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Addressing Iron deficiency anemia in Bangladesh: The role of west Bengal chemical industries ltd., Kolkata, India to manufacture ferric citrate in enhancing bioavailability and reducing side effects

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Abstract

Anemia, a condition marked by reduced red blood cell or hemoglobin levels, affects over 1.92 billion people globally, with a particularly high prevalence in Bangladesh. This condition impedes oxygen delivery, leading to fatigue, weakness, and diminished physical productivity, contributing to economic challenges, especially in developing regions. Iron supplementation remains central to anemia management, yet traditional iron salts, such as ferrous sulfate and ferrous fumarate, often result in gastrointestinal discomfort, limiting patient adherence. Ferric citrate, with its improved bioavailability, enhanced gastrointestinal tolerance, and stability across varying pH levels, represents a promising alternative. Furthermore, ferric citrate offers additional benefits, such as reducing serum phosphate levels and binding uremic toxins, making it advantageous for populations with kidney disease and for pregnant women who require safer iron supplementation.

West Bengal Chemical Industries Ltd. (WBCIL) manufactures a high-purity ferric citrate with stringent quality standards, ensuring minimal contaminants like heavy metals and organic acids, which enhances safety and efficacy. Despite these advantages, ferric citrate is underutilized in Bangladesh, where traditional iron salts dominate the market. Increasing awareness and accessibility of ferric citrate could significantly improve anemia management, particularly for vulnerable populations. This review highlights the potential of ferric citrate in addressing Bangladesh's anemia burden, emphasizing its clinical benefits, safety profile, and need for broader adoption in public health initiatives.

Keywords: Anemia; Ferric Citrate; Hemoglobin; Fatigue; Weaknesses

1. Introduction

Anemia, defined as a deficiency in red blood cells or hemoglobin, remains a significant public health issue worldwide, impacting both individual health and economic productivity. It is estimated that around one-third of the global population suffers from anemia, making it one of the most prevalent health conditions [1,2]. Anemia affects the body's ability to transport oxygen, leading to symptoms such as fatigue, weakness, and reduced physical and mental capacity. Severe cases can result in complications like cardiovascular strain, shortness of breath, and even loss of consciousness [3]. The condition can also manifest in physical signs like pallor, cool skin, and tachypnoea, while specific indicators like jaundice, glossitis, and cheilitis can suggest underlying causes such as hemolysis or deficiencies in iron and vitamins. [2,4] The condition not only undermines individual well-being but also reduces workforce efficiency, thereby hampering economic growth, particularly in developing countries.

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2. The Global and National Burden of Anemia

Anemia continues to affect millions of individuals worldwide, particularly women of reproductive age, pregnant women, and young children. These vulnerable populations suffer from higher anemia rates due to increased nutritional demands and limited access to essential nutrients like iron [5]. However, this burden is not evenly distributed. Children under five and women of reproductive age, particularly pregnant women, are demonstrably more vulnerable [6]. Globally, 40% of children aged 6 to 59 months and 37% of pregnant women are estimated to suffer from anemia. Bangladesh, in particular, has struggled with high rates of anemia, where 46.8% of children and adolescents are affected, as revealed in a meta-analysis conducted between 1997 and 2019. In Bangladesh, the prevalence is highest among children under two, with a staggering 61% affected by anemia [7].

In non-pregnant women, anemia remains a significant issue, with 41% of women aged 15–49 found to be anemic, especially those in rural areas or from low-income households [8]. Although progress has been made through public health initiatives, anemia continues to pose a significant health challenge, particularly for women and children in Bangladesh. Despite ongoing efforts to combat anemia, the condition persists, largely due to a combination of poor nutrition, parasitic infections, and inadequate healthcare access [9].

3. Iron Deficiency and the Importance of Supplementation

Iron deficiency is the leading cause of anemia, though other factors like vitamin deficiencies, chronic diseases, and genetic conditions also contribute. Addressing iron deficiency through proper supplementation is critical to reducing anemia prevalence, especially among high-risk groups. In Bangladesh, various iron supplements have been used over the years, including ferrous sulfate, ferrous fumarate, and iron sucrose etc. These supplements, though effective in treating iron deficiency, often come with side effects that limit patient adherence, such as gastrointestinal discomfort, constipation, and nausea [7].

