MAJOR ARTICLE

Is Methicillin-Resistant *Staphylococcus aureus* More Virulent than Methicillin-Susceptible *S. aureus*? A Comparative Cohort Study of British Patients with Nosocomial Infection and Bacteremia

M. Melzer,[1] S. J. Eykyn,[2] W. R. Gransden,[4] and S. Chinn[3]

[1]King George Hospital, Goodmayes, Essex, [2]Department of Infection, Lucy's and St. Thomas' Hospital, and [3]Department of Public Health Studies, King's College, London, and [4]Department of Microbiology, Royal Bournemouth Hospital, Bournemouth, England

Staphylococcus aureus **is the most common cause of hospital-acquired bacteremia. From 1995 through 2000, data on age, sex, patient specialty at time of first bacteremia, primary and secondary sites of infection, delay in initiating antimicrobial therapy, and patient outcome were prospectively recorded for 815 patients with nosocomial *S. aureus* bacteremia. The proportion of patients whose death was attributable to methicillin-resistant *S. aureus* (MRSA) was significantly higher than that for methicillin-susceptible *S. aureus* (MSSA) (11.8% vs. 5.1%; odds ratio [OR], 2.49; 95% confidence interval [CI], 1.46–4.24; $P < .001$). After adjustment for host variables, the OR decreased to 1.72 (95% CI, 0.92–3.20; $P = .09$). There was no significant difference between rates of disseminated infection (7.1% vs. 6.2% for MRSA-infected patients and MSSA-infected patients, respectively; $P = .63$), though the rate of death due to disseminated infection was significantly higher than death due to uncomplicated infection (37% vs. 10% for MRSA-infected patients [$P < .001$] and 37% vs. 3% for MSSA-infected patients [$P < .001$]). There was a strong statistical trend toward death due to nosocomial MRSA infection and bacteremia, compared with MSSA.**

Staphylococcus aureus is the most common cause of hospital-acquired infection [1] and contributes significantly to patient morbidity and mortality [2–4]. In the 1960s, shortly after the introduction of methicillin, methicillin-resistant *Staphylococcus aureus* (MRSA) was isolated from clinical specimens obtained from hospitalized patients [5]. In the 1970s and 1980s, small outbreaks of infection occurred that were caused by epidemic MRSA strains (EMRSA-1 and EMRSA-3), but these were controlled by screening, isolation, and topical decolonization of patients. A decade later, new epidemic strains EMRSA-15 and EMRSA-16 emerged, and, unlike before, these soon became endemic in most British hospitals [6]. In the United Kingdom, search-and-destroy policies failed, and MRSA guidelines were recently revised to emphasize control and risk management rather than eradication [7]. In 2000, prompted by a national audit highlighting the risk to patients from hospital infection [8], the Department of Health in Whitehall, London, introduced the mandatory reporting of MRSA bacteremia and later published "league tables" to compare the effectiveness of infection-control policies in different British hospitals [9].

Although patients rarely die of nosocomially acquired *S. aureus* bacteremia, whether due to MRSA or methicillin-susceptible *S. aureus* (MSSA), the organism possesses a variety of virulence factors, including adhesion molecules, cell wall peptidoglycan, extracellular enzymes, and toxins [10, 11]. With the exception of toxin-mediated disease, the relative importance of

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Reprints or correspondence: Dr. M. Melzer, Dept. of Microbiology, King George Hospital, Barley Lane, Goodmayes, Essex IG3 8XJ, England (Mark.Melzer@bhr.hospitals.nhs.uk).

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these virulence factors and their role in pathogenesis remains unclear. In vitro studies have demonstrated no difference in virulence between MRSA and MSSA [12–17], and clinical studies of bacteremic patients, limited by small sample sizes and retrospective data collection, give conflicting results [18–21]. The aim of the present study was 2-fold: first, to compare the incidence of mortality directly attributable to nosocomially-acquired MRSA and MSSA infection and bacteremia, and, second, to compare the incidence of disseminated or secondary site infection. The study was undertaken at Guy's and St. Thomas' Hospitals in south London, which serve a population of ~750,000 persons. In addition to general medical and surgical patients, these hospitals have large specialist units for intensive care, renal, oncological, hematological, and cardiothoracic surgical patients.

