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Bacterial resistance to azithromycin: causes, effects, and the fight against COVID-19

Resistência bacteriana à azitromicina: causas, efeitos e combate ao COVID-19

Resistencia bacteriana a la azitromicina: causas, efectos y la lucha contra el COVID-19

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Abstract
Introduction: azithromycin was one of the most employed medications during the beginning of the SARS-CoV2 pandemic, despite the lack of scientific basis for its use treatment of COVID-19. Its uncontrolled adoption has risen as a public health problem, as it promotes the appearance of drug-resistant bacterial strains, making it difficult to effectively treat many bacterial infections. Objective: to understand the implications of bacterial resistance to azithromycin in the treatment of infections in the fight against COVID-19. Methods: we surveyed a total of 38 scientific articles. The inclusion criteria were: studies whose central theme was bacterial resistance to azithromycin in the treatment of bacterioses and azithromycin in the fight against COVID-19, published from 2015 to 2022. Results: the widespread use of antibiotics may act in the selection of bacterial strains which had long held genetic traits for drug resistance, but which, not representing adaptative advantages, did not proliferate in the subsequent lineages. This direct proportionality between the widespread use and bacterial resistance to azithromycin is yet more aggravated in COVID-19 times, when part of the medical community and layman population self-medicates with azithromycin, without a scientific basis that justifies choosing this drug. Conclusion: there is a direct relationship between the indiscriminate use of azithromycin and a potential bacterial resistance to this drug. The appearance of resistant bacteria represents a serious public health problem due to the broad use of azithromycin against several bacterial infections.
Keywords: Azithromycin; Antibacterial drug resistance; COVID-19; Virology.

Resumo

Introdução: a azitromicina foi um dos medicamentos mais empregados durante o início da pandemia de SARS-CoV2, apesar da falta de embasamento científico para seu uso no tratamento da COVID-19. Sua adoção descontrolada tem se tornado um problema de saúde pública, pois promove o aparecimento de cepas bacterianas resistentes aos medicamentos, dificultando o tratamento eficaz de muitas infecções bacterianas. Objetivo: compreender as implicações da resistência bacteriana à azitromicina no tratamento de infecções no combate à COVID-19. Métodos: pesquisamos um total de 38 artigos científicos. Os critérios de inclusão foram: estudos cujo tema central fosse resistência bacteriana à azitromicina no tratamento de bacterioses e azitromicina no combate à COVID-19, publicados de 2015 a 2022. Resultados: o uso generalizado de antibióticos pode atuar na seleção de cepas bacterianas que detinham por muito tempo traços genéticos para resistência a drogas, mas que, não representando vantagens adaptativas, não proliferaram nas linhagens subsequentes. Essa proporcionalidade direta entre o uso generalizado e a resistência bacteriana à azitromicina é ainda mais agravada em tempos de COVID-19, quando parte da comunidade médica e população leiga se automedicam com azitromicina, sem base científica que justifique a escolha desse medicamento. Conclusão: existe uma relação direta entre o uso indiscriminado de azitromicina e uma potencial resistência bacteriana a esta droga. O aparecimento de bactérias resistentes representa um grave problema de saúde pública devido ao amplo uso da azitromicina contra diversas infecções bacterianas.
Palavras-chave: Azitromicina; Farmacorresistência bacteriana; COVID-19; Virologia.

Resumen

Introducción: la azitromicina fue uno de los medicamentos más empleados durante el inicio de la pandemia por SARS-CoV2, a pesar de la falta de base científica para su uso en el tratamiento de la COVID-19. Su adopción descontrolada se ha convertido en un problema de salud pública, ya que favorece la aparición de cepas bacterianas resistentes a los medicamentos, lo que dificulta el tratamiento eficaz de muchas infecciones bacterianas. Objetivo: comprender las implicaciones de la resistencia bacteriana a la azitromicina en el tratamiento de infecciones en la lucha contra la COVID-19. Métodos: se encuestaron un total de 38 artículos científicos. Los criterios de inclusión fueron: estudios cuyo tema central fuera la resistencia bacteriana a la azitromicina en el tratamiento de bacteriosis y azitromicina en la lucha contra el COVID-19, publicados de 2015 a 2022. Resultados: el uso generalizado de antibióticos puede actuar en la selección de cepas bacterianas que había tenido durante mucho tiempo rasgos genéticos para la resistencia a los medicamentos, pero que, al no representar ventajas adaptativas, no proliferaron en los linajes posteriores. Esta proporcionalidad directa entre el uso generalizado y la resistencia bacteriana a la azitromicina se agrava aún más en tiempos de COVID-19, cuando parte de la comunidad médica y la población profana se automedica con azitromicina, sin una base científica que justifique la elección de este fármaco. Conclusión: existe una relación directa entre el uso indiscriminado de azitromicina y una potencial resistencia bacteriana a este fármaco. La aparición de bacterias resistentes representa un grave problema de salud pública debido al amplio uso de la azitromicina contra diversas infecciones bacterianas.
Palabras clave: Azitromicina; Farmacorresistencia bacteriana; COVID-19; Virología.