National policy documents/reports on existing interventions of the country have been analysed. Nearly half of pregnant and lactating women experience anemia, with factors such as inadequate diets, poor hygiene, infections, and infestations contributing significantly to high deficiency levels. Despite various interventions and approaches making some notable progress, challenges still persist, particularly concerning coverage, quality, and adherence to iron supplements. While current intervention programs have made strides in addressing severe deficiencies, micronutrient deficiencies continue to be a significant issue in Bangladesh. There is a need for more cohesive strategies to enhance and strengthen the existing programs [10].

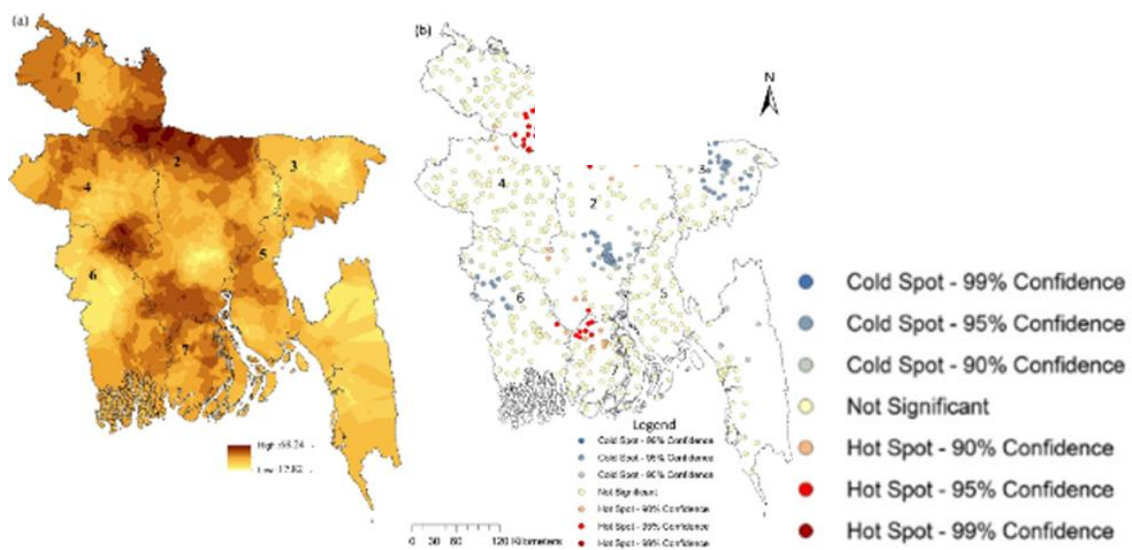


Figure 1 Spatial distribution (a) and hotspots (b) of the prevalence of anaemia among women in Bangladesh. Note: 1.Rangpur, 2. Dhaka, 3.Sylhet 4.rajshahi,5.chittagong, 6.Khulna 7.Barisal [2]

