Comparing the Epidemiology and Health Burden of Lyme Disease and Babesiosis Hospitalizations in the United States

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Background. Lyme disease (LD) and babesiosis are increasing in the United States. We sought to characterize and compare their epidemiology and health burden using a nationally representative sample of hospitalizations.

Methods. Data were extracted from the National Inpatient Sample (NIS) pertaining to LD and babesiosis for 2018 and 2019. The NIS is a comprehensive database of all-payer inpatient hospitalizations, representing a stratified systematic random sample of discharges from US hospitals. Patient demographics, clinical outcomes, and admission costs were evaluated, in addition to hospital-level variables (eg, location/teaching status and census division). Annual incidence of hospitalizations was calculated using US Census Bureau data.

Results. The annual incidence of hospitalizations of LD-related and babesiosis-related hospitalizations were 6.98 and 2.03 per 1 000 000 persons/year. Of the 4585 LD hospitalizations in 2018–2019, 60.9% were among male patients, 85.3% were White, and 39.0% were ≥60 years; 70.0% of LD and 91.7% of babesiosis hospitalizations occurred in Middle Atlantic or New England. Lower disease severity was noted in 81.8% of LD hospitalizations compared with 49.3% of babesiosis hospitalizations, whereas those suffering from high severity were 2.3% and 6.0%, respectively. The mean hospital charges for LD and babesiosis hospitalizations were $33 440.8 and $40 689.8, respectively.

Conclusions. Despite overlap between the 2 diseases, LD has a broader geographic range and a greater number of hospital admissions, whereas babesiosis is more severe, incurring longer hospital stays, higher inpatient costs, and deaths.

Keywords. babesiosis; database; epidemiology; hospitalization; Lyme disease.

Lyme disease (LD) is the leading vector-borne illness in the United States and is caused primarily by the spirochete Borrelia burgdorferi [1]. Common acute manifestations include erythema migrans (EM) “bull’s eye” rash and flu-like symptoms such as fever, chills, headache, fatigue, myalgia, arthralgia, and lymphadenopathy. Lyme disease can also lead to arthritis, carditis, and a host of neurological sequelae, including cranial nerve palsy, lymphocytic meningitis, and radiculitis [2].

Babesia is a genus of intraerythrocytic protozoan parasites that cause babesiosis. Babesia microti, the most common species causing babesiosis in humans, is highly endemic in the Northeast and upper Midwest United States, and it has a shared tick vector (Ixodes scapularis). The geographic distribution of human B microti infection overlaps that of B burgdorferi infection but is not as widespread [3]. The pathology and clinical manifestations of babesiosis are similar to those of Plasmodium (malaria), a related intraerythrocytic protozoan. Symptomatic infection causes hemolytic anemia and complications that include cardiac, respiratory, and renal, failure [4]. Persistent parasitemia is well described and may last months to years after acquisition, leading to relapsing disease, which is mostly seen in immunocompromised hosts [5]. Several species of Babesia are also readily transfusion-transmissible, and immune intact individuals with chronic asymptomatic infection may donate blood, conferring a high risk of morbidity and mortality in transfusion recipients [6].

Reported cases of LD and babesiosis have been shown to be increasing in the United States [4, 7–9]. The estimated incidences vary widely, in part reflecting differences in the sampling methods that have been used. Analysis of a commercial insurance claims database representing greater than 25 million US residents less than 65 years of age revealed an increase in the
incidence of LD from 49.1/100,000 in 2010 to a high of 87.9/100,000 enrollees in 2017 [9]. This was markedly higher than that reported through public health surveillance, yielding a median annual incidence of LD among those <65 years of age of 9.3 cases/100,000 population. Similarly, there has been an observed increase in cases of babesiosis [4, 7, 8]. Despite the importance of LD and babesiosis to public health, a paucity of studies have directly compared the health burden of these 2 diseases [10–13]. Accordingly, we sought to characterize and compare their recent epidemiology and health burden in the United States using a nationally representative sample of hospitalizations.

