defervescence within 72 hours of initiating effective therapy, and no evidence of metastatic sites of infection.

[d] Median [range].

glyco/lipopeptide group received vancomycin (80%), while the others received daptomycin. Patients in the β-lactam group received ceftaroline combined with daptomycin (58.3%), while others received oxacillin or cefazolin alone or oxacillin combined with vancomycin. All of these therapies were maintained for at least 14 days of treatment with the exception of 2 patients who initially received oxacillin plus vancomycin. These patients had definitive MSSA, and they were deescalated to oxacillin alone as the β-lactam therapy for full bacteremia treatment duration.

Table 2. Antibiotic Therapy Initiated Within 48 Hours of Presentation

Antibiotic	Glyco/Lipopeptide n = 35	β-Lactam n = 24
Vancomycin	28	…
Daptomycin	7	…
Oxacillin	…	6
Cefazolin	…	2
Vancomycin plus oxacillin[a]	…	2
Daptomycin plus ceftaroline	…	14

[a] Vancomycin was discontinued after 48 hours due to definitive methicillin-sensitive *Staphylococcus aureus*, and oxacillin was continued for the duration of treatment of bacteremia.

Consistent with prior data, patients who died in both groups had higher IL-10 serum concentrations at day 1 of presentation compared to survivors ($P = .008$) and no differences in median IL-1β concentration (Figure 1). For bacteremia >4 days duration, IL-10 was also higher than in patients with rapid bacteremia clearance ($P = .034$), with no observed difference in IL-1β (Figure 2).

All SaB patients had serum samples collected on day 1 of hospital presentation and then on days 3 and 7 following initiation of therapy. There were no significant differences in IL-1β concentrations between the 2 groups at patient presentation (Figure 3). The median IL-1β concentration prior to antibiotic therapy was 6.1 pg/mL for β-lactam–treated patients and 2.8 pg/mL for glyco/lipopeptide-treated patients ($P = .090$). On day 3, patients treated with a β-lactam had significantly higher IL-1β levels than glyco/lipopeptide-treated patients (median, 7.5 pg/mL vs 1.9 pg/mL, respectively; $P = .007$). The

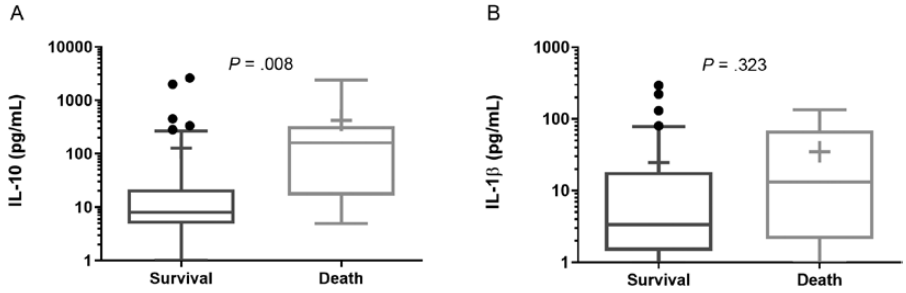

Figure 1. (*A*) IL-10 and (*B*) IL-1β concentrations in patient sera on day 1 of presentation compared by outcome of 30-Day survival or mortality. The Mann-Whitney *U* test was used for statistical analysis. Median (line) and mean (+). Abbreviation: IL, interleukin.

difference between groups was also noted at day 7 of therapy, with β-lactam treatment resulting in higher IL-1β concentrations (median, 12.5 pg/mL) than glyco/lipopeptide treatment (1.6 pg/mL; P = .016). Comparatively per patient, β-lactam treatment resulted in 23% and 105% median increases in IL-1β at days 3 and 7, respectively, while glyco/lipopeptide treatment resulted in 32% and 44% reduction in IL-1β at those same time points following presentation (Figure 3). Of interest, this difference also occurred among MRSA patients treated with daptomycin plus ceftaroline vs daptomycin or vancomycin alone (Supplementary Figure 1A).

Patient sera were also analyzed for IL-10 concentrations at presentation (day 1) and on days 3 and 7 of treatment (Figure 4). On clinical presentation prior to antibiotic therapy, patients in the β-lactam–treated group had a median IL-10 level of 17.6 pg/mL, and patients treated with glyco/lipopeptides had a median IL-10 level of 10.5 pg/mL (P = .133). By day 3, IL-10 levels were lower in patients treated with β-lactams than in patients treated with glyco/lipopeptides (median, 7.0 pg/mL vs 8.8 pg/mL; P = .745). On day 7, IL-10 levels were also lower in patients treated with β-lactams (2.5 pg/mL vs 6.0 pg/mL for glyco/lipopeptides; P = .864). Overall, patients treated with β-lactam had a 60% reduction in IL-10 levels from day 1 to day 3 and a 64% reduction from day 3 to day 7 (86% total reduction in first 7 days). For glyco/lipopeptide-treated patients, reduction in IL-10 levels was only 16% from presentation to day 3 and 32% between day 3 and day 7 (42% overall; Figure 4). This trend was similar in the MRSA bacteremia patients treated with daptomycin plus ceftaroline vs vancomycin or daptomycin alone (Supplementary Figure 1B). Most notably, IL-10 concentrations in patients treated with daptomycin plus ceftaroline were within normal range (<5 pg/mL) at days 3 and 7 but they remained elevated with vancomycin or daptomycin monotherapy.

