DOI: *10.4081/aiua.2026.14694*

REVIEW

Antimicrobial resistance in *Mycoplasma genitalium* and *Mycoplasma hominis*: A systematic review in urology

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Summary ***Introduction: Mycoplasma genitalium and Mycoplasma hominis are urogenital mycoplasmas associated with urethritis, prostatitis, epididymitis, and pelvic inflammatory disease. In the last decade, acquired resistance to macrolides and fluoroquinolones in M. genitalium, together with intrinsic and acquired resistance to tetracyclines in M. hominis, have emerged as growing challenges in urology and sexual medicine.***

Material and methods: A systematic review was conducted following the PRISMA guideline, searching PubMed, Scopus, and Web of Science (2015-2025). Clinical, epidemiological, and molecular studies describing genetic resistance mechanisms, as well as meta-analyses and clinical guidelines, were included. After applying inclusion and exclusion criteria, 42 articles were selected.

Results: In M. genitalium, macrolide resistance is associated with mutations in 23S rRNA (A2058G, A2059G), while fluoroquinolone resistance is linked to variants in parC and gyrA (S83I, D87N). In M. hominis, intrinsic macrolide resistance is complemented by the presence of tet(M), which contributes to doxycycline treatment failures. Globally, macrolide resistance in M. genitalium reaches 30-50% in Europe and the Americas, and over 60% in Asia; dual macrolide-fluoroquinolone resistance is emerging, with epidemic foci in Japan and China. In M. hominis, tetracycline resistance ranges from 10-30%, with regional variability.

Conclusions: Antimicrobial resistance in M. genitalium and M. hominis limits the effectiveness of traditional empirical therapies and requires the implementation of molecular detection and resistance testing. Resistance-guided treatment and epidemiological surveillance are essential to optimize clinical management and curb the spread of multidrug-resistant strains.

KEY WORDS: *Mycoplasma genitalium; Mycoplasma hominis; Antimicrobial resistance; Urology; Systematic review.*

Submitted 2 December 2025; Accepted 4 January 2026

INTRODUCTION

Urogenital mycoplasmas and clinical relevance

Mycoplasma genitalium (M. genitalium) and *Mycoplasma hominis* (M. hominis) belong to the group of mollicutes, small-genome bacteria that lack a cell wall. This characteristic makes them intrinsically resistant to β-lactam antibiotics and other drugs targeting the cell wall, restricting therapeutic options to compounds that inhibit protein synthesis, such as macrolides, tetracyclines, and lincosamides, or DNA replication, as with fluoroquinolones (1).

M. genitalium is a sexually transmitted pathogen of increasing relevance, estimated to cause 10-35% of non-gonococcal, non-chlamydial urethritis in men (2). In women, it has been associated with cervicitis and pelvic inflammatory disease (PID) in 10-25% of cases, with sequelae such as tubal infertility (3). *M. hominis* is part of the normal genital microbiota, present in 20-50% of sexually active women. However, under certain circumstances, it may behave opportunistically and cause bacterial vaginosis, postpartum endometritis, chorioamnionitis, puerperal fever, or even neonatal sepsis (4). In men, it has been detected in chronic prostatitis and epididymitis, and like *M. genitalium*, may play a role in these urological conditions (5). Both mycoplasmas have also been linked to infertility: *M. genitalium* through chronic pelvic inflammation in women, and *M. hominis* through semen alterations; however, many of these associations remain debated and may reflect colonization rather than direct causality (6).

Emerging antimicrobial resistance

Over the last two decades, *M. genitalium* has shifted from being susceptible to multiple antibiotics to becoming a pathogen with alarming rates of acquired resistance to macrolides and fluoroquinolones (7). The widespread use of azithromycin in sexually transmitted infections and the introduction of moxifloxacin as a rescue therapy have favored the selection of resistant strains. In the case of *M. hominis*, resistance is intrinsic to macrolides such as erythromycin and azithromycin, due to ribosomal variations. In addition, the presence of mobile determinants such as *tet(M)* accounts for tetracycline resistance (8). Although resistance to other antibiotic classes has been less common, there is a potential risk of multidrug resistance, particularly in settings with intensive use of broad-spectrum antibiotics (9).