1. Introduction

In 2020, the COVID-19 pandemic broke out, caused by the SARS-CoV2 virus, and provoking several deaths throughout the world. In this context, we observed an increase in the curve of self-medication by individuals, oftentimes influenced by the propagation of fake news in social and broadcast media, generally with no scientific basis. From there on, one of the most self-prescribed drugs used in a supposed fight against COVID-19 was azithromycin. The spread of indiscriminate use of this drug opened doors to an increase in bacterial resistance to this drug and its class. (Freires & Rodrigues Júnior, 2022).

Azithromycin is a broad-spectrum macrolide antibiotic of the azalide subgroup, derived from erythromycin. It presents an increased activity against gram-negative bacteria and coverage against many gram-positive organisms. It is effective against infections by *Chlamydia trachomatis*, *Chlamydophila psittaci*, *Legionella pneumophila*, *Mycobacterium avium*, *Streptococcus pneumoniae*, *Hemophilus influenzae,* and *Moraxella catarrhalis*, among others (Sandman & Iqbal, 2021).

In this context, the indiscriminate use of azithromycin emerges as a public health issue, as it promotes the emergence of bacterial strains resistant to the drug, hindering the effectiveness of the treatment of many bacterioses. (Freires & Rodrigues Júnior, 2022). Given the above, the objective of this review was to understand the implications of bacterial resistance to

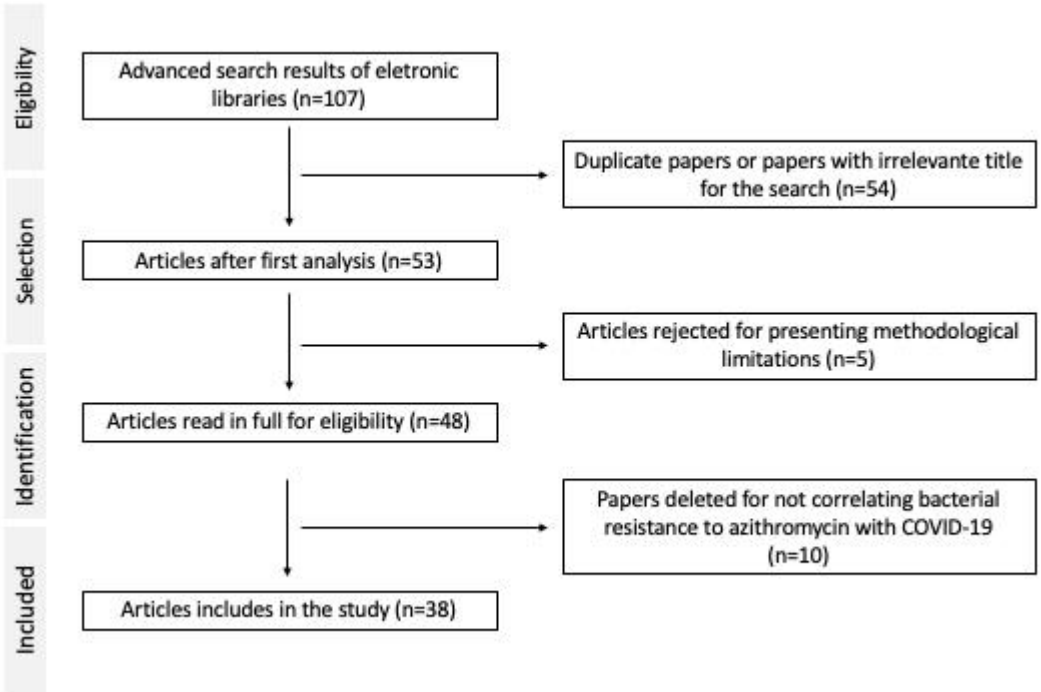
azithromycin in the treatment of bacterioses, in the context of the fight against COVID-19.

