Macrolide Resistance in Bacteremic Pneumococcal Disease: Implications for Patient Management

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Background. Despite pneumococcal antibiotic resistance rates in excess of 25%, macrolides remain first-line agents for the treatment of community-acquired pneumonia.

Methods. Prospective, population-based surveillance was conducted to identify cases of pneumococcal bacteremia in Toronto and Peel, Canada, between 2000 and 2004. "Macrolide failures" were defined as cases of bacteremia occurring during outpatient treatment with macrolide antibiotics or within 2 days after treatment. Macrolide susceptibility was determined according to Clinical Laboratory Standards Institute guidelines; common macrolide resistance mechanisms were determined by genotyping.

Results. During the 5 years of surveillance, there were 1696 episodes of pneumococcal bacteremia (8.5 cases/100,000 population/year), of which 60 (3.5%) were failures of outpatient macrolide therapy. Resistant isolates were more common among cases of bacteremia after failure of macrolide therapy (37 [64%] of 58 cases) than among cases of bacteremia after failure of nonmacrolide antibiotics (16 [22%] of 74 cases; $P < .001$) or cases of bacteremia that occurred without prior antibiotic therapy (193 [12%] of 1569 cases; $P < .001$). Macrolide failures were significantly more common among cases of pneumococcal bacteremia with isolates exhibiting an erythromycin MIC of 1 μg/mL than among isolates exhibiting MICs $\leqslant$0.25 μg/mL (3 [38%] of 8 cases vs. 21 [1.5%] of 1394 cases of bacteremia; $P < .001$). Increases in the MIC to 1 μg/mL were not associated with further increases in the likelihood of macrolide failure. Low-level resistance conferred by *mefA* and high-level resistance conferred by *ermB* were equally overrepresented among macrolide failures.

Conclusions. Macrolide resistance contributes to an increased risk of macrolide failure, irrespective of the underlying resistance mechanism or of the degree of elevation in erythromycin MIC.

Streptococcus pneumoniae is the most commonly identified cause of serious bacterial illness in young children and of community-acquired pneumonia (CAP) in adults. Macrolide antibiotics are currently the second most commonly prescribed class of antibiotics in the United States [1] and are often recommended as empirical therapy for patients with suspected pneumococcal infections, including CAP, despite reported rates of pneumococcal macrolide resistance in excess of 29% [2–4]. Macrolide resistance in *S. pneumoniae* occurs via 2 major mechanisms: methylation of ri-

bosomal macrolide target sites, encoded by the *ermB* gene, and drug efflux, encoded by *mefA* [3]. Pneumococcal macrolide resistance in the United States is predominantly mediated by drug efflux (70%) [4]. Efflux-mediated resistance is a low-level resistance (erythromycin MIC usually 0.5–8 μg/mL), whereas ribosomal methylation is associated with high-level resistance (MIC, $\geqslant$16 μg/mL) [3].

In the past 2 decades, there have been an increasing number of reports of macrolide treatment failure for pneumococcal infections with macrolide-resistant isolates [5]. Although it is not surprising that highly resistant strains (MIC, $\geqslant$16 μg/mL) may lead to clinical failure, the relevance of low-level resistance (MIC, 0.5–8 μg/mL) has been brought into question. Clinical reports of macrolide-resistant pneumococcal failures and evidence from animal models suggest that infections caused by isolates with MICs $\leqslant$8 μg/mL may respond to clarithromycin [5]. We sought to use pro-

spective, population-based surveillance to determine whether macrolide resistance is a cause of failure of macrolide therapy for serious pneumococcal disease.

METHODS

Population-based surveillance. The Toronto Invasive Bacterial Disease Network (TIBDN) has conducted prospective, population-based surveillance of invasive pneumococcal disease in metropolitan Toronto and the adjacent regional municipality of Peel, in Ontario, Canada (population, 4 million), since 1 January 1995. The surveillance network includes all hospital-based laboratories in hospitals to which residents of the population area may be admitted, as well as the 2 largest of the 3 laboratories that serve physician offices. Personnel from these laboratories telephone the central TIBDN study office at the Mount Sinai Hospital in Toronto whenever *S. pneumoniae* is isolated from a sterile site specimen [6]. For each case, initial demographic data and the pneumococcal isolate are forwarded to the central TIBDN study office. Additional clinical data, including patient comorbidities, clinical course and outcome, antimicrobial therapy in the 3 months before presentation, and outpatient therapy for the current episode before the blood sample was obtained for culture, are acquired by chart review, patient interview, and by contacting the patient's primary care physician and other attending physicians. Annual audits are conducted in each laboratory to ensure complete reporting. Surveillance and associated studies are approved by the research ethics boards of all participating institutions.