METHODS

From January 1995 through December 2000, adult patients (age, ⩾16 years) with nosocomial MRSA and MSSA bacteremia were seen on the ward by a clinical microbiologist and were managed in conjunction with their medical or surgical team. Patients with nosocomial infection (defined as infection acquired ⩾48 h after hospital admission) also included persons admitted from the community with intravascular devices, such as renal hemodialysis–dependent patients and some hematological and oncological patients. Data were collected prospectively, and data for patients with community-acquired bacteremia were excluded.

Medical and surgical teams were advised to treat confirmed or suspected MSSA infection with flucloxacillin. When MRSA infection was confirmed or suspected on the basis of colonization or isolation of MRSA from other sites, vancomycin was used with additional fusidic acid or gentamicin for disseminated infection. All intravascular catheters were removed, and surgeons were encouraged to review and, if necessary, debride surgical wounds. Patients were investigated for secondary sites of infection; those with infective endocarditis were considered for early valve replacement, and infected joints were washed out and paravertebral collections were drained. All blood isolates were considered clinically significant except for those obtained from a small number of dermatological patients with severe exfoliative skin disease (<10 patients). The automated blood culture system used was Vital (bioMérieux), and the Public Health Laboratory Service (PHLS) at Colindale, London, typed blood culture isolates.

The data, collected by 2 consultant microbiologists over the 6-year period, were age, sex, patient specialty at the time of the first episode of bacteremia, primary site of infection, secondary site(s) of infection, time from first positive blood culture to initiation of appropriate antimicrobial therapy, and patient outcome. Primary sites were classified as intravascular access sites (central or peripheral), wounds (sternal or nonsternal), lower respiratory tract, "other," or not known. Secondary sites were heart valves, vertebrae, joints, respiratory tract, "other," or not known. After discussion with attending medical or surgical teams and on the basis of clinical, microbiological, and, when performed, autopsy data, patient outcomes were classified as "died of infection," "died of causes other than infection," and "recovery." For all patients, time from first positive blood culture to death was, when available, retrospectively recorded.

Comparisons of outcomes between groups were made using the χ^2 test or, when numbers were small, Fisher's exact test. Risk of death due to infection was compared between patients with MRSA bacteremia and those with MSSA bacteremia using relative risks (RRs) and ORs, which were calculated by logistic regression and adjusted for age and other factors found to be related to overall mortality and death due to infection. In addition, adjusted rate ratios were calculated using Cox proportional hazard regression [22]. This was not used as the primary method of analysis, because date of death was unknown for 15 patients. In this analysis, these patients were treated as survivors until the last date that they were known to be alive. Times from first positive blood culture to receipt of appropriate antibiotic treatment were compared using the Wilcoxon rank sum test. Statistical significance was defined as $P < .05$.

RESULTS

During the period of 1995–2000, blood samples were obtained for culture from 46,580 adult patients with suspected clinical infection, and cultures for 4085 patients (8.8%) yielded clinically significant blood isolates. Sixty percent of patients with clinically significant blood cultures had nosocomially acquired infection; *S. aureus* accounted for 33% of cases (figure 1). Two hundred three MRSA blood isolates were typed, and >95% were found to be EMRSA-15 or EMRSA-16.

Patient characteristics are presented in table 1. In both groups of patients, primary sites of infection were predominantly intravascular access sites, and secondary sites were heart valves, vertebrae, and joints. Compared with the MSSA cohort, patients infected with MRSA were older and more often in the intensive care unit at the first episode of bacteremia, but fewer were renal unit patients who depended on hemodialysis. Sternal and nonsternal wounds were more common in MRSA-infected patients, and peripheral intravascular access sites were less common primary sites of infection, compared with MSSA-infected patients.