2. Methodology

The bibliographic survey was carried out in January 2022. Our research focused on the problem "Bacterial resistance to azithromycin: causes, effects and the fight against COVID-19". We used the following electronic libraries: Scielo; Research Society and Development; BVS; PubMed; MDPI; and Google Scholar. The descriptors used for the advanced search were: “azithromycin”, “bacterial resistance”, “azithromycin resistance”, “COVID-19”, and “coronavirus azithromycin”.

Over the course of two weeks, we found 107 articles, out of which we selected 53, since 54 of these publications were duplicate articles, or articles with titles that were irrelevant for our research focus. From the selected works, 5 were rejected during the reading of the abstracts because they did not directly or indirectly correlate bacterial resistance to azithromycin with COVID-19, or talked about the topic tangentially, and 10 were rejected because they had methodological limitations, such as: sample small population; lack of randomization; and omission of important clinical data, with the exception of two studies, which, despite having the problems highlighted above, were used to refine the critical discussion throughout this review. As a result, a total of 38 articles were included in the study. Our inclusion criteria were centered on papers whose central theme was bacterial resistance to azithromycin in the treatment of bacterioses, and azithromycin in the fight against COVID-19, published from 2015 to 2022. The articles found in the search went through the steps of analysis of the abstracts, followed by full text reading and analysis for inclusion.

Figure 1: Steps for selecting articles for bibliographic review:



Source: Authors.

3. Results and Discussion

3.1 Azithromycin:

Azithromycin is a macrolide whose molecular structure has a methyl substituted nitrogen atom incorporated into the

lactone ring, making the lactone ring 15 carbons. Its pharmacological action prevents bacteria from growing, so they are bacteriostatic agents. (Adam *et al*., 2021).

Davidson (2019) states that azithromycin is active against many gram-positive organisms, including erythromycin-susceptible *Streptococcus pneumoniae*; Groups A, B, C, and G streptococci; and methicillin-susceptible *Staphylococcus aureus*. This drug presents expanded activity against susceptible gram-negative organisms, including *Haemophilus* spp., *Moraxella catarrhalis*, *Escherichia coli*, *Salmonella* spp., *Yersinia enterocolitica*, *Shigella* spp., *Campylobacter jejuni*, *Vibrio cholerae*, *Neisseria gonorrhoeae*, *Helicobacter pylori*, and *Bordetella pertussi*. Thus, in clinical practice, many professionals prescribe azithromycin for the treatment of streptococcal pharyngitis, pneumonia, otitis media, gonorrhea, and chlamydia.

Regarding its mechanism of action, azithromycin acts on bacteria susceptible to its antibacterial activity, binding itself to the 23S portion of the bacterial 50S ribosomal subunit, inhibiting the synthesis of new proteins by the bacteria and preventing the transit of aminoacyl-tRNA and of the growing protein through the ribosome (Sandman; Iqbal, 2021). In addition to its antibiotic action, azithromycin has a potent immunomodulatory action, reducing airway neutrophilia, IL-8 expression and C-reactive protein levels in lung transplant recipients (Sandman & Iqbal, 2021).

3.2 Use of azithromycin in the treatment against SARS-CoV2:

The fact that patients with COVID-19 present complications of pneumonia and acute respiratory distress is used as the justification for therapeutic application of azithromycin during the current pandemic (Firth & Prathapan, 2020). In addition, an antiviral effect of this drug has been long since observed in *in vitro* studies, garnering interest on the part of the population in using this drug for the experimental treatment of SARS-CoV2 (Sandman & Iqbal, 2021).