This analysis included data from cases of community-acquired pneumococcal bacteremia that occurred from 1 January 2000 through 31 December 2004. An episode was defined as a macrolide treatment failure if both of the following criteria were met: (1) an oral macrolide was prescribed for the infection (alone or in combination with other antibiotics), and (2) *S. pneumoniae* was isolated from a blood culture performed after the initiation of, or within 2 days of completing, the course of macrolide therapy. For the assessment of 30-day mortality, patients who were cured or improving at discharge before 30 days and not readmitted to the same hospital were assumed to have survived. Note that, because up to 4% of episodes are missing data from some fields, and because 69 isolates (4.1%) could not be retrieved for susceptibility testing, denominators may vary for different analyses.

Laboratory analysis. In the central study laboratory, all surveillance isolates are confirmed to be *S. pneumoniae* by standard methodology [7–9], including confirmatory genotyping [10]. Antimicrobial susceptibility testing is performed using broth microdilution in accordance with the Clinical Laboratory Standards Institute (CLSI) guidelines; therefore, macrolide-susceptible, -intermediate, and -resistant isolates were defined by

erythromycin MICs of $\leqslant 0.25$ μg/mL, 0.5 μg/mL, and $\geqslant 1.0$ μg/mL, respectively [7–9]. For the purposes of this analysis, low-level resistance to macrolides was defined as an erythromycin MIC of 1–8 μg/mL. Serotyping of all isolates is performed at the central study laboratory and the National Streptococcal Centre in Edmonton, Alberta, according to standard methodology [11]. The *mefA* and *ermB* genes are detected by PCR, as described by Katz et al. [12].

Statistical analysis. All clinical and laboratory data were stored, sorted, and analyzed using SAS statistical software, version 9.1 (SAS Institute). Differences in group proportions were assessed by Fisher's exact test (2-tailed), and differences in medians were assessed by the Wilcoxon rank sum test. The primary outcome was the difference in the proportion of macrolide-resistant isolates in episodes of macrolide treatment failure compared to other episodes of pneumococcal bacteremia. Secondary analyses included reanalysis using different MIC breakpoints, comparisons of the prevalence of *mefA* and *ermB* genes, exclusion of patients with meningitis, and inclusion, as failures, of those patients still receiving macrolides at the time their blood culture was performed. Multivariable logistic-regression models were used to assess risk factors for macrolide failure. Variables included in the models were those potentially associated with these outcomes in univariate analysis ($P < .15$), after assessment for colinearity.