METHODS

Data Source

The National Inpatient Sample (NIS) is the most comprehensive database of all-payer inpatient hospitalizations in the United States and was developed as part of the Healthcare Cost and Utilization Project (HCUP) by the Agency for Healthcare Research and Quality (AHRQ). The NIS is a stratified systematic random sample of discharges. The sample unit was a 20% stratified sample of discharges from US hospitals, covering approximately 98% of the US population in 2018 and 2019. The NIS systematically selected a stratified random sample from a list of discharges and sorted on characteristics, including diagnosis-related group (DRG) and admission month. Hospitals were stratified based on census division, location, teaching status, ownership, and bed size. Each record in NIS represented 1 inpatient hospital discharge, and a patient could be included more than once. Each observation included both patient-level and hospital-level data. Patient-level variables included demographics (age, sex, race), clinical outcomes (all patient-refined diagnosis-related group [APRDRG] severity, mortality, length of stay, total charges), and up to 40 International Classification of Diseases, Tenth Revisions, Clinical Modification (ICD-10-CM) diagnosis codes, and up to 25 ICD-10-CM procedure codes. Hospital-level variables include location/teaching status and census division. Survey weights to generate national estimates were provided by HCUP. The APRDRG was developed by 3M Health Information Systems, and it categorizes severity of illness into 4 subclasses: (1) minor loss of function (includes cases with no comorbidity or complications), (2) moderate loss of function, (3) major loss of function, (4) extreme loss of function [14]. The APRDRG severity 1 and 2 are considered low-risk classes, and 3 and 4 are high-risk groups.

Study Population

Two years of data (2018–2019) from the NIS were included in the primary analysis. The primary outcomes of the analysis were LD- and babesiosis-associated hospitalizations. Each record’s primary (first) ICD-10-CM diagnosis code was used to identify hospitalizations associated with the 2 tickborne diseases. Lyme disease was identified by ICD-10 code A69.2X and babesiosis was defined by B60.0X. The tickborne disease-related hospitalizations and co-infections were identified using the secondary (2nd to 40th) ICD-10-CM diagnosis codes. In a secondary analysis, data using ICD-10 codes from 2015 Q4 to 2019 Q4 were included to visualize monthly trends of tickborne disease hospitalizations in the United States. United States population and subgroup population data of July 1, 2019 were retrieved from the US Census Bureau to calculate the annual incidence of tickborne disease-related hospitalizations in the US population.

Table 1. Annual Incidence of Hospitalizations (95% Confidence Interval) of Lyme Disease and Babesiosis per 100,000 Population in the United States From 2018 to 2019

| Characteristics          | Lyme Disease | Babesiosis |
|--------------------------|--------------|------------|
| Overall                  | 6.98 (6.55–7.42) | 2.03 (1.77–2.28) |
| Sex                      |              |            |
| Male                     | 8.63 (7.96–9.30) | 2.97 (2.54–3.40) |
| Female                   | 5.39 (4.84–6.03) | 1.11 (0.83–1.40) |
| Age                      |              |            |
| <18                      | 6.50 (5.30–7.70) | 0.04 (0.00–0.11) |
| 18–29                    | 4.10 (3.21–4.98) | 0.28 (0.03–0.52) |
| 30–39                    | 5.21 (4.18–6.24) | 0.45 (0.14–0.77) |
| 40–49                    | 5.52 (4.44–6.60) | 0.81 (0.37–1.24) |
| 50–59                    | 7.32 (6.02–8.62) | 2.48 (1.71–3.25) |
| ≥60                      | 11.99 (10.74–13.25) | 6.60 (5.63–7.56) |
| Race*                    |              |            |
| White                    | 7.80 (7.27–8.34) | 2.10 (1.80–2.39) |
| Black                    | 1.76 (1.17–2.35) | 0.57 (0.22–0.92) |
| Census Division of Hospital |            |            |
| New England              | 35.53 (30.52–40.55) | 19.20 (15.56–22.84) |
| Middle Atlantic          | 26.19 (23.46–28.93) | 7.90 (6.38–9.42) |
| East North Central       | 5.06 (4.69–5.44) | 0.27 (0.04–0.50) |
| West North Central       | 6.07 (4.99–7.14) | 1.17 (0.58–1.75) |
| South Atlantic           | 3.27 (2.82–3.72) | 0.23 (0.05–0.40) |
| East South Central       | 1.69 (1.17–2.22) | 0     |
| West South Central       | 0.37 (0.37–0.37) | 0     |
| Mountain                 | 0.50 (0.30–0.70) | 0.10 (0.00–0.30) |
| Pacific                  | 0.84 (0.84–0.84) | 0     |

NOTES: Annual incidence of hospitalizations was calculated using number of hospitalizations × subgroup population of July 1, 2019 = 2 × 100,000 and was rounded to 2 decimal places.