COVID-19 is marked by hyperinflammation. SARS-CoV-2 infection leads to a dysregulated inflammatory response known as macrophage activation syndrome. (Merad & Martin, 2020) Reducing concentrations of IL-1b, a key inflammatory mediator produced by monocytes and macrophages, is therefore one of many therapeutic strategies currently under exploration (Cavalli *et al*., 2020). Although initially used as antibiotics, the concept of using macrolides primarily for their immunomodulatory activities was introduced in the 1970s. Today, their ability to influence airway inflammation in particular is well established. An examination of the pharmacological profile of azithromycin unsurprisingly reveals a plethora of anti-inflammatory properties that treat both hyperinflammation and progressive pneumonia of the lungs (Firth & Prathapan, 2020).

IL-1b is a key mediator of the inflammatory response and is most abundantly produced by monocytes and macrophages that infiltrate the lungs during the COVID-19 pathogenesis (Firth & Prathapan, 2020). Evidence from animal and *in vitro* studies demonstrates that IL-1b inhibition by azithromycin occurs through disruption of pro-inflammatory intracellular signaling transduction pathways and gene expression, even in the absence of an infectious agent (Zimmermann *et al*., 2018).

The clinical success of macrolides is largely due to their excellent tissue penetration; azithromycin concentrations in macrophages, in particular, were observed to be 5 to 200-fold higher in tissue compared to serum, suggesting a lower dosage requirement when compared to other classes of antibiotics (Zimmermann *et al*., 2018). Most crucially, the localization of azithromycin in macrophages can rapidly alleviate COVID-19-associated macrophage activation at sites of infection within the lung (Firth & Prathapan, 2020).

As the COVID-19 disease progresses, activated monocyte-derived macrophages release pro-inflammatory cytokines, leading to a cytokine storm and acute respiratory distress syndrome (ARDS) (Mehta *et al*., 2020). The potential benefit of the immunomodulatory and anti-inflammatory actions of macrolides was assessed in these respiratory viral infections, although in small studies, and with contradictory results (Stein *et al*., 2015).

The immunomodulatory and antiviral action of azithromycin, thus, happens due to the drug mimicking a ganglioside similar in volume and with characteristics analogous to monosialoganglioside (GM1). Therefore, as the SARS-CoV2 spike

protein exhibits a ganglioside binding site, competition occurs between the drug and this protein for the binding site (Esnal, 2021).

However, the real effectiveness of azithromycin for the treatment of COVID-19 is quite controversial, as there is a scarcity of studies that justify its use for this purpose. The adoption of this medication during the SARS-CoV2 pandemic was mainly based on political pressure from some countries, such as Brazil, rather than on scientific evidence (Imperator *et al*., 2020).

From recent observational studies, there is strong evidence pointing to an absence of association between azithromycin and any clinical benefits in the management of COVID-19 (Ayerbe *et al*., 2022).

Another relevant aspect to be considered is that no difference was found regarding deaths for those treated with or without azithromycin in observational studies [OR: 0.90 (0.66–1.24)], RCTs [OR: 0.97 (0. 87–1.08)], and when studies with both designs were pooled together [OR: 0.95 (0.79–1.13)] (Ayerbe *et al*., 2022).

In this case, the main evidence that actually displays a direct benefit of azithromycin in the fight against COVID-19 comes from an open, non-randomized study, carried out in France. In this study, 42 patients hospitalized with COVID-19 for 14 days were recruited. Six of these subjects were treated with 600 mg hydroxychloroquine daily, and azithromycin (500 mg on day 1, followed by 250 mg daily for the next 4 days). They observed that 100% of patients had no detectable viral load after 6 days of infection, compared with 57.1% in patients treated with hydroxychloroquine monotherapy (n = 14) and 12.5% in the control group (n=16). However, this paper contains several methodological limitations that critically affect the quality of the research, such as poor reporting, missing PCR data, unjustified exclusion of patients with clinically relevant outcomes, very small population, and lack of randomization (Sultana *et al*., 2020).

A larger study recruited 1,438 hospitalized patients diagnosed with COVID-19, out of which 735 individuals received hydroxychloroquine plus azithromycin, 271 received only hydroxychloroquine, and 211 were medicated with other drugs. Statistical analyses, in turn, showed no significant differences in in-hospital mortality for patients who received hydroxychloroquine plus azithromycin, hydroxychloroquine alone, or azithromycin alone, compared with patients who received neither drug (Sultana *et al*., 2020).