RESULTS

Clinical characteristics of patients for whom macrolide therapy failed. During the 5-year period of active surveillance, 1696 episodes of pneumococcal bacteremia were detected, corresponding to a rate of 8.5 cases per 100,000 population-year. Of these cases, 60 (3.5%) represented failures of outpatient macrolide therapy, including 32 clarithromycin failures, 22 azithromycin failures, 3 erythromycin failures, 2 failures of combined azithromycin and clarithromycin, and 1 failure of clarithromycin and erythromycin. All patients were taking oral therapy. Detailed data permitting the assessment of appropriateness of dosing was not requested in the surveillance system, but diagnosis and dose of macrolides were frequently provided. Of the 28 persons for whom dosing information permitting assessment of appropriateness was available, 27 [96%] had received recommended doses.). Six of the 60 patients for whom macrolide therapy failed had also been treated with another antibiotic (2 had received amoxicillin, and 1 each had received sulfamethoxazole, cefaclor, penicillin, and combined sulfamethoxazole and amoxicillin). The clinical diagnoses were: pneumonia (36 [60%] of 60), primary bacteremia (8 [13%]), meningitis (7 [12%]), otitis media (5 [8%]), pneumonia and meningitis (3 [5%]), and osteomyelitis (1 [2%]). Almost all
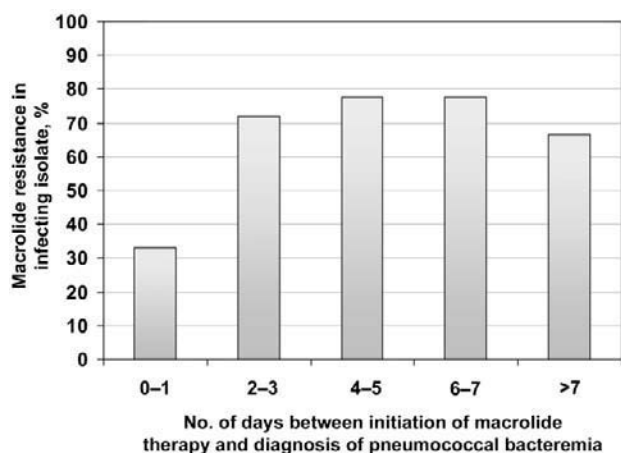
Figure 1. The probability that *Streptococcus pneumoniae* isolated from blood was resistant to erythromycin in patients for whom outpatient therapy with a macrolide failed, according to the duration of macrolide therapy before presentation with bacteremia. Patients presenting on the first or second day of therapy (days 0 and 1, respectively) were more likely to have a macrolide-resistant isolate than were patients who had not received therapy before presentation (5 of 15 vs. 193 of 1569 patients; $P = .03$), but they were less likely to have a macrolide-resistant isolate than those who had received ⩾2 days of therapy (5 of 15 vs. 31 of 42 patients; $P = .01$).

patients (56 [93%] of 60) were admitted to the hospital, and 9 (15%) of 60 died.

Pneumococcal isolates were available for 58 of the 60 episodes of bacteremia associated with macrolide failure: 21 (36%) were macrolide susceptible, and 37 (64%) were macrolide resistant. Sixteen different serotypes were associated with macrolide failures: the most common were 14 (17 cases), 6B (14 cases), 6A (5 cases), and 19F (4 cases). Compared with failures associated with macrolide-resistant isolates, failures associated with macrolide-susceptible isolates were more likely to occur in patients who were ⩾65 years of age (10 [48%] of 21 vs. 5 [14%] of 37; $P = .01$), who had underlying cardiac disease (7 [33%] of 21 vs. 3 [8%] of 37; $P = .03$), and who were residents of nursing or retirement homes (7 [33%] of 21 vs. 2 [5%] of 37; $P = .008$).

The median time from initiation of macrolide therapy to the development of a positive blood culture result was 3 days (range, 0–17 days). Five (33%) of 15 isolates obtained from patients presenting with bacteremia <48 h after initiating macrolide therapy were macrolide resistant, compared with 31 (74%) of 42 isolates from patients who experienced treatment failure >2 days after initiation of therapy (figure 1) ($P = .01$). The timing of macrolide failure and the likelihood of obtaining a resistant isolate were similar for cases of pneumonia and nonrespiratory foci of infection (data not shown). Twenty-nine (66%) of 44 patients who were still taking a macrolide at pre-

sentation to the hospital with bacteremia had a macrolide-resistant isolate, compared with 8 (57%) of 14 who had completed or discontinued macrolide therapy in the 48 h before presentation ($P = .78$).

Comparison of cases of macrolide failure with other cases of pneumococcal bacteremia. Macrolide-resistant isolates were much more common among the cases of macrolide failure than among other cases of pneumococcal bacteremia (37 [64%] of 58 cases vs. 193 [12%] of 1569 cases; $P < .001$) (figure 2). Macrolide-resistant isolates were also more common among patients for whom macrolide therapy failed than among those for whom nonmacrolide antibiotic therapy failed (37 [64%] of 58 cases vs. 16 [22%] of 74 cases; $P < .001$) (figure 2).