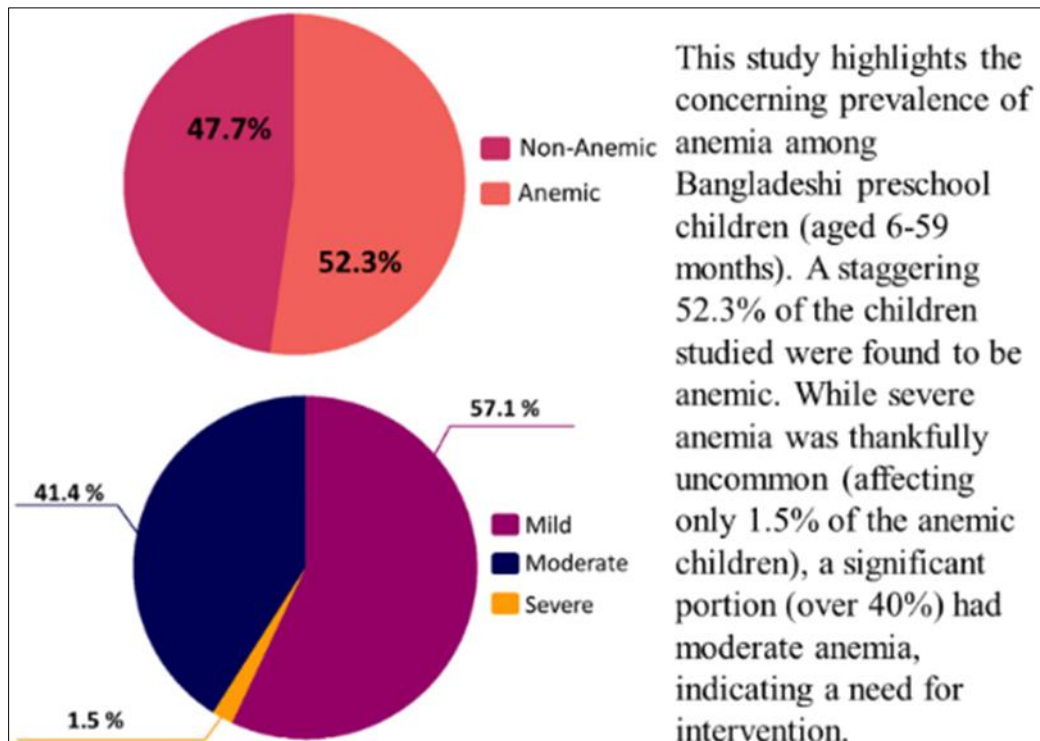
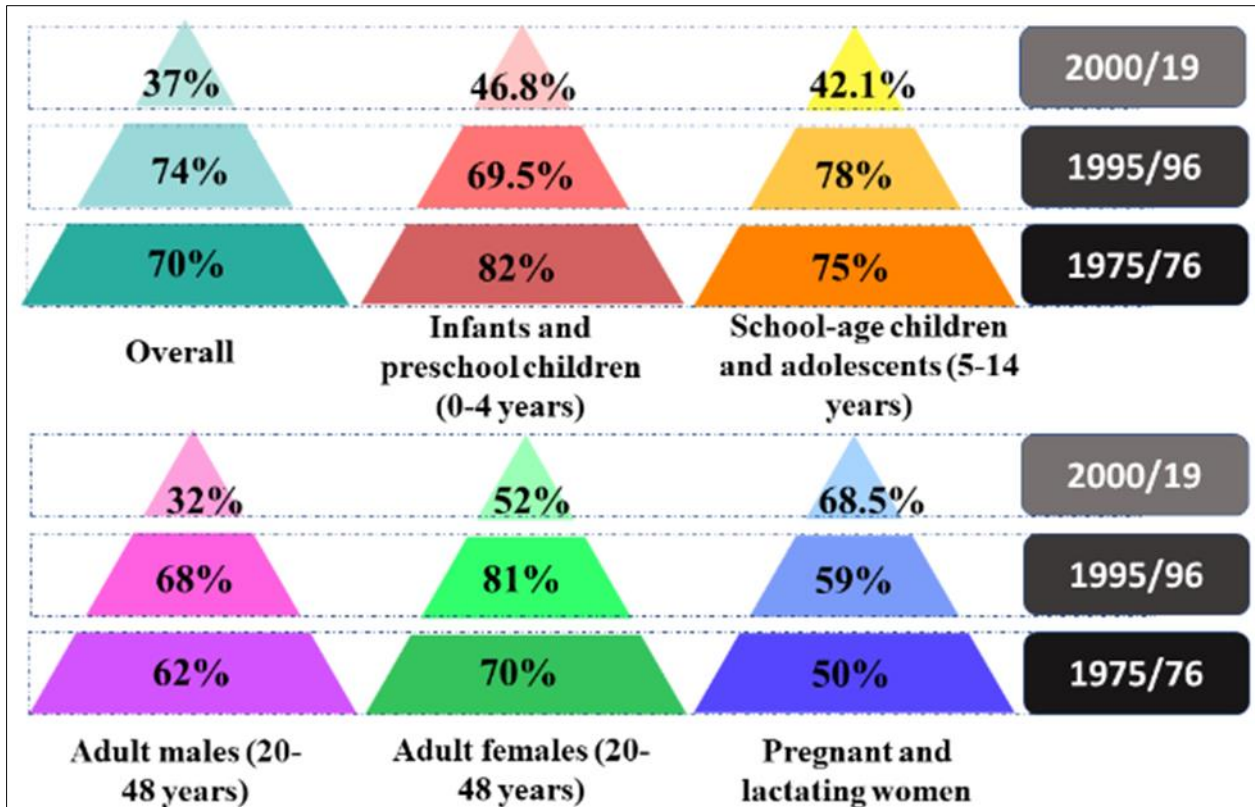