The proportion of bacteremic patients for whom death was attributable to MRSA infection was significantly higher than the proportion of bacteremic patients who died of MSSA infection (45 [11.8%] of 382 patients vs. 22 [5.1%] of 433 pa-

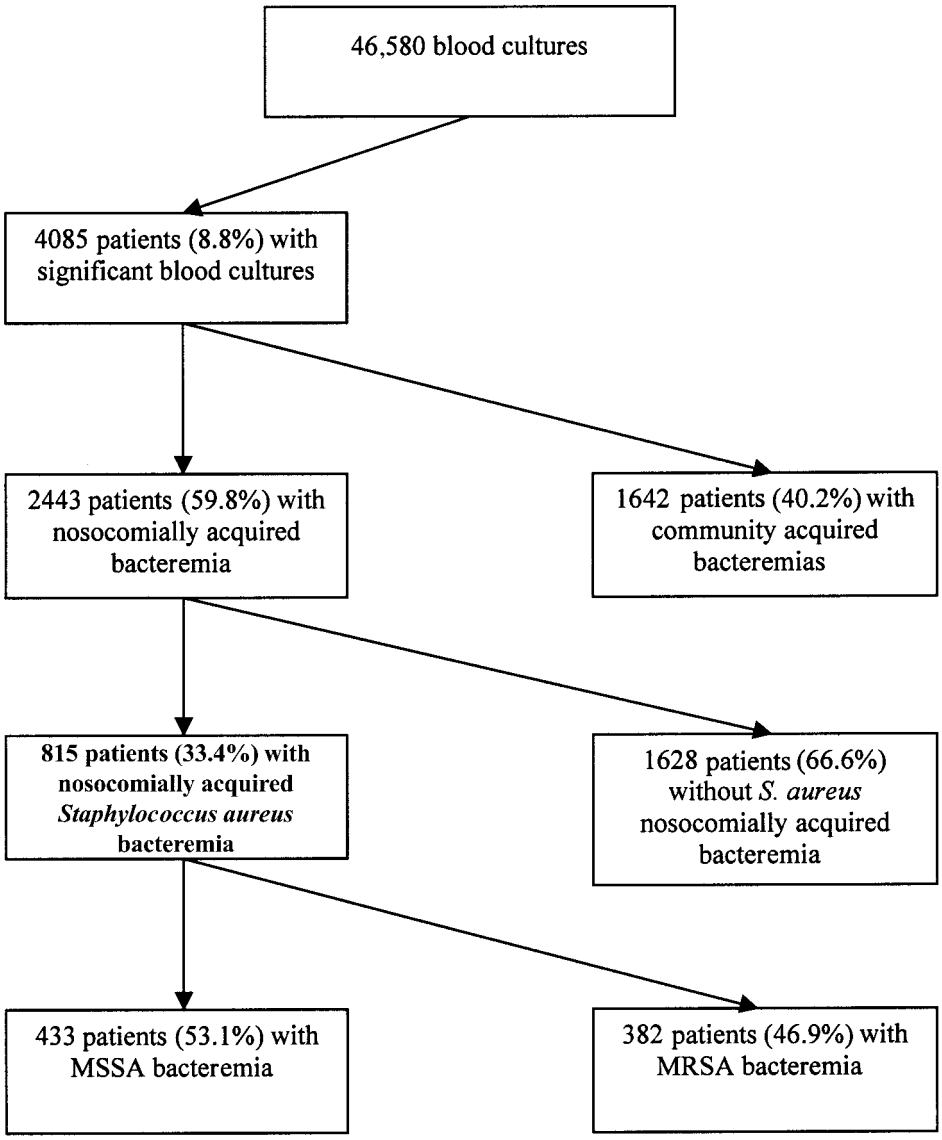

Figure 1. Results of cultures of blood samples obtained from adult patients (age, ⩾16 years) at Guy's and St. Thomas' Hospital, 1995–2000. MRSA, methicillin-resistant *Staphylococcus aureus;* MSSA, methicillin-susceptible *S. aureus.*

tients; RR, 2.32; 95% CI, 1.42–3.79; $P < .001$) (table 2). The rate of mortality attributable to infection increased with age and was related to hospital specialty at the time of the first episode of bacteremia and primary site of infection. After adjustment for age, the OR was 2.07 (95% CI, 1.21–3.56), and after adjustment for age, hospital specialty at the time of first bacteremia, and primary site of infection, the RR was not estimable, but the OR decreased to 1.72 (95% CI, 0.92–3.20; $P = .09$). Rate ratios, which were estimated by proportional hazard regression, were as follows: unadjusted rate ratio, 2.83 (95% CI, 1.67–4.80); and fully adjusted rate ratio, 1.80 (95% CI, 1.02–3.20; $P = .04$).