According to another meta-analysis study, the absence of a beneficial effect of azithromycin for the treatment of COVID-19 was evidenced. This same study, in turn, also highlighted an increase in mortality in patients with SARS-CoV2 due to the combined use of azithromycin and hydroxychloroquine for COVID-19 therapy, since a first study observed that 6 out of 18 patients (33%) developed a significant increase in the QT interval on their electrocardiograms. A second study found that, in 84 patients treated with hydroxychloroquine and azithromycin, nine had severe QT prolongation. Another New York study with 1,438 patients found that cardiac arrest was significantly more likely in patients who received hydroxychloroquine with azithromycin compared with patients who received neither (Fiolet *et al*., 2020).

Concomitantly, a study carried out using the WHO database, gathering more than 167,000 patients, found an increased risk of potentially fatal acute cardiac events in patients treated with azithromycin or hydroxychloroquine alone. The combination of both drugs resulted in an even greater risk of life-threatening acute cardiac effects (Dolladille *et al*., 2020).

Tabela 1: Resultado terapêutico da azitromicina (isolada ou combinada com outra medicação) nos principais estudos publicados nos últimos dois anos.

Medications	Dose	Population sample (n)	Results	Author
Hydroxychloroquine + Azithromycin	Hydroxychloroquine: 600 mg a day Azithromycin: 500 mg on the first day, followed by 250 mg for the next 4 days	n = 6	100% patients treated (n = 6) within 6 days of the treatment	GAVTRET *et al*., 2020
Hydroxychloroquine + Azithromycin	Hydroxychloroquine: 600 mg a day Azithromycin: 500 mg on the first day, followed by 250 mg for the next 4 days	n = 11	8 patients (73%) still tested positive for SARS-CoV2; 1 patient died and 2 patients were transferred to ICU	MOLINA *et al*., 2020
Hydroxychloroquine + Azithromycin	Not informed in the study.	n = 735	There was no significant difference in mortality with SARS-CoV2	ROSENBERG *et al*., 2020
Azithromycin	Not informed in the study.	n = 211	There was no significant difference in mortality with SARS-CoV2	ROSENBERG *et al*., 2020
Hydroxychloroquine + Azithromycin	Not informed in the study.	n = 8,081	1,603 deaths	FIALET *et al*., 2020
Azithromycin	500 mg daily for 3 days	n = 540	Findings did not justify the routine use of Azithromycin to reduce hospitalization times	BUTLER *et al*, 2021
Azithromycin	1,2 g in a single oral dose	n = 171	The use of azithromycin presented no significant efficacy when compared to the control group	BROGDON *et al*., 2021
Azithromycin	500 mg daily, orally, for 14 days	n = 145	Azithromycin did not reduce the risk of hospital admission or death	HINKS *et al*., 2021
Hydroxychloroquine + Azithromycin	Azithromycin: 500 mg daily, for 3 days, followed by 250 mg for 12 days more Hydroxychloroquine: 200 mg, twice a day, for 15 days	n = 61	The medication combination did not improve patient survival	SILVAPALAN *et al*., 2022
Hydroxychloroquine + Azithromycin	Hydroxychloroquine: 200 mg, twice a day, for 7 days Azithromycin: 500 mg on the first day, followed by 250 mg for the next 4 days	n = 36	Viral shedding rates did not change with hydroxychloroquine and azithromycin treatment compared to placebo	RODRIGUES *et al*., 2021
Hydroxychloroquine + Azithromycin + Lopinavir/Ritonavir (LPV/r)	Azithromycin: 500 mg daily, orally, for 5 days LPV/r: 400/100 mg, orally, twice a day for 5 days Hydroxychloroquine: 200 mg daily, for 7 days	n = 56	A shorter hospital stay was observed, but no medication was shown to be significantly efficient	SEKHAVAT *et al*., 2020
Azithromycin	500 mg daily, for 10 days	n = 561	Azithromycin did not improve survival or clinical aspects for the patients	RECOVERY, 2021
Azithromycin	500 mg orally, nasogastrically, or intravenously, daily, for 10 days	n = 214	Azithromycin did not present results that would justify its use	FURTADO *et al*., 2020
Hydroxychloroquine + Azithromycin	Hydroxychloroquine: 400 mg, twice a day, for 7 days Azithromycin: 500 mg daily for 7 days	n = 217	The use of these medications did not generate better results in patients hospitalized with COVID-19	CAVALCANTI *et al*., 2020
Azithromycin	500 mg orally, nasogastrically, or intravenously, daily, for 10 days or until hospital discharge	n = 2,582	Azithromycin did not present clinical benefits	HORBY *et al*., 2020

Source: Authors.