Figure 2 Prevalence of anaemia in Bangladesh [11,12]

In Bangladesh, high prevalence rate of anaemia affect many young individuals. This leads to reduced physical productivity and increased healthcare costs, with broader economic consequences. The condition is especially concerning for pregnant and lactating women, further perpetuating a cycle of lower economic output and higher expenditures. Iron supplementation is a key intervention, with various salt of iron available, such as, ferrous sulfate

(FeSO₄), ferrous gluconate (Fe(C₆H₁₁O₇)₂), ferrous fumarate (C₄H₂FeO₄), and iron hydroxide polymaltose complex each with distinct advantages and limitations [13,14].

Table 1 Iron supplements vary in effectiveness and side effects by decreasing order of severity

Iron Supplement	Common Side Effects	Severity	Remarks
Ferrous Sulfate	Nausea, constipation, abdominal pain, dark stools, diarrhea, metallic taste [15]	High	Commonly causes gastrointestinal discomfort. High risk of oxidative stress due to Fe ²⁺ .
Ferrous Fumarate	Constipation, nausea, vomiting, dark stools, stomach cramps [16]	High	Similar to ferrous sulfate but with slightly less gastrointestinal irritation.
Iron Sucrose	Nausea, hypotension, headache, dizziness, joint pain, injection site reactions [17,18]	Moderate to Severe	May require multiple doses and clinical supervision. Risk of injection-related side effects.
Ferrous Gluconate	Gastrointestinal discomfort, constipation, nausea, diarrhea [14]	Moderate to High	Better tolerated than ferrous sulfate, but still associated with significant gastrointestinal side effects.
Iron (III) Hydroxide Polymaltose	Constipation, nausea, flatulence, diarrhea [19]	Moderate	Less gastrointestinal irritation compared to ferrous salts, but still causes mild to moderate digestive issues.
Ferrous Ascorbate	Nausea, vomiting, constipation, diarrhea, dark stools, metallic taste [20]	Moderate	Generally well-tolerated, but may cause gastrointestinal side effects.
Ferric Citrate	Mild and less frequent gastrointestinal incidence, low risk of oxidative stress [21]	Low	Well tolerated with minimal side effects. Provides controlled iron release and reduces oxidative stress.

4. The Case for Ferric Citrate in Bangladesh

The extensive use of ferrous sulphate and other iron-based APIs, such as ferrous gluconate and ferrous fumarate, has been hindered by the frequent occurrence of gastrointestinal side effects. These adverse reactions—including nausea, abdominal pain, and severe constipation—have significantly impacted patient adherence. Although these iron salts are clinically effective, their poor tolerability often prevents patients from completing their treatment regimens, thereby impeding successful therapeutic outcomes.

To illustrate this progression, the following chart presents the timeline of key iron APIs introduced in Bangladesh, along with the current number of local manufacturers producing these APIs. This data highlights the ongoing efforts by the pharmaceutical industry to expand the availability of iron supplements and optimize anaemia management strategies.

Table 2 Iron APIs (Active Pharmaceutical Ingredients) used in Bangladesh along with their approval dates: source Directorate General of Drug Administration (DGDA)[18]

Iron API	Approval Date in Bangladesh	Total number of manufacturers
Ferrous Sulfate	1970s	130
Ferrous Fumarate	1980s	20
Ferrous Gluconate	1980s	7
Iron Sucrose	2000s	23
Iron (III) Hydroxide Polymaltose	2000	13
Ferrous Ascorbate	2020s	3
Ferric Citrate	2022	3

Despite the multitude of iron APIs available in the market, the quest for an ideal formulation that offers maximum efficacy with minimal side effects continues. Traditional iron salts such as ferrous sulfate, ferrous fumarate, and iron sucrose are produced by a large number of manufacturers—130 for ferrous sulfate, 20 for ferrous fumarate, and 23 for iron sucrose. However, these widely used APIs are often associated with severe gastrointestinal side effects, poor absorption, and low patient compliance, which ultimately result in suboptimal treatment outcomes. This has left iron deficiency anemia (IDA) as a persistent health challenge, particularly in regions like Bangladesh, where an ideal solution has yet to be found.