The mortality rate for patients with disseminated infection, regardless of whether death was due to MRSA or MSSA infection, was significantly higher than that for bacteremic patients without dissemination (MRSA-infected patients, 10 [37%] of 27 patients vs. 35 [9.9%] of 355 patients [$P < .001$]; MSSA-infected patients, 10 [37%] of 27 patients vs. 12 [3.0%] of 406 patients [$P < .001$]). There was no significant difference between the rate of dissemination of MRSA and of MSSA to secondary sites (27 [7.1%] 382 patients vs. 27 [6.2%] of 433 patients; 95% CI for difference, −2.6% to 4.3%; $P = .63$). Sternal wound infections, often involving mediastinitis, occurred most frequently in patients who died without disseminated infection, and infective endocarditis was the commonest cause of death among patients with disseminated infection.

One hundred two patients did not receive appropriate antimicrobial therapy. Among treated patients, the percentage

Table 1. Characteristics of patients with nosocomial *Staphylococcus aureus* bacteremia.

Characteristic	MRSA-infected patients (n = 382)	MSSA-infected patients (n = 433)	P
Age, years			<.001
16–29	12 (3.1)	35 (8.1)	
30–49	63 (16.5)	110 (25.4)	
50–70	156 (40.8)	177 (40.9)	
>70	151 (39.5)	111 (25.6)	
Sex			.25
Male	219 (57.3)	304 (70.2)	
Female	163 (42.7)	129 (29.8)	
Patient specialty at the time of the first episode of bacteremia			<.001
Medical			
Renal			
Hemodialysis-dependent patients	63 (16.5)	146 (33.7)	
Non–hemodialysis-dependent patients	5 (1.3)	8 (1.8)	
Oncology	17 (4.5)	41 (9.5)	
Hematology	12 (3.1)	17 (3.9)	
Other	78 (20.4)	122 (28.2)	
Surgical			
Cardiothoracic	41 (10.7)	43 (9.9)	
Orthopedic	8 (2.1)	10 (2.3)	
Other	53 (13.9)	23 (5.3)	
Intensive care	105 (27.5)	23 (5.3)	
Primary site of infection			.002
Intravascular catheter			
Central	157 (41.1)	173 (40.0)	
Peripheral	34 (8.9)	79 (18.2)	
Wound			
Sternal	32 (8.4)	26 (6.0)	
Nonsternal	36 (9.4)	28 (6.5)	
Other	23 (6.0)	32 (7.4)	
Not known	100 (26.2)	95 (21.9)	
Secondary site of infection			.02[a]
Heart valve			
Native	9 (2.4)	11 (2.5)	
Prosthetic	5 (1.3)	1 (0.2)	
Vertebral column	6 (1.6)	9 (2.1)	
Peripheral joints			
Native	6 (1.6)	0 (0)	
Prosthetic	7 (1.7)	0 (0)	
Other	1 (0.3)	3 (0.7)	

NOTE. Data are no. (%) of patients, unless otherwise indicated. MRSA, methicillin-resistant *S. aureus;* MSSA, methicillin-susceptible *S. aureus.*

[a] Determined by Fisher's exact test.

Table 2. Clinical outcomes for patients with nosocomial *Staphylococcus aureus* bacteremia, with or without disseminated infection.

Outcome group	MRSA-infected patients	MSSA-infected patients	Relative risk (95% CI)	OR (95% CI)	*P*
Patients who recovered	269/382 (70.4)	374/433 (86.4)	…	…	
Patients who died of other causes	68/382 (17.8)	37/433 (8.5)	…	…	
Patients who died of infection	45/382 (11.8)	22/433 (5.1)	2.32 (1.42–3.79)	2.49 (1.46–4.24)	<.001
Patients with bacteremia and disseminated infection					
All patients	27/382 (7.1)	27/433 (6.2)	1.14 (0.66–1.99)	…	.63
Patients who died	10/27 (37)	10/27 (37)	1.0 (0.5–2.0)	…	1.0
Site of dissemination in patients who died					
Heart valves	8	4	…	…	
Vertebrae	0	2	…	…	
Joints	1	2	…	…	
Other	1	2	…	…	
Patients with bacteremia and without disseminated infection					
All patients	355/382 (92.9)	406/433 (93.8)	…	…	
Patients who died of infection	35/355 (9.9)	12/406 (3.0)	3.34 (1.76–6.33)	…	<.001
Primary site of infection in patients who died					
Wounds					
Sternal	12	6	…	…	
Nonsternal	9	1	…	…	
Intravascular catheter					
Central	4	2	…	…	
Peripheral	1	0	…	…	
Other or not known	9	3	…	…	