3.3 Bacterial resistance to azithromycin:

Over time, it is natural for some bacteria to acquire resistance against the action of antibiotics, since the drug selects the most resistant microorganisms, which can take place through several mechanisms of action. This phenomenon is a natural ecological event, a product of billions of years of evolution, in the absence of human action, due to the exposure of microorganisms to antimicrobial substances, produced by other microorganisms. This process favors the selection of resistance genes, which in turn can be transferred to human pathogens (Blair *et al*., 2015).

Antimicrobial resistance, in turn, occurs through physiological mechanisms of the bacterium. Among those, it is worth mentioning exposure to drugs, through genetic mutation, by plasmids, which are small fragments of DNA that carry resistance from one bacterium to another through genetic recombination by conjugation, transformation, transduction, or transposition. There are also defense mechanisms present in the bacterial cell such as porins and efflux pumps (Moreno, 2017).

Regarding azithromycin, the main mechanism for increasing bacterial resistance to this antibiotic is changing the target of the active ingredient on the ribosome. This is because the erm gene of the bacteria demethylates the adenine nucleotide of the 23S subunit and alters its conformation 12, preventing the macrolide from binding to the ribosome, thus interrupting the translocation of the peptide chain (Griffith, 2019).

Staphylococci and streptococci, in turn, produce proteins responsible for the flow of macrolides out of the cytoplasm, reducing the effective concentration of antibiotics in the cell, thus preventing their effective effects. Gram-negative bacteria, on the other hand, may have different pore proteins in their cell membranes, preventing azithromycin from entering the cytoplasmic space, which is a less common mechanism (OPAL, 2015).

Widespread use of antibiotics can act in the selection of bacterial strains that have had genetic characteristics for a long time, but which, because they do not provide adaptive advantages, did not proliferate in the following strains. With the drug acting only on sensitive lines, the hereditary transmission of the resistant trait will stand out in the following generations, originating a population resistant to the drug (OPAL, 2015).

This direct proportion between widespread use and bacterial resistance to azithromycin is even worse in times of COVID-19, when part of the medical community and the lay population make use of azithromycin self-medication without a scientific basis that justifies the adoption of this drug. This practice, in turn, is largely stimulated by the spread of fake news on social and broadcast media (Guimarães & Carvalho, 2020).

In most cases, the use of azithromycin was proven to be unnecessary, evidencing the indiscriminate prescription of the medication, which in turn aggravates bacterial resistance to the antibiotic in question. According to the World Health Organization (WHO, 2020), only 15% of those infected with SARS-CoV2 develop a bacterial co-infection that justifies the use of antibiotic therapy, whereas in 59% of COVID-19 hospitalizations, azithromycin was administered, even without the presence of bacterial co-infection (Wei, 2020).

4. Conclusion

There is a direct relationship between the indiscriminate use of azithromycin and potential bacterial resistance to this drug. The emergence of resistant bacteria is a serious public health issue, due to the widespread use of azithromycin for several bacteria. Therefore, caution and care must be taken when prescribing this drug during a SARS-CoV2 pandemic, into consideration the clinical condition of the patient, and its use is advisable only when there is a bacterial co-infection that justifies it.

Furthermore, a considerable part of the population that adopted azithromycin for the treatment of SARS-CoV2 did not have a bacterial co-infection that justifies its use, administering the drug on their own, without a proper medical indication, which may lead to a greater predisposition to the generation of drug resistant bacterial strains.

Concomitantly, the latest published studies reveal that azithromycin is not efficient for combating COVID-19, being associated with a series of adverse effects, such as prolongation of the QT interval on the electrocardiogram. Therefore, the use of this drug in the treatment against SARS-CoV2 should be avoided.

It is necessary to carry out more laboratory research to assess the magnitude of the resistance acquired by different bacterial strains in relation to the antibiotic action of azithromycin, so, in this case, it is possible to establish a definitive relationship of the impacts generated by the indiscriminate use of this drug.

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