This scenario represents a challenge in urological practice: *M. genitalium* infections that once responded to classical treatments now require resistance-guided management, while *M. hominis* should be considered in unexplained therapeutic failures, particularly in urinary or postsurgical infections in immunocompromised patients (5).

This study aims to provide a comprehensive evaluation of the genetic mechanisms driving antimicrobial resistance

in Mycoplasma genitalium and Mycoplasma hominis, as well as to determine their clinical relevance and impact in urological practice through a systematic review of the literature published from 2015 to 2025.

Materials and methods

Evidence acquisition

A systematic review was conducted following PRISMA (*Preferred Reporting Items for Systematic Reviews and Meta-Analyses*) guidelines (10). Searches were performed in PubMed, Scopus, and Web of Science using combinations of English and Spanish keywords such as: "*Mycoplasma genitalium resistance 23S parC*," "*Mycoplasma hominis antimicrobial resistance*," "*macrolide resistance Mycoplasma 23S rRNA*," "*tet(M) Mycoplasma hominis*," and "*M. genitalium fluoroquinolone mutations*." Studies published since 2015 in English or Spanish with full-text availability were included.

Inclusion criteria

Clinical, epidemiological, or molecular biology studies describing genetic resistance mechanisms in *M. genitalium* or *M. hominis* were considered, either through point mutations in target genes or the presence of acquired resistance genes. Systematic reviews, meta-analyses, and relevant clinical guidelines were also included. Case reports and case series related to urological infections caused by multidrug-resistant strains were considered.

Exclusion criteria

Articles published before 2015 and studies restricted to highly specific populations, such as pediatric or HIV-positive patients, whose extrapolation to the general population was limited, were excluded.

After applying the criteria, 60 full-text articles were retrieved; ultimately, 42 studies met the eligibility requirements, encompassing epidemiological surveillance studies, molecular analyses, clinical trials, meta-analyses, and clinical practice guidelines. The main characteristics of these studies are summarized in Table 1, which details the author, year, country or region, study design, population, genes and resistance mechanisms analyzed, as well as relevant comments from each study. This synthesis allows for a critical comparison of methodological and geographical differences among studies and facilitates the interpretation of findings in the clinical urological context.

Evidence synthesis

Genes and mechanisms of antimicrobial resistance

In *M. genitalium*, macrolide resistance is almost exclusively due to point mutations in domain V of the 23S rRNA gene, most commonly A2058G and A2059G. These alterations modify the ribosomal binding site and confer high-level resistance to macrolides, resulting in azithromycin failure rates exceeding 90% (11). *M. hominis* exhibits intrinsic resistance to most commonly used macrolides due to natural sequence variations (G2057A and C2610U), which significantly reduce antibiotic affinity (1). Exceptionally, acquired mutations such as A2059G have been reported, conferring an phenotype (combined resistance to macrolides, lincosamides, and streptogramin B), which is rare but clinically relevant (12).

Fluoroquinolones act on bacterial topoisomerases, interfering with DNA *gyras*e and topoisomerase IV. In *M. genitalium*, resistance is primarily due to mutations in the QRDR region of the *parC* gene, most frequently affecting codons Ser83 and Asp87 (13). Variants such as S83I, S83R, D87N, or D87Y increase *minimum inhibitory concentrations* (MICs) against moxifloxacin and are associated with treatment failures. Although *gyrA* mutations may also occur, these alone have little impact; however, when combined with *parC* mutations, they enhance resistance (14). Most moxifloxacin-resistant strains harbor at least one *parC* mutation, often accompanied by another in *parC* or *gyrA* (14). In *M. hominis*, fluoroquinolone resistance is less common, but strains carrying QRDR mutations in *parC* and *gyrA* have already been identified (12), leading to elevated MICs for levofloxacin, ciprofloxacin, and moxifloxacin (15).

Tetracyclines inhibit protein synthesis by binding to the 30S ribosomal subunit. In *M. genitalium*, doxycycline efficacy is limited, with clinical cure rates of only 30-40%. This poor performance appears to be related more to pharmacodynamic factors than to acquired genetic resistance mechanisms (16). In *M. hominis*, tetracycline resistance occurs through exogenous genes, the most relevant being *tet(M)*. This gene encodes a ribosomal protection protein capable of displacing the antibiotic from its binding site and is associated with Tn916-type conjugative transposons (8). Some *tet(M)*-positive strains show intermediate susceptibility to minocycline, indicating that not all tetracyclines are equally affected. Nevertheless, the presence of *tet(M)* reliably predicts doxycycline failure and necessitates consideration of alternative classes of antibiotics (17). Table 2 summarizes the most relevant genes or mutations described in the last decade, their clinical impact, and the average prevalence reported globally and regionally.