IL-1β is a multipotent cytokine with diverse effects on host immune and inflammatory responses including the recruitment and activation of neutrophils [16]. Thus, elevated IL-1β responses in β-lactam therapy likely impact *S. aureus* clearance and clinical features in multiple ways. As a pilot experiment to determine whether IL-1β signaling could have short-term effects within the blood compartment relevant to *S. aureus* clearance, we assessed whole blood killing of MRSA with or without the addition of the IL-1 receptor antagonist anakinra. After MRSA infection of human whole blood from 6 healthy donors in the presence of either 2500 ng/mL anakinra or carrier control, significantly higher bacterial counts were seen in 4 of 6 of the anakinra-treated samples following 2 hours of incubation (Supplementary Figure

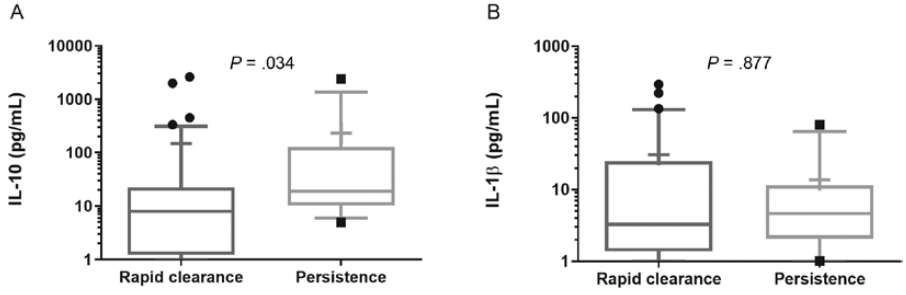

Figure 2. (*A*) IL-10 and (*B*) IL-1β concentrations in patient sera on day 1 of presentation compared by outcome of rapid bacteremia clearance (≤4 days) or persistent bacteremia (>4 days). The Mann-Whitney *U* test was used for statistical analysis. Median (line) and mean (+). Abbreviation: IL, interleukin.

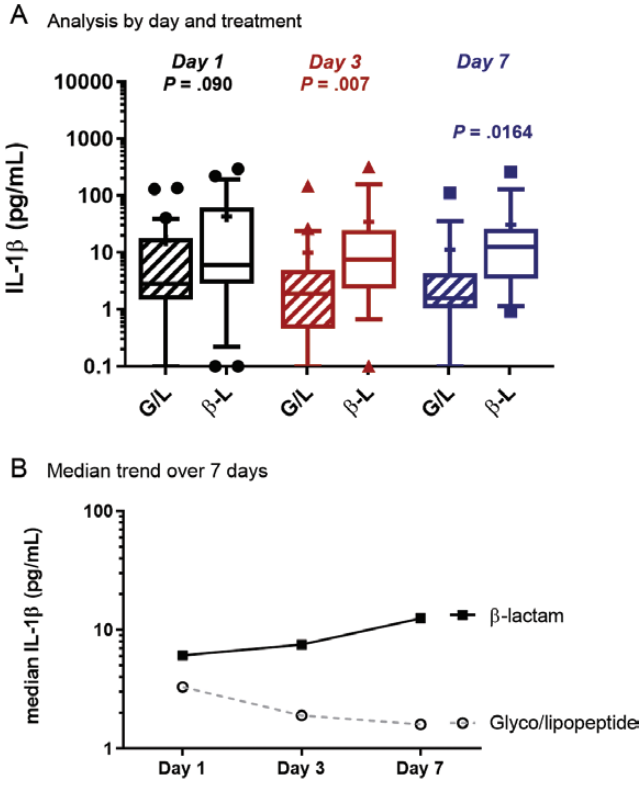

Figure 3. IL-1β concentrations in patient sera treated with G/L or β-L antibiotic at day 1, day 3, and day 7 of therapy. The Mann-Whitney U test was used for statistical analysis. Median (line) and mean (+). Abbreviations: B-L, β-lactam; G/L, glyco/lipopeptide; IL, interleukin.