In univariate analysis, patients for whom macrolide therapy failed were more likely than other patients to be children (age, <15 years), to have no chronic underlying illness, and to have received a macrolide antibiotic for another reason during the previous 3 months (table 1). However, there was no difference in the 30-day mortality rate (9 [15%] of 60 cases of macrolide failure vs. 291 [18%] of 1594 other cases; $P = .96$). In multivariate logistic regression, erythromycin resistance in the infecting isolate (OR, 12.3; 95% CI, 7.0–22; $P < .001$), age (OR per decade, 1.15; 95% CI 1.04–1.27; $P = .005$), and residence
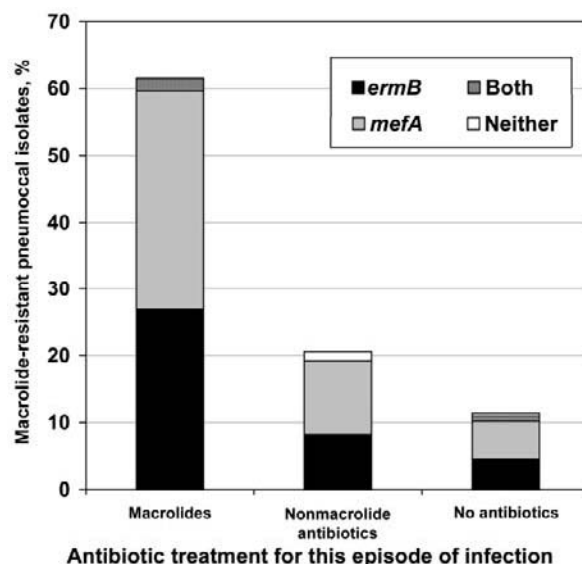

Figure 2. Prevalence of erythromycin resistance and distribution of resistance mechanisms in *Streptococcus pneumoniae* isolated from blood samples from patients for whom outpatient macrolide therapy failed, for whom outpatient therapy with other classes of antibiotics failed, or who presented without having received antibiotic therapy. The solid bars represent isolates containing *ermB* genes, hatched bars those containing *mefA* genes, dotted bars those containing both *ermB* and *mefA* genes, and open bars those containing neither *ermB* nor *mefA* genes. There is no difference in the distribution of resistance genes in the 3 different categories of isolates (see Results).

in a nursing or retirement home (OR, 4.3; 95% CI, 1.8–11; $P = .001$) were the only patient variables associated with macrolide failure.

Mechanisms of macrolide resistance. Among the 32 macrolide-resistant isolates recovered from patients who experienced macrolide failure available for PCR analysis, 17 (53%) were positive for *mefA*, 14 (44%) were positive for *ermB*, and 1 (3%) was positive for both *mefA* and *ermB* (figure 3).

The efflux gene *mefA* was overrepresented among macrolide failure cases than among cases of pneumococcal bacteremia that were not associated with failure of macrolide therapy (34% vs. 6.6% were PCR positive for *mefA*; $P < .001$). Similarly, ribosomal modification (*ermB*) was overrepresented among macrolide failure cases (32% vs. 5.1% were PCR positive for *ermB*; $P < .001$). The distribution of *ermB* and *mefA* genotypes in erythromycin-resistant isolates from cases for which macrolide failure occurred (17 *ermB*:14 *mefA*:1 both) was not different from the distribution of these genotypes in other cases (94 *ermB*:70 *mefA*:10 both; $P = 0.80$).

Low-level versus high-level macrolide resistance. Of macrolide-resistant isolates from cases of macrolide failure, 17 (46%) of 37 had low-level resistance (erythromycin MIC, 1–8 μg/mL), compared with 83 (43%) of 193 macrolide-resistant isolates not associated with failure of macrolide therapy ($P = .74$).

Macrolide failures were significantly more common among patients with pneumococcal bacteremia with isolates exhibiting an erythromycin MIC of 1 μg/mL compared with isolates exhibiting MICs ≤0.25 μg/mL (3 [38%] 8 vs. 21 [1.5%] of 1394
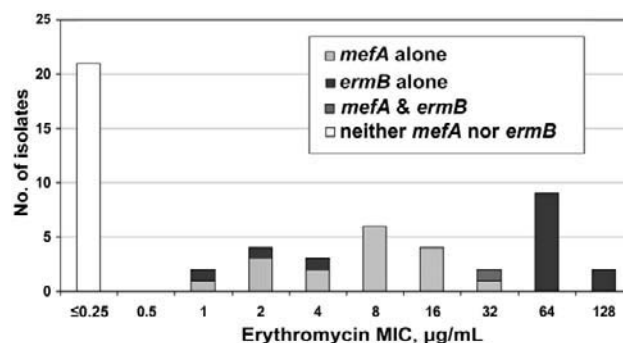

Figure 3. Distribution of erythromycin MIC and resistance genes in *Streptococcus pneumoniae* isloates recovered from blood cultures in patients for whom outpatient therapy with macrolides failed. The solid bars represent isolates containing *ermB* genes, hatched bars those containing *mefA* genes, dotted bars those containing both *ermB* and *mefA* genes, and open bars those containing neither *ermB* nor *mefA* genes.

cases of bacteremia; $P < .001$). Increases in the MIC >1 μg/mL were not associated with further increases in the likelihood of macrolide failure (figure 4).