Geographic distribution of resistance

Macrolide resistance in *M. genitalium* was uncommon until the late 2000s, with global prevalence close to 10% (1). Over the past decade, this has changed dramatically, increasing to an average prevalence of 35% (18). The magnitude of the problem varies by region. The highest rates are concentrated in Asia-Pacific and the Americas, while in Europe, although lower, an upward trend is evident. In Australia, resistance rose from 19% in 2010 to 66% in 2016, exceeding 80% among men who have sex with men (19). In Europe, countries such as France reported an increase to over 35% by 2017, paralleling the rise in azithromycin consumption (20).

The most complex scenario involves dual resistance to macrolides and fluoroquinolones. Although its global prevalence initially appeared low (~2%), alarming epidemic foci have been reported in Asia. In Japan, some studies documented up to 30% of strains with combined resistance (21). The situation in China is particularly concerning due to the rapid increase in multidrug-resistant *M. genitalium* strains. More than 60% of isolates have been reported to harbor mutations conferring resistance to both macrolides and fluoroquinolones, and nearly half

Table 1.
Main characteristics of the studies included in the systematic review on antimicrobial resistance in M. genitalium and M. hominis.

Author (Year)	Country/ Region	Study design	Population/Participants	Genes/Mechanisms studied	Relevant comments
Pereyre et al. (2006)	France	Observational/Molecular	Clinical isolates of *M. hominis*	23S rRNA (mutations)	Loss of intrinsic macrolide resistance due to point mutation
Jensen et al. (2022)	Europe	Clinical guideline	STI patients	Management and resistance testing	Updated European recommendations for *M. genitalium*
Lis et al. (2015)	Global	Meta-analysis	Women with reproductive tract infections	Association *M. genitalium*–disease	Association with cervicitis/PID
Waites et al. (2005)	Global	Review	Neonates	*Mycoplasma*/Ureaplasma pathogenicity	Perinatal relevance; pathophysiological basis
CDC (2021)	USA	Clinical guideline	STI patients	Therapeutic algorithms	CDC 2021 guidelines for *M. genitalium*
Qiu et al. (2024)	China	National review	Genitourinary infections	23S, parC, *tet(M)*	Diagnostic and management advances in China
Sandri et al. (2023)	Global	Review/Clinical study	Patients with *M. genitalium*	Resistance and outcomes	Link between resistance and clinical failure
Chalker et al. (2021)	UK	Molecular	Patients with *M. hominis*	*tet(M)* (variable ICEs)	Variability of conjugative elements carrying *tet(M)*
Pereyre et al. (2017)	France/Europe	Observational	*M. hominis*	Resistance profile	Emergence of resistance and clinical relevance
Page et al. (2021)	Global	Methodological guideline	Systematic reviews	PRISMA 2020	Reporting standard for systematic reviews
Piñeiro et al. (2022)	Europe	Observational/Surveillance	*M. genitalium*	23S rRNA (macrolides)	European increase in macrolide resistance
Katsuta et al. (2018)	Japan	Molecular	*M. hominis*	A2059G; MLSB phenotype	Rare but relevant MLSB phenotype
Braam et al. (2022)	Global	Molecular/Observational	*M. genitalium*	parC/gyrA (QRDR)	Mutations associated with FQ resistance
Hamasuna et al. (2018)	Japan	Molecular/Comparative	Resistant *vs* susceptible *M. genitalium*	parC, gyrA (moxifloxacin)	Association mutations-MIC/moxifloxacin
Meygret et al. (2018)	France	Observational/Molecular	*Ureaplasma spp.* and *M. hominis*	Tetracyclines, fluoroquinolones	Resistance rates 2010–2015
Manhart et al. (2015)	Global	Review	*M. genitalium*	Antimicrobial efficacy	Variable efficacy of doxycycline/azithromycin/moxifloxacin
Ahmadi (2021)	Global	Meta-analysis	*M. hominis*/Ureaplasma	*tet(M)*/tetracyclines	Significant regional differences