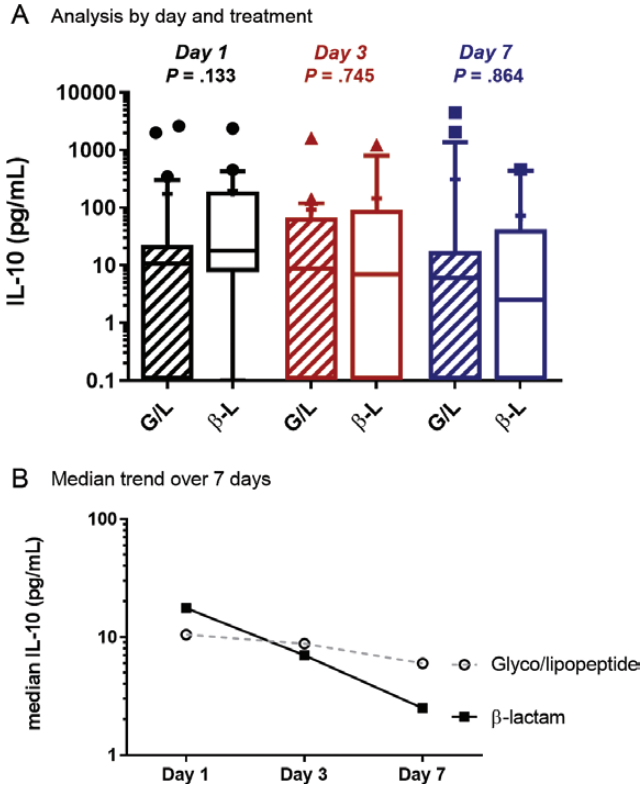

Figure 4. IL-10 concentrations in patient sera treated with G/L or β-L antibiotic at day 1, day 3, and day 7 of therapy. The Mann-Whitney *U* test was used for statistical analysis. Median (line) and mean (+). Abbreviations: B-L, β-lactam; G/L, glyco/lipopeptide; IL, interleukin.

2). Collectively among the 6 donors, bacterial counts with anakinra were higher than without anakinra (median, 1.3 fold; range, 0.8–2.6).

DISCUSSION

Despite the availability of new antibiotics with activity against *S. aureus*, the standard of care for bacteremia overall has remained unchanged for the past several decades, with a preference for empiric β-lactam therapy for MSSA and vancomycin for MRSA. Daptomycin has emerged as a viable treatment alternative to vancomycin for MRSA [17] but it has been effectively relegated to second-line therapy for those patients who fail vancomycin or who have allergies to first-line agents. β-lactams are the treatment of choice for MSSA bacteremia, and recent evidence of their ability to synergize with vancomycin and daptomycin have made them an intriguing combination option for complex MRSA infections. Further, β-lactams enhance host innate immune recognition and killing, which may augment antibacterial activity. This study reveals that β-lactam therapy may result in a more favorable host cytokine response profile to *S. aureus* in the bloodstream.

Staphylococcus aureus possesses several mechanisms to establish colonization and infection by subverting human innate immune recognition. Given the key role of inflammasome activation and IL-1β signaling for *S. aureus* recognition and clearance of infection [10, 18], the results of our study have important clinical implications. Here, we demonstrate that monotherapy with vancomycin or daptomycin does not elicit a robust IL-1β response in patients. However, β-lactam therapy that includes oxacillin, cefazolin, or ceftaroline, either alone or in combination with vancomycin or daptomycin, enhanced IL-1β at days 3 and 7 of therapy. We suspect that the muted IL-1β response with non–β-lactam therapy may be a predisposing factor for the longer bacteremia that has been reported in MRSA compared to MSSA [19, 20]. Our pilot experiment results suggest the potential for short-term blockade of IL-1β signaling of reduced MRSA killing in human whole blood ex vivo and support further analysis of a direct role of sustained differences in IL-1β levels in supporting clearance of MRSA bacteremia. Future studies should evaluate how cytokine signaling with treatment correlates with bacterial clearance when considering other factors for persistent bacteremia, including infection source, source control, *S. aureus* lineage, and susceptibility.