Given these limitations, pharmaceutical companies and healthcare providers are constantly seeking a new and improved iron API. However, despite numerous efforts to find a superior alternative that addresses both safety and efficacy concerns, success has been limited. This gap underscores the need for more research and innovation in the field of iron supplementation.

Amidst this ongoing search, ferric citrate has emerged as a promising alternative with significant clinical benefits and improved tolerability compared to conventional iron salts. Its unique dual mechanism of action—providing iron supplementation and acting as a phosphate binder—offers a safer and more effective approach for managing iron deficiency anemia.

The market landscape in Bangladesh shows a disparity between the availability of older iron APIs and newer, more advanced options. As shown in Table 2, ferrous sulfate, which was approved in the 1970s, has the highest number of manufacturers at 130, reflecting its longstanding presence and availability. Ferrous fumarate and ferrous gluconate, both approved in the 1980s, have 20 and 7 manufacturers respectively, indicating a moderate level of production. Similarly, iron sucrose, approved in the 2000s, is manufactured by 23 companies, while iron (III) hydroxide polymaltose, introduced in the same decade, is produced by 13 manufacturers. Ferric maltol, which received approval in the 2020s, has 10 manufacturers currently producing it. In contrast, ferric citrate, the most recent entrant approved in 2022, is produced by only three manufacturers, highlighting its limited market penetration despite its clinical advantages.

Given this scenario, it is essential to create greater awareness and promote the use of ferric citrate. Increased advocacy and education about its distinct benefits and improved tolerability profile can help position it as a superior option for iron supplementation. Establishing a stronger platform for ferric citrate and encouraging its broader adoption could pave the way for it to become a leading choice in the management of iron deficiency anemia, ultimately contributing to better patient outcomes and addressing the current gaps in iron supplementation.

5. Benefits of Ferric Citrate

Ferric citrate is an iron supplement that offers several unique benefits over traditional iron salts. These benefits include improved absorption, better gastrointestinal tolerance, and the added ability to bind uremic toxins in the gastrointestinal tract, making it particularly beneficial for patients with kidney disease or those exposed to toxins [19,20]. Ferric citrate also helps reduce serum phosphate levels, making it useful in managing both iron deficiency and hyperphosphatemia in certain patient populations [21,22].

Some of the key advantages of ferric citrate in treating anaemia include:

- Ferric citrate offers superior bioavailability, gastrointestinal tolerance, and stability compared to other iron supplements.
- Its enhanced absorption ensures effective replenishment of iron stores, even in cases of severe deficiency.
- Ferric citrate's gentle action on the digestive system minimizes gastrointestinal side effects [23].
- It maintains its efficacy across a wide range of pH levels, making it suitable for patients with various gastric conditions [24].
- In addition to treating iron deficiency, ferric citrate can reduce serum phosphate levels [25].

The pharmaceutical industry in Bangladesh should actively explore the integration of ferric citrate into their product offerings, ensuring that a larger segment of the population has access to effective and affordable anemia therapies.

6. Ferric Citrate in Pregnancy and Chronic Conditions

Ferric citrate also holds promise for pregnant women, who are at increased risk of both iron deficiency and toxin exposure. The ability of ferric citrate to reduce oxidative stress and bind harmful toxins offers an additional protective benefit during pregnancy, helping to mitigate potential complications arising from oxidative damage [26,27]. Its use in

patients with chronic kidney disease further underscores its versatility as an iron supplement that not only addresses anemia but also reduces systemic toxicity.

7. Toxin Binding Property of Ferric Citrate:

Ferric citrate, an iron-based compound, offers a dual mechanism for addressing both iron deficiency and toxin accumulation. In the gastrointestinal tract, unabsorbed iron can form insoluble complexes with substances like phytates, oxalates, tannins, and polyphosphates, commonly found in foods such as grains, legumes, tea, coffee, and processed meats, reducing its absorption and leading to excretion [28,29,30]. Pregnant and lactating women often experience anemia but frequently struggle with conventional iron supplements due to gastrointestinal intolerance. Ferric citrate offers a unique solution by addressing iron deficiency and binding harmful gastrointestinal toxins, making it especially beneficial for pregnant women. By reducing maternal exposure to toxins such as indoxyl sulfate and p-cresylsulfate, ferric citrate not only supports fetal development but also promotes easier delivery and better new born health outcomes.