Machalek et al. (2020)	Global	Meta-analysis	*M. genitalium*	23S rRNA; parC (FQ)	Global overview of AMR in *M. genitalium*
Murray et al. (2017)	Australia	Observational	MSM with *M. genitalium*	23S rRNA (macrolides)	Rapid escalation in MSM networks
Le Roy et al. (2016)	France	Surveillance	*M. genitalium*	Fluoroquinolones (mutations)	Description of FQ resistance in SW France
Deguchi et al. (2018)	Japan	Surveillance	*M. genitalium*	Macrolides/fluoroquinolones	National surveillance 2016–2018
Li et al. (2023)	China	Clinical observational	Symptomatic *M. genitalium*	23S and parC	Therapeutic failure due to multidrug resistance
Mardassi et al. (2012)	Tunisia	Molecular	U. parvum/*M. hominis*	*tet(M)* (clonal predominance)	Single dominant *tet(M)* type
Abavisani & Keikha (2023)	Global	Meta-analysis	*M. genitalium*/*M. hominis*/Ureaplasma	Multidrug-resistance mutations	Global synthesis of AMR mutations
Durukan et al. (2020)	Australia	Prospective trial/Series	*M. genitalium*	Resistance-guided therapy	Doxy→moxi *vs* doxy→azitro 2.5 g
Trinchieri et al. (2021)	Europe	Observational	Bacterial prostatitis	AMR rates in multiple pathogens	Urological context; resistance spectrum
Hinić et al. (2021)	Switzerland	Case series	Renal transplant recipients	*M. hominis*	Unexpected opportunistic infection
Ahmadi et al. (2017)	Iran	Observational	Infertile men	Asymptomatic *M. hominis*	Negative impact on semen parameters
Horner et al. (2018)	Europe	Review + Recommendations	*M. genitalium* screening/testing	Clinical reasoning	No routine screening; targeted approach
Waites et al. (2016)	USA	*In vitro*	*Mycoplasmas*/Ureaplasma	Gyrase inhibitor (AZD0914)	New class (gyr) with *in vitro* activity
Clarke et al. (2023)	Australia	Observational	*M. genitalium* treated with minocycline	Clinical response	Minocycline as alternative
Jensen et al. (2014)	Europe	*In vitro*	*M. genitalium*	Solithromycin (fluoroketolide)	*In vitro* activity against resistant *M. genitalium*
Ke et al. (2020)	China	Retrospective	MSM in STI clinic	Macrolide/FQ mutations	Local overview 2016–2018
Chua et al. (2025)	Global	Meta-analysis	*M. genitalium*	Macrolides/fluoroquinolones	2025 trends (update of Machalek)
UKHSA (2024)	UK	Surveillance	*M. genitalium*	AMR mutations	National AMR report 2023
Melendez et al. (2022)	Uganda	Retrospective	Men with urethritis	*M. genitalium* (macrolide AMR)	Macrolide resistance detected
Song et al. (2022)	China	Observational	Ureaplasma/*M. hominis*	Resistance profiles	Prevalence and regional AMR
Ramaloko et al. (2025)	Global	Review	*Mycoplasma*/Ureaplasma	AMR mechanisms	Global synthesis 2025
Boujemaa et al. (2020)	Tunisia	Observational/Molecular	*M. hominis*	*tet(M)* clonal spread	Clonality of tetracycline resistance

Table 2.
Antimicrobial resistance in M. genitalium and M. hominis (Macrolides, Fluoroquinolones, Tetracyclines) by region.

Pathogen	Region	Macrolide resistance (23S rRNA)	Fluoroquinolone resistance (parC/gyrA)	Tetracycline resistance (tet(M)/others)	References
M. genitalium	Asia-Pacific	Very high (50–70%)	High and increasing (15–60%)	Low (< 5%)	19, 21, 24, 33
	Europe	Moderately high (25–40%)	Moderate (10–15%)	No reports	19, 34, 35
	Americas	High (30–50%)	Low-moderate (5–15%)	No known dissemination	34
	Africa	Low-moderate (< 15%)	Very low (< 5%)	No reports	36
M. hominis	Asia-Pacific	Intrinsic (100%)	High (> 70%)	Very low (< 5%)	1, 38
	Europe	Intrinsic (100%)	Low (< 7%)	Variable (5–30%)	1, 39
	Americas	Intrinsic (100%)	Very low (< 1%)	Low (5–15%)	38
	Africa	Intrinsic (100%)	Low (< 3%)	High in some regions (> 15%)	39

display dual resistance to these two antimicrobial classes. Even more worrisome is the detection of cases with combined resistance to three antibiotic groups, which anticipates serious therapeutic challenges and underscores the urgent need to strengthen molecular surveillance and develop new treatment alternatives (22).