In several independent studies of MRSA bacteremia, β-lactam therapy when combined with vancomycin or daptomycin reduces the duration of bacteremia [21–24]. Our current results

indicate a beneficial role of β-lactam administration in supporting increased IL-1β responses in SaB, regardless of the organism's β-lactam susceptibility. Based on prior experimental evidence, we hypothesize that β-lactams may induce IL-1β expression through multiple mechanisms. First, increased shedding of small amounts of *S. aureus* pathogen-associated molecular patterns such as peptidoglycan, lipoteichoic acid, and superantigens may improve macrophage recognition and release of IL-1β. Second, β-lactams increase expression of the proinflammatory *S. aureus* α-toxin [25], which induces host IL-1β expression via the NLRP3 inflammasome [26, 27] and has been inversely correlated with virulence in endovascular infection [28]. Third, a modified peptidoglycan with reduced cross-linking is produced by MRSA upon β-lactam treatment and is sensed differently by macrophages to elicit a more robust IL-1β response [29]. Finally, β-lactam–mediated reduction of peptidoglycan O-acetylation by o-acetyl transferase [30] renders *S. aureus* more vulnerable to macrophage killing and induces IL-1β release [31].

The functional significance of IL-1β induction is supported by studies in which genetic or pharmacological blockade of IL-1R signaling in mice led to increased bacterial burden during *S. aureus* infection including septic arthritis and pneumonia [32, 33]. Here, we show in short-term ex vivo whole blood killing assays, a potential for attenuated MRSA killing by addition of IL-1 receptor blocker anakinra. Although the causality of this effect is not conclusive, these results suggest that the IL-1β–driven *S. aureus* killing may be recapitulated in part by the subset of the innate immune cells present in whole blood. This is a topic that should be of interest for subsequent mechanic analyses.

Poor outcomes of *S. aureus* bacteremia are associated with immune imbalance at clinical presentation. Cell wall peptidoglycan is a known stimulator of IL-10 production in animals, and we have previously linked bacterial burden in the bloodstream with elevated IL-10 production in patients. The bactericidal nature of β-lactams against MSSA is well described via potent inhibition of cell wall transpeptidation/transglycosylation triggering autolytic enzyme release and ultimately cell lysis. For MRSA, β-lactams strongly synergize with vancomycin or daptomycin through enhanced potency or inhibition of penicillin-binding proteins as a dual mechanism of action [22, 34, 35]. In addition, we have shown considerable synergy between β-lactams and various arms of the innate host response in providing potent staphylocidal activity, a property not shared by daptomycin, vancomycin, or linezolid [36]. In this study, the greater IL-10 reduction with β-lactam therapy compared to vancomycin or daptomycin alone may reflect more rapid reduction in bacterial inoculum by β-lactams. However, the effects of β-lactams on IL-10 and, therefore, on mortality appear to be less robust than the effect on IL-1β, a cytokine linked to bacteremia duration. This is consistent with recently published clinical data wherein addition of flucloxacillin to vancomycin for the treatment of MRSA bacteremia had a notable impact on shortening bacteremia duration but did not reduce mortality [6]. However, a more recent study that did demonstrate a mortality reduction with daptomycin plus ceftaroline when used up front in MRSA bacteremia suggests that the use of combination therapy where both drugs exert simultaneous antibacterial activity and provide enhanced immune-mediated clearance may be most beneficial for the most difficult infections.

These findings further point to the clinical relevance of the increasingly appreciated properties of antibiotics beyond what is predicted by their activities in classic bacteriological media, including minimum inhibitory concentration, and bactericidal activity. Given the fact that these important antimicrobial attributes are totally missed in bacteriological media, it is not surprising that the bactericidal vs bacteriostatic characteristics defined in such media are of questionable clinical relevance [37].

This study is limited in that it was retrospective and the cytokine responses examined were limited to IL-10 and IL-1β. In addition, most of the β-lactam therapy in the MRSA arm was for patients treated with ceftaroline in combination with daptomycin, so this may not be generalizable to other β-lactam combinations. A prospective study to examine a larger cadre of cytokines, other innate host immune responses, and acquired immunity would add further insights, particularly if study designs integrate medical decision making with the results of the host response assays, including stratifying patients by IL-10 or other host biomarkers in order to escalate or deescalate novel therapies. Such studies would help address the continuing challenges experienced with clinical trials of antibiotics for SaB [38] and are essential before host response factors are incorporated into mainstream clinical management of SaB.

In conclusion, we have demonstrated that patients with SaB who receive β-lactam antibiotic therapy generate a more favorable host immune response as it relates to increased IL-1β and decreased IL-10 production over the first 7 days. These factors may strongly influence the favorable clinical outcomes in β-lactam–treated patients. Benefits of β-lactam combination therapy for MRSA bacteremia remain an area of investigation, with attention shifting to identifying the patient subset for which such therapy is beneficial.

Supplementary Data

Supplementary materials are available at *Clinical 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. G. S. has received speaking honoraria from Allergan, Theravance, and Melinta; consulting fees from Allergan and Paratek Pharmaceuticals; and is on the Cidara Therapeutics Scientific Advisory Board. W. E. R. has received grant funding from Merck and speaking honoraria from Melinta. V. N. reports grants from Roche and personal fees from Cidara outside the submitted work. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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