Subgroup population of July 1, 2019 was retrieved from US Census Bureau: Annual Estimates of the Resident Population for the United States, Regions, States, and Puerto Rico: July 1, 2010 to July 1, 2019 (NST-EST2019-01), Population Division, US Census Bureau (https://www.census.gov/data/tables/time-series/demo/popest/2010s-state-total.html). A categorization of race restricted to those races depicted in the table given differences between Healthcare Cost and Utilization Project (HCUP) and Census Bureau.

Statistical Analysis

All statistical analyses were conducted in Stata/MP version 15.1 (StataCorp, College Station, TX) and R version 4.1.0 (R Core Team, Vienna, Austria). The national estimates of tickborne disease hospitalizations were calculated using svy command in Stata and incorporated sampling weights provided by HCUP. Taylor series linearization was used to estimate variance. The annual incidence of hospitalizations was computed using the number of tickborne diseases hospitalizations.
divided by 2 times the US population on July 1, 2019 derived from the US Census Bureau. Among the tickborne disease hospitalizations in 2018–2019, the distribution of characteristics and clinical outcomes were compared between LD and babesiosis-associated hospitalizations. \(P\) values were calculated using Rao-Scott design-adjusted \(\chi^2\) tests for categorical variables and \(F\) tests for continuous variables. A 2-tailed \(P < .05\) was considered statistically significant.

**Patient Consent Statement**

The Johns Hopkins Medical Institutions Institutional Review Board deemed the study exempt from review because the NIS is a deidentified, publicly available dataset. The HCUP data use agreement guidelines were followed in this analysis.

**RESULTS**

The annual incidence of hospitalizations for LD and babesiosis was 6.98 and 2.03/1,000,000 persons/year, respectively, from 2018 to 2019. Differences in incidence were observed by sex, age, race, location/teaching status, and census division (region) of the admitting hospitals (Table 1). Incidence of hospitalization was seasonal for LD and babesiosis with peaks in the summer and nadir in winter months (Figure 1).

During the study’s observation period (2018–2019), there were 4585 hospitalizations in which LD was listed as the primary diagnostic code (Table 2). Most hospitalizations were among patients who were male \((n = 2790, 60.9%)\), White \((n = 3910, 85.3\%)\), and either \(\leq 18\) years \((n = 900, 19.6\%\) or \(\geq 60\) years \((n = 1709, 39.0\%)\). The 3 highest regions for LD-associated hospitalizations were Middle Atlantic \((n = 2155, 47.0\%)\), New England \((n = 1055, 23.0\%)\), and East North Central \((n = 475, 10.4\%)\), and most hospitalizations \((n = 3455, 75.4\%)\) occurred in urban teaching hospitals.

There were 1330 hospitalizations in which babesiosis was listed as the primary diagnostic code. As with LD, most hospitalizations were among male \((n = 960, 72.2\%)\) and White \((n = 1050, 78.9\%)\) patients. Unlike LD, very few babesiosis hospitalizations were among patients who were children \((<18\) years), and a higher percentage were \(\geq 60\) years \((n = 985, 74.1\%)\). Most babesiosis-associated hospitalizations occurred in the Middle Atlantic \((n = 650, 48.9\%)\) or New England states \((n = 570, 42.9\%)\) and most occurred in urban teaching hospitals \((n = 980, 73.7\%)\). Characteristics of LD and babesiosis-associated hospitalizations are provided stratified by geographic census region (Supplementary Table 1).