This toxin-binding property helps minimize the absorption of harmful compounds, reducing complications that could affect both the mother and the baby during pregnancy and childbirth [31]. In addition to supporting maternal health, ferric citrate's ability to stabilize iron in its ferric form (Fe^{3+}) prevents the formation of reactive oxygen species (ROS), reducing oxidative stress, which is linked to pregnancy complications like preeclampsia and intrauterine growth restriction [32,33]. By minimizing oxidative stress, ferric citrate promotes a healthier pregnancy, reducing the risk of preterm delivery and ensuring smoother labor.

Moreover, by enhancing iron stores and reducing toxin exposure, ferric citrate contributes to improved new born health, supporting better birth weight and reducing risks associated with early iron deficiency in infants. This makes ferric citrate an ideal option for pregnant women seeking a safe, effective, and well-tolerated iron supplement that benefits both maternal health and the well-being of their new-borns. It is a powerful tool for improving pregnancy outcomes, facilitating easier delivery, and promoting healthier children.

8. Ensuring Purity in Ferric Citrate manufactured by West Bengal Chemical Industries

The ferric citrate produced by West Bengal Chemical Industries Ltd. (WBCIL) stands out for its superior quality and adherence to strict purity standards. Free from contaminants such as heavy metals (vanadium, lead, nickel, aluminum, mercury), chlorides, and organic acids (aconitic, oxalic, and acetoacetic acids), WBCIL's ferric citrate ensures a safer and more effective treatment for anemia, setting a high standard in the industry.

Among the available ferric citrate options, the product of West Bengal Chemical Industries Ltd., Kolkata, India (WBCIL) stands out for its superior quality and stringent adherence to purity standards.

- **Heavy metals impurity:** WBCIL's ferric citrate is a meticulously formulated iron supplement designed to minimize the risk of contamination with harmful heavy metals. These contaminants, including vanadium, nickel, lead, aluminium, mercury, and cobalt, can pose significant health risks to individuals of all ages. By ensuring a cleaner and safer iron supplement, WBCIL's ferric citrate offers a superior choice for those seeking to maintain optimal iron levels.
- **Organic impurity:** Unlike other iron supplements that may contain excessive levels of chloride, itaconic acid, aconitic acid, oxalic acid, acetoacetic acid, oxaloacetic acid, methacrylic acid, acetone, formic acid, or diacetone alcohol, WBCIL's ferric citrate ensures a cleaner and safer product. These impurities can contribute to various health issues, including electrolyte imbalances, kidney stones, metabolic disorders, and respiratory problems.

Whether you're a pregnant woman striving for a healthy pregnancy outcome or an individual looking to improve your overall well-being, WBCIL's ferric citrate provides a reliable and effective solution. Its purity and safety make it a trustworthy option for individuals seeking to address iron deficiency without compromising their health.

9. Conclusion

Ferric citrate offers a superior alternative to traditional iron supplements like ferrous sulfate, ferrous fumarate, iron sucrose etc addressing common issues such as gastrointestinal discomfort and poor patient adherence. Despite its clear benefits—enhanced bioavailability, fewer side effects, and additional toxin-binding properties—ferric citrate is significantly underutilized in Bangladesh. While there are 130 manufacturers of ferrous sulfate, 20 of ferrous fumarate,

and 23 of iron sucrose, only 3 manufacturers currently produce ferric citrate. This underutilization presents a unique opportunity for pharmaceutical companies to capitalize on an emerging market need. By increasing the production and promotion of ferric citrate, manufacturers can meet the growing demand for safer, more effective iron supplements. This will not only enhance patient outcomes but also differentiate their product offerings in an increasingly competitive market. West Bengal Chemical Industries Ltd. (WBCIL) is already setting a high standard with its high-purity ferric citrate, ensuring a safer and more efficient anemia treatment option.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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