Isolates with low-level resistance contributed to 4 (29%) of 14 failures of azithromycin alone and 10 (56%) of 18 failures of clarithromycin alone ($P = .24$). The median erythromycin MIC was not different among isolates from patients who experienced clarithromycin failure and those from patients who experienced azithromycin failure (2 μg/mL vs. 8 μg/mL; $P = .19$).

Secondary analyses. All analyses described above were also

Table 1. Comparison of clinical characteristics and of outcomes for patients with pneumococcal bacteremia for whom macrolide therapy failed or did not fail, Toronto Invasive Bacterial Diseases Network, 2000–2004.

Clinical characteristic	Macrolide failure with pneumococcal bacteremia	Other cases of pneumococcal bacteremia	P
Age <15 years	27/60 (45)	400/1636 (24)	<.001
Female sex	25/60 (42)	724/1636 (44)	.79
Chronic underlying illness	23/59 (39)	928/1599 (58)	.006
Macrolide use in prior 3 months[a]	5/60 (8.3)	57/1636 (3.5)	.06
Year of infection			
2000	9 (15)	356 (22)	.21
2001	19 (32)	320 (20)	
2002	10 (17)	321 (20)	
2003	9 (15)	282 (17)	
2004	13 (22)	357 (22)	
ICU admission	7/60 (12)	352/1572 (22)	.07
30-day mortality	9/60 (15)	229/1594 (18)	.96

NOTE. Data are no. (%) of patients or no. of patients with finding/no. studied (%). ICU, intensive care unit.

[a] Received a macrolide antibiotic for a reason other than treatment of this episode of infection at some time in the 3 months before this infection.
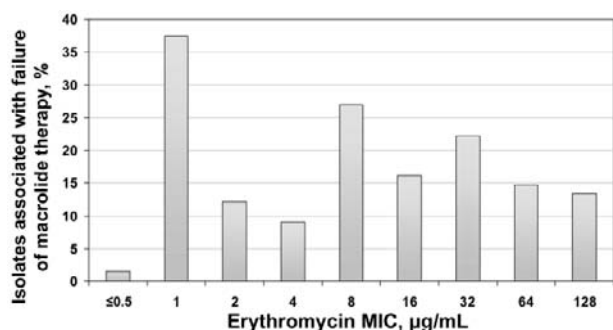
Figure 4. Percentage of pneumococcal blood culture isolates associated with failure of outpatient macrolide therapy, by erythromycin MIC. Overall, failures account for 21 (1.5%) of 1397 episodes with isolates susceptible to erythromycin and 37 (16%) of 230 episodes with isolates resistant to erythromycin ($P < .0001$). There is no statistically significant difference in the proportion of isolates associated with failure for erythromycin MIC $\geqslant 1$ μg/mL.

performed on subsets of the data, excluding subjects with meningitis, and considering macrolide treatment failures only in persons who were taking macrolides at the time of presentation with bacteremia. Analyses were also performed separately for patients taking azithromycin and clarithromycin. Results were not significantly different from the primary analysis (data not shown).

DISCUSSION

Although pneumococcal resistance rates to macrolide antimicrobial agents exceed 25% in many parts of the world, these agents are still recommended as empirical therapy for CAP in most guidelines [13]. Previous studies may have failed to detect true macrolide treatment failures as a result of methodologic limitations, such as a reliance on rare failure end points like mortality, or by not focusing on cases of discordant therapy [14]. The current study sought to overcome these methodologic challenges by first identifying macrolide failures that resulted in pneumococcal bacteremia and then evaluating the relative proportion of macrolide-resistant isolates among these failures.