In 1.9% of LD-associated hospitalizations, babesiosis was listed as a secondary (ie, codiagnosis) diagnosis. By contrast, 23.7% of babesiosis-associated hospitalizations listed LD as a secondary (ie, codiagnosis) diagnosis (Table 3). The APRDRG disease severity scores were 1 and 2 in 3750 \((81.8\%)\) hospitalizations for LD, whereas 2.3% \((n = 105)\) were scored as 4 (Table 4). In babesiosis-associated hospitalizations, 90.6% \((n = 1205)\) were scored as APRDRG 2 and 3% and 6.0% \((n = 40)\) were scored as

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**Figure 1.** Monthly temporal trends in tickborne disease-related hospitalizations in the United States between 2015 Q4 and 2019 Q4. Note: Number of US population of first for each month from October 2015 to December 2019 was retrieved from US Census Bureau: Annual Estimates of the Resident Population for the United States, Regions, States, and Puerto Rico: July 1, 2010 to July 1, 2019 (NST-EST2019-01), Population Division, US Census Bureau (https://www.census.gov/data/tables/time-series/demo/popest/2010s-state-total.html). The population rate (incidence) of hospitalizations was calculated using number of LD or babesiosis hospitalizations divided by 2 times the US population on July 1, 2019.
DISCUSSION

Analysis of the National Inpatient Sample offers contemporary insight into the epidemiology, clinical, and economic burden of LD and babesiosis in the United States. The patient demographic of hospitalized patients with either disease was predominantly White, male, and focused in the New England and the Middle-Atlantic regions. There was a well defined seasonal incidence in hospitalizations, predictably aligning with known transmission characteristics from the life cycle of the shared Ixodid tick vector. Hospitalizations represent an appreciable health burden for both diseases, which were greater for babesiosis in terms of individual disease severity, length of stay, and associated per hospital costs but less in regard to number of hospital admissions. Babesiosis-associated hospitalizations had a higher index of severity than LD, with half of babesiosis hospitalizations reporting a severity score of 3 or greater compared with only one fifth of LD hospitalizations. Greater babesiosis disease severity caused a longer average length of stay and higher per-patient admission costs. Although in-hospital deaths were higher in those with babesiosis, the mortality was low in both groups (less than 1%). The babesiosis fatality rate has previously been reported from 2% to 9% in hospitalized patients. It has ranged from 4% to 27% among those who are immunosuppressed, such as those with asplenia, malignancy, human immunodeficiency virus/acquired immune deficiency syndrome, and immunosuppressive therapy or who have acquired the disease through blood transfusion [15–19]. The disparity in mortality rates for hospitalized babesiosis patients in our study and past studies is unclear but may reflect advancements in critical care, and/or earlier diagnosis through greater disease awareness.

The age difference is a possible cause of increased disease severity among babesiosis patients. Almost all (95%) babesiosis admissions were aged 40 years or greater and 75% were 60 years or greater, compared with 62% and 39%, respectively, of LD patients. Advanced age is a known risk factor for severe babesiosis, whereas children generally experience asymptomatic or mild symptomatic infection [20]. Although age may be an independent risk (eg, through immune senescence), there are associated comorbid risk factors (eg, cardiorespiratory disease, malignancies, anemia, and blood transfusions) that also place older patients at greater risk of complications. By contrast, LD—as was reflected by this hospitalized population—has a bimodal age distribution. One contributing factor that may place the young and elderly at increased risk is the inability to see and remove ticks. Nymphal ticks are tiny and readily go unnoticed, especially in children and older adults. One study demonstrated that B. microti seroreactivity rates were not significantly different between those who did and did not report tick bites [21].

Almost all Babesia hospitalizations (~92%) occurred in New England and Mid-Atlantic regions, whereas hospitalizations for LD reflect a broader distribution, whereby nearly one fifth of LD-associated hospitalizations originated in East North Central and South Atlantic regions. This is consistent with prior reports of LD expansion in the Southeastern United States [22]. Concern for continued expansion, particularly of LD, has been observed elsewhere (eg, to the north, Canada) [23]. Indeed, in an analysis of a large commercial insurance database, one quarter of all US residents lived in a state deemed to have high incidence of LD [9]. There was also a difference in the proportion of rural hospitalizations for