Data on *M. hominis* are more limited, partly due to its opportunistic nature and the absence of systematic surveillance programs. Regarding tetracyclines, low resistance rates (< 10%) predominate in Europe, whereas in the Americas, prevalence between 25% and 30% has been described, generally associated with acquisition of the *tet(M)* gene (23). A global meta-analysis published in 2023, including more than 900 urogenital isolates, showed that resistance in *M. hominis* reached approximately 14% for tetracycline, 5% for doxycycline, and 12% for minocycline (24). Although these figures indicate that tetracyclines remain generally effective, they also reveal marked interregional differences related to uneven antibiotic use. This highlights that, although tetracyclines remain a useful therapeutic option, resistance in *M. hominis* cannot be overlooked and requires continuous surveillance.

Clinical relevance in urological practice

Resistance in *M. genitalium* and *M. hominis* directly impacts the management of persistent urethritis, some cases of prostatitis and epididymitis, postoperative urinary tract infections in immunosuppressed patients, and, to a lesser extent, fertility. Current guidelines recommend the use of molecular diagnostics and resistance-guided treatment for *M. genitalium*, while for *M. hominis* a more pragmatic approach is advised, adapted to the local susceptibility profile (5).

M. genitalium is a well-established cause of non-gonococcal urethritis. Macrolide resistance explains empirical azithromycin treatment failures and symptom recurrence (18). In women, it is associated with cervicitis and pelvic inflammatory disease (PID); when resistance is present, standard PID regimens may be insufficient and targeted coverage is required (25). *M. hominis* rarely causes urethritis on its own, and its intrinsic resistance to macrolides explains the lack of efficacy of azithromycin-based regimens. In most cases, it responds to doxycycline unless the *tet(M)* gene is present (1).

In chronic prostatitis, these pathogens should be considered in refractory cases, particularly in patients with prior macrolide or fluoroquinolone exposure (26). In epididymitis, *M. genitalium* may occasionally appear and persist when *parC* mutations are present, which are responsible for fluoroquinolone treatment failures (2). As an opportunistic pathogen, *M. hominis* may cause pyelonephritis, abscesses, or sepsis in transplanted or catheterized patients, often with negative results from conventional cultures. In these cases, specific culture media or molecular methods such as PCR are essential (27).

Regarding fertility and pregnancy, in women, persistent *M. genitalium* infection has been linked to subclinical PID and an increased risk of tubal infertility, particularly when resistance leads to ineffective treatment (3). In men, the evidence regarding *M. hominis* and semen parameters is variable, though the clinically relevant point is the difficulty of eradicating resistant strains, and asymptomatic infections have been documented as having a negative impact on fertility (28).

Routine screening for *M. genitalium* or treatment of incidental findings in asymptomatic patients is not recommended, since some asymptomatic infections resolve spontaneously and indiscriminate antibiotic use fosters resistance. In urological practice, if a multiplex PCR detects *M. genitalium* without evident clinical manifestations, observation may be considered (29).

Discussion

Most of the evidence on *M. genitalium* resistance comes from observational studies conducted in STI clinics and meta-analyses pooling such data. Although these studies may overestimate prevalence by focusing on populations with high antibiotic exposure, the consistency of findings across regions such as Europe, Asia, and the Americas supports the existence of a global upward trend (3, 5). Even in less selected cohorts focused on patients with urethritis, macrolide resistance rates exceed 30%, confirming that this is a widespread phenomenon (18). For *M. hominis*, prevalences range from 10% to 20% across different regions, adding consistency to the findings (17).