NOTE. Data are no. of patients with outcome/total no. patients (%), unless otherwise indicated. MRSA, methicillin-resistant *S. aureus;* MSSA, methicillin-susceptible *S. aureus.*

who died of infection was 8.3%, compared with 7.0% of untreated patients (95% CI for difference in percentages, −7.6% to 5.0%; $P = .71$). Mean and median times to initiation of treatment were longer for MRSA-infected patients than for MSSA-infected patients (table 3). However, there was not a statistically significant relationship between death due to infection (as determined by logistic regression analysis) or rate of death (as determined by Cox regression analysis) and time to initiation of appropriate antimicrobial therapy. For appropriately treated patients, the OR for death for MRSA-infected patients versus MSSA-infected patients, after adjustment for age, hospital specialty at the time of the first episode of bacteremia, and primary site of infection, was 2.08 (95% CI, 1.08–4.02); after additional adjustment for delay in initiation of antimicrobial therapy, the OR was 2.01 (95% CI, 1.03–3.91). The corresponding rate ratios were 2.25 (95% CI, 1.22–4.15) and 2.19 (95% CI, 1.78–4.08), respectively.

DISCUSSION

This is the first large study from the United Kingdom to assess by clinical criteria the virulence of MRSA versus MSSA in bacteremic patients after adjustment for host variables. Patients with community-acquired *S. aureus* bacteremia were excluded from the study to avoid bias, as most community-acquired infections are methicillin susceptible and, compared with nosocomial infection, more frequently associated with disseminated infection, shock, and worse clinical outcome. Unlike other studies, primary and secondary sites of infection were defined, and specific primary sites, such as surgical wounds, were found to be associated with death due to infection. We also prospectively determined whether patients died as a direct result of infection or of other causes. Failure to exclude death due to other causes might also have biased our results because more MRSA-infected patients died of causes other than infection. Also, most MRSA isolates recovered from blood were EMRSA-15 and EMRSA-16, the most prevalent strains in the United Kingdom, so these results are likely to reflect rates of mortality associated with MRSA infection and bacteremia in other British hospitals.

Our results, which demonstrated a higher relative rate of death due to infection in patients with nosocomial MRSA bacteremia, could have been confounded by host variables. The 2 cohorts were not matched by age, and elderly patients with

Table 3. Time from first episode of *Staphylococcus aureus* bacteremia to initiation of appropriate antimicrobial therapy.

Variable	Patients with nosocomial MRSA bacteremia	Patients with nosocomial MSSA bacteremia	P[a]
Death due to infection in patients who received appropriate antibiotic therapy			
No. of patients	12	19	
Time from first episode of bacteremia to initiation of appropriate antibiotic therapy, days			
Mean	1.79	1.21	
Median	2	0	.012
Death due to other causes in patients who received appropriate antibiotic therapy	51	32	
No. of patients	51	32	
Time from first episode of bacteremia to initiation of appropriate antibiotic therapy, days			
Mean	2.47	0.69	
Median	1	0	.023
Recovery in patients who received appropriate antibiotic therapy	242	357	
No. of patients	242	357	
Time from first episode of bacteremia to initiation of appropriate antibiotic therapy, days			
Mean	1.62	0.67	
Median	1	0	<.0001

NOTE. MRSA, methicillin-resistant *S. aureus;* MSSA, methicillin-susceptible *S. aureus.*

[a] Determined by Wilcoxon rank sum test.

MRSA or MSSA bacteremia have higher mortality rates than do younger patients [23]. After adjustment for age, the difference in mortality rates remained statistically significant; however, after further adjustment for hospital specialty at the time of the first episode of bacteremia and primary site of infection, the OR decreased from 2.07 to 1.72. We did not adjust further for other less easily measurable host variables, such as severity of illness and comorbidities on admission to the hospital, as adjustment made for the specialty unit at the time of the first episode of bacteremia, such as intensive care, indirectly reflects the severity of illness and likelihood of comorbidities. Also, in a recent meta-analysis [24], the association between MRSA bacteremia and mortality persisted even when more specific severity of illness adjustments were made. The likeliest explanation is that patients with MRSA and MSSA nosocomial infection and bacteremia have similar severities of illness and that more-specific adjustments seem unlikely to have further reduced our calculated OR for mortality.