### Table 2. Characteristics of Tickborne Diseases Hospitalizations in the United States From 2018 to 2019 in the National Inpatient Sample

| Characteristics                                         | Lyme Disease, n (%) | Babesiosis, n (%) | *P* Values |
|----------------------------------------------------------|---------------------|-------------------|------------|
| **Sex**                                                  |                     |                   |            |
| Male                                                     | 2790 (69.0)         | 960 (72.2)        | .002       |
| Female                                                   | 1795 (39.1)         | 370 (27.8)        |            |
| **Age**                                                  |                     |                   |            |
| < 18                                                     | 900 (19.6)          | *               | <.001      |
| 18–29                                                    | 370 (8.1)           | *               |            |
| 30–39                                                    | 460 (10.0)          | *               |            |
| 40–49                                                    | 445 (9.7)           | 65 (4.9)         |            |
| 50–59                                                    | 620 (13.5)          | 210 (15.8)       |            |
| ≥ 60                                                     | 1790 (39.0)         | 985 (74.1)       |            |
| **Race**                                                 |                     |                   |            |
| White                                                    | 3910 (85.3)         | 1050 (78.9)       | .001       |
| Black                                                    | 155 (3.4)           | 50 (3.8)         |            |
| Hispanic                                                 | 175 (3.8)           | 95 (7.1)         |            |
| Asian or Pacific Islander                                | *                   | 50 (3.8)         |            |
| Other                                                    | 155 (3.4)           | 60 (4.5)         |            |
| **Location/Teaching Status of Hospital**                 |                     |                   |            |
| Rural                                                    | 465 (10.1)          | 85 (6.4)         | .034       |
| Urban nonteaching                                        | 665 (14.5)          | 265 (19.9)       |            |
| Urban teaching                                           | 3455 (75.4)         | 980 (73.7)       |            |
| **Census Division of Hospital**                          |                     |                   |            |
| New England                                              | 1055 (23.0)         | 570 (42.9)       | <.001      |
| Middle Atlantic                                           | 2155 (47.0)         | 650 (48.9)       |            |
| East North Central                                       | 475 (10.4)          | *               |            |
| West North Central                                       | 260 (5.7)           | 50 (3.8)         |            |
| South Atlantic                                            | 430 (9.4)           | *               |            |
| East South Central                                       | 65 (1.4)            | 0                |            |
| West South Central                                       | *                   | 0                |            |
| Mountain                                                 | *                   | *                |            |
| Pacific                                                  | 90 (2.0)            | 0                |            |

NOTES: Categorical variables were presented in n (%). Column percentages may not sum to 100% due to missingness. *P* values were calculated using Rao-Scott design-adjusted *χ*² tests.

*Weighted numbers <50 were suppressed per HCUP guidelines to avoid the identification of individuals.

4, and the difference of APRDRG severity was statistically significant (*P* < .001). Deaths were <1% for both LD and babesiosis.

The mean hospital charges were $33440.8 and $40689.8 for LD and babesiosis-associated hospitalizations, respectively, and mean lengths of stay were 3.8 and 4.5 days, respectively (Table 4).
both diseases transpired in urban teaching hospitals. Only 6% of babesiosis-associated admissions occurred in rural hospitals. There are several possible explanations, including difficulty of diagnosis, which may prompt referral to tertiary level expertise for diagnosis and management. Babesiosis presents as an undifferentiated febrile illness. Complications of LD such as neurologic and rheumatologic sequelae mimic a host of other conditions that affect the nervous system and the joints.

Estimates of reported coinfection (eg, between B burgdorferi and B microti) are known to vary substantially. Almost one quarter (23.7%) of babesiosis-associated hospitalizations in our study were noted to have a codiagnosis of LD. By contrast, we noted a much lower proportion of LD-associated hospitalizations with a codiagnosis with babesiosis (1.9%). Prior reports suggest that 9% (range, 2%–12%) of LD patients are coinfected with Babesia, whereas 33% (range, 2%–72%) of patients with babesiosis are coinfected with B burgdorferi [4, 24–29]. Several factors may account for the observed variability. For one, studies of co-infection are relatively few and differ with respect to sample size, case definition (eg, clinical disease vs serologic evidence of pathogen exposure), methods of ascertainment (serological surveillance vs clinical case reporting), the test methods in use (serology vs molecular testing vs symptom review), and—pertinent to our study—the sampling location(s). Specifically, the scope of sampling between studies in national versus regional datasets are likely to impact the estimates. A national dataset is expected to yield much lower rates of coinfection with babesiosis given that sampling includes areas where Babesia is known to be rare if not entirely absent. By contrast, regional studies of babesiosis select for areas (eg, New England) where LD is highly endemic, thus yielding estimates that approximate what was observed in our national database analysis. Although coinfection between B burgdorferi and B microti (and vice versa) may influence disease severity, the data are limited. Three studies have reported an increase in the number of symptoms and/or longer duration of illness in patients with LD and a codiagnosis of babesiosis than those with LD alone [24–26]. Conversely, patients with babesiosis and a codiagnosis with LD have shown no change or fewer symptoms than those with babesiosis alone [24, 25].