A major limitation is the absence of randomized clinical trials to guide second- or third-line management in *M. genitalium*. Most recommendations are based on prospective series, uncontrolled studies, and expert consensus (2, 16). This highlights the need for direct comparative studies, such as moxifloxacin versus pristinamycin in dual-resistant strains. For *M. hominis*, therapeutic guidelines rely more on pharmacological and in vitro data than on specific clinical trials (4).

M. genitalium has shifted from being managed with simple empirical regimens to requiring specific diagnosis and resistance-guided therapy (2). The documented transmission of multidrug-resistant strains in MSM networks reinforces the need for active surveillance and targeted strategies, similar to those applied for resistant Neisseria gonorrhoeae (5). *M. hominis* behaves mainly as an opportunistic commensal. In practice, good therapeutic options remain available, such as doxycycline and clindamycin; although in sporadic cases of multidrug resistance, escalation to fluoroquinolones or even linezolid may be required (9, 30).

Detection of *M. genitalium* in the absence of symptoms poses a clinical dilemma since indiscriminate treatment increases selective pressure without clear benefit. This paradigm shift from "eradicating everything detected" to prioritizing clinical relevance is critical to curb resistance (30).

The reasons for the low efficacy of doxycycline in *M. genitalium* go beyond pharmacodynamics and pathogen biology (19, 25). Systematic sequencing studies of strains after treatment failure could provide answers. It is also crucial to characterize host factors influencing spontaneous clearance, such as bacterial load or local immunity, and virulence markers that help distinguish inflammatory strains from mere colonizers. For *M. hominis*, a key research line is the dynamics of horizontal transfer of *tet(M)* and how it is modulated by local tetracycline use (8, 23).

Beyond sequential regimens of doxycycline plus azithromycin or moxifloxacin, alternative options are needed for dual resistance. Pristinamycin and minocycline have

shown utility in selected contexts, while sitafloxacin has produced encouraging results in countries where it is available (25, 31). New antibiotics, such as lefamulin or solithromycin, demonstrate in vitro activity against resistant *M. genitalium*, but robust clinical trials are lacking (30, 32).[2] For severe multidrug-resistant *M. hominis*, linezolid has been effective in isolated reports, although toxicity limits its use (35).

Our findings are consistent with recent IUSTI/Europe and CDC recommendations, which discourage single-dose azithromycin for *M. genitalium* and advocate resistance-guided therapy (2, 5). Standardizing molecular testing and integrating it into routine management of urology and STIs has become essential. Surveillance programs should include *M. genitalium* alongside gonorrhea and chlamydia to detect local trends early and adapt treatment guidelines accordingly. Collaboration between urology, gynecology, infectious diseases, and public health will be essential to close care gaps (29, 33).

Conclusions

Antimicrobial resistance in *M. genitalium* and *M. hominis* represents a real problem in urological and sexual medicine practice. In *M. genitalium*, mutations in 23S rRNA, *parC*, and *gyrA* explain the progressive rise of strains resistant to macrolides and fluoroquinolones, while in *M. hominis*, tetracycline resistance is mainly related to the presence of the *tet(M)* gene. In daily practice, this translates into patients with urethritis or cervicitis unresponsive to standard treatment, cases of pelvic inflammatory disease, and resistant urinary tract infections—forcing a shift away from traditional empirical regimens toward more individualized management based on laboratory testing for both diagnosis and treatment selection.

Declarations

Ethical approval and consent for participate: *This study did not involve human participants, human data, or human tissue.Not applicable.*

Consent for publication: *This manuscript does not contain personal data, images, or videos from identifiable individuals. Not applicable.*

Availability of data and material: *All data supporting the findings of this review derive from previously published articles. No new datasets were generated. Available upon reasonable request.*

Competing interests: *The authors declare no competing interests.*

Funding: *No funding from public agencies, commercial sectors, or nonprofit organizations was received for this study.*

Authors' contributions: *Néstor Casillas-Vega and Jorge Llaca-Díaz contributed to the conceptualization of the study, literature search, data extraction, evidence synthesis, manuscript drafting, and final approval of the submitted version.*

Acknowledgments: *The authors wish to acknowledge the contributions of the researchers whose work forms the foundation of this systematic review.*

Looking ahead, it is crucial to strengthen epidemiological surveillance, promote more rational antibiotic use, and update therapeutic guidelines according to local realities. Educating both clinicians and patients are key steps to curb this threat and preserve effective treatment options.

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