One possible explanation for our observed difference in virulence, as measured by clinical outcomes, might have been the greater propensity of MRSA to disseminate to secondary sites. Patients with disseminated infection had high rates of mortality, which were significantly different than the rates for patients without disseminated infection ($P < .001$). If MRSA is more virulent than MSSA, and if adherence factors are important determinants of virulence, then MRSA might have had a greater tendency to adhere to and cause infection at secondary sites. Although in vitro experiments have demonstrated that different types of MSSA have different tendencies to adhere to bone [25] and heart valves [26], our clinical study suggests that adherence factors do not substantially differ between MRSA and MSSA. Therefore, adherence factors seem unlikely to explain the difference in mortality we observed between the 2 groups of patients.

The timing and effect of different antibiotics regimens on patient outcomes might also have explained this observed difference. Some patients died before antibiotics could be administered, and others refused antibiotic therapy or had been discharged from the hospital before blood culture results became positive. Also, in some cases, no antimicrobials were given because removal of an intravascular catheter had already resulted in clinical improvement. Because of unanticipated resistance, patients with MRSA infection experienced more delays in receiving antimicrobial therapy, although these delays were not significant, and the majority of patients received appropriate treatment within 48 h of their first clinically significant blood culture result. With regard to the effect of different antibiotic regimens, there is in vitro evidence that vancomycin is less

bactericidal than β-lactam antibiotics [27]. Also, therapeutic levels of vancomycin were not always achieved, and vancomycin tolerance, which was not specifically determined for these MRSA isolates, is well described [28]. Therefore, it is not clear whether these factors could have facilitated dissemination or led to a worse prognosis in MRSA-infected patients, although we found no significant difference in the rates of death due to infection in patients treated appropriately with antimicrobials, compared with patients who were not treated with antimicrobial therapy.

The importance of central and peripheral intravascular catheters access sites as a primary site of MRSA or MSSA infection, as described elsewhere [29], is highlighted by this study. All intravascular catheters with associated erythema and induration should be removed [30], and we also advocate their removal when there is heavy colonization with *S. aureus* at access sites. Sternal wound infections, which are often associated with mediastinitis and high rates of mortality [31, 32], were the most common cause of death among patients without disseminated infection. The prevalence of sternal wound infections was highest in the MRSA-infected cohort, and some of the deaths were potentially preventable by preoperative screening for MRSA colonization, attention to sterile techniques, and by minimizing the risk of MRSA cross-infection postoperatively [33].

Because vertebrae, joints, and heart valves were common secondary sites of infection, patients with MRSA or MSSA bacteremia should be assessed to determine whether infection is present at these sites. Patients with infective endocarditis should be considered for early valve replacement, because clinical studies demonstrate that this increases the chances of survival [34]. Patients with vertebral infection may have associated paravertebral abscesses that require drainage, and patients with infected *S. aureus* joints require washouts, sometimes repeatedly. What remains unclear is the timing of dissemination in relation to primary bacteremia, because even removal of an infected intravascular catheters, surgical debridement of a wound, and prompt administration of appropriate antimicrobials sometimes fail to prevent dissemination. Current recommendations are that uncomplicated *S. aureus* bacteremia should be treated for $\geqslant$1 week and that complicated infection should be treated longer [35], but whether the duration of these antibiotic regimens is sufficient to prevent or treat early secondary site infection remains undetermined.

This study demonstrated a strong statistical trend toward attributable death due to infection in patients with nosocomial MRSA bacteremia, compared with MSSA bacteremia, in the United Kingdom. Both groups of patients had a similar incidence of dissemination. Additional studies to identify new EMRSA-15 and EMRSA-16 virulence factors and prospective, randomized, control trials to assess the efficacy and duration of different antibiotic regimes in well-matched cohorts of patients are necessary. Meanwhile, efforts to limit the spread of MRSA, particularly among patients with intravascular catheters and surgical wounds, should be intensified.

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