The study’s limitations are not unique and have been described in the context of similar analyses [4]. For one, the NIS focuses on hospitalized cases, selecting patients with the most severe disease. The latter is only a small proportion of the overall disease burden that includes cases managed in ambulatory settings [5]. Although the study of hospitalized patients has previously been validated and proven robust [30, 31], the NIS does not capture all pediatric patients. Another limitation is the inability to distinguish between unique and readmissions; however, readmission for babesiosis is very uncommon. In a cohort of 163 patients with babesiosis, only 1 patient (<1%) underwent repeat hospitalization [28]. The rates of readmission for LD are uncertain. However, although readmission is plausible given the spectrum of disease and treatment-related complications, this is thought to be uncommon. Another potential limitation is the assumption that primary diagnosis is indeed the major reason for hospitalization rather than a comorbid diagnosis.

### Table 4. Severity and Cost of Tickborne Diseases Hospitalizations in the United States From 2018 to 2019 in the National Inpatient Sample

| Characteristics | Lyme Disease | Babesiosis | P Value |
|-----------------|--------------|------------|---------|
| APDRG Severity$ |              |            |         |
| 1               | 1560 (33.8)  | *          | <.001   |
| 2               | 2200 (48.0)  | 610 (45.9) |         |
| 3               | 730 (15.9)   | 595 (44.7) |         |
| 4               | 105 (2.3)    | 80 (6.0)   |         |
| Died during hospitalization | | | |
| Alive           | 4580 (99.9)  | 1320 (99.2) | .066 |
| Died            | *            | *          |         |
| Length of stay, days | 3.8 (0.1)    | 4.5 (0.2)  | .001   |
| Total charges$  | 33440.8 (1284.0) | 40689.8 (2725.7) | .014 |

Abbreviations: APDRG, patient-refined diagnosis-related group.

NOTES: Categorical variables were presented in n (%) and continuous variables were presented in mean (standard deviation). P values of categorical variables were calculated using Rao-Scott design-adjusted $\chi^2$ tests, and continuous variables were calculated using design-adjusted Wald tests.

*Weighted numbers <50 were suppressed per Healthcare Cost and Utilization Project guidelines to avoid the identification of individuals.

$All$ APDRG severity of illness subclass: (0) no class specified, (1) minor loss of function (includes cases with no comorbidity or complications), (2) moderate loss of function, (3) major loss of function, (4) extreme loss of function. The APDRG classes 1 and 2 are considered low risk and classes 3 and 4 are considered high risk.
for both infections appear uncommon. Despite overlapping features, LD has a broader geographic range and a bimodal age distribution, unlike severe babesiosis that is largely restricted to those over 50 years of age. As the burden of tickborne illnesses increases, proactive, environmental surveillance is imperative with increased sampling of tick populations, especially in regions that are situated on the known fringes of endemic areas. Such an approach can help to alert clinicians to the possibility of infections in their patients. Human serosurveillance and reservoir host surveillance are also useful but are more challenging. Not all states are compelled to report data (eg, babesiosis), thus accounting for an incomplete assessment of the burden of disease. Nonetheless, there are innovative examples of regional reporting, which may be used to characterize the expansion of tickborne pathogens [32].

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.

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Disclaimer. Any views or opinions that are expressed in this manuscript are those of the author’s, based on his own scientific expertise and professional judgment; they do not necessarily represent the views of either the Blood Products Advisory Committee or the formal position of US Food and Drug Administration (FDA), and they also do not bind or otherwise obligate or commit either Advisory Committee or the Agency to the views expressed.

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