Our results establish that macrolide resistance among pneumococci is a cause of failure of outpatient pneumonia therapy. Clinicians should be aware that macrolide resistance precludes the use of macrolide therapy for pneumococcal pneumonia. Unfortunately, pathogens are isolated in fewer than one-half of CAP episodes [15, 16]. Even when a pathogen is isolated, a critical period of time elapses, during which the treating physician must select appropriate antimicrobials although identification and susceptibility testing results are not available [17].

Therefore, it would be wise to avoid empirical macrolide therapy when a patient is at risk of being infected with a macrolide-resistant pathogen, either as a result of patient-specific characteristics or the overall rate of resistance in the com-

munity. Treatment guidelines recommend avoiding macrolide use in patients with macrolide exposure within the previous 3 months [18, 19]. Other clinical parameters associated with macrolide resistance among pneumococci include recent use of a penicillin or trimethroprim-sulfamethoxazole [6, 20], extremes of age [20], HIV infection [6], and exposure to siblings colonized with resistant isolates [21].

Our results indicate that methylation of the ribosomal target site, conferred by the *ermB* gene, and efflux, conferred by the *mefA* gene, are equally overrepresented among cases of pneumococcal bacteremia that occur after macrolide failure. Furthermore, azithromycin and clarithromycin failures were associated with both low-level and high-level resistance. Therefore, macrolide resistance contributes to an increased risk of macrolide failure independent of the underlying resistance mechanism, the degree of elevation in erythromycin MIC, or the macrolide being used for therapy. This contradicts the arguments of some authorities, who believe that the ability of macrolide antibiotics to concentrate within the epithelial lining fluid of the lung might allow drugs to overcome low-level MICs associated with the presence of the *mefA* genotype [22].

A proportion of patients might be expected to experience outpatient oral antimicrobial therapy failure despite the presence of a drug-susceptible isolate, on the basis of noncompliance with therapy, impaired absorption, an overwhelming bacterial burden, or multiorgan failure resulting from the systemic inflammatory response syndrome [23]. In this study, patients with susceptible isolates for whom therapy failed were older, more likely to have underlying cardiac disease, more likely to live in nursing homes, and more likely to be admitted to the hospital within the first 48 h of therapy. This suggests that, in addition to discordant therapy, inadequate host response is an important reason for treatment failure. The apparent contradiction between our results and those of an earlier case-control study of macrolide failures resulting in pneumococcal bacteremia, which detected no macrolide failures with macrolide-susceptible isolates, is explained by study design. Macrolide failures constituted only 1.4% of infections with macrolide-susceptible isolates in our cohort, a proportion low enough that failures might not be detected with a sample size of 136 control subjects [24].

Our data reveal that macrolide resistance is overrepresented, even among early macrolide failures. This is consistent with recent pneumonia studies that have documented that the median time to defervescence and normalization of respiratory rate is 1 day and that the median time to stabilization of chest radiography and normalization of oxygenation is 2 days [25]. Therefore, if a patient is admitted to the hospital with worsening pneumonia while receiving macrolide therapy, it would

be prudent to switch to a different class of agents, even if macrolide therapy was initiated within the preceding 24–48 h.

One of the greatest strengths of our surveillance approach is its sensitivity to detect cases of macrolide failure by evaluating cases of pneumococcal bacteremia. Indeed, the number of cases detected during our investigation ($n = 60$) is nearly double the number of cases reported in the literature to date. However, a limitation of this approach is that the rate of macrolide failure cannot be evaluated, because cases of successful macrolide therapy are not identified and cannot be counted. The goal of this study was not to determine the rate of failure of macrolide therapy, but to identify whether in vitro macrolide resistance is associated with failure of macrolide therapy. Another limitation of this study is that the power to detect differences in subgroups is low. For instance, although we did not detect differences in the rates of resistance to erythromycin in infecting isolates in patients failing different macrolide antibiotics, it is not possible to conclude that such differences do not exist.

Our study demonstrates that macrolide resistance is an important cause of macrolide therapy failure. Therefore, macrolide antibiotic use should be avoided for patients with known clinical risk factors for macrolide resistance and for patients residing in areas with high rates of macrolide resistance. Patients admitted to the emergency department with CAP who are deteriorating despite receiving macrolide therapy should receive therapy with a different class of antibiotics.

THE TORONTO INVASIVE BACTERIAL DISEASES NETWORK

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