

Optimizing HPV management: A comprehensive Review Exploring treatment strategies with PEG and Pyrazomycin

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ABSTRACT:

Human papillomavirus (HPV) remains a significant public health concern globally due to its association with various health risks, including cervical cancer and other malignancies. This comprehensive review delves into the diverse aspects of HPV, encompassing its types, transmission, associated risk factors, causes, and treatment strategies. The objectives include providing a detailed examination of HPV, exploring its underlying causes and mechanisms, investigating current treatment approaches, analyzing market trends, and discussing broader public health implications. Notably, the review evaluates the efficacy and safety of existing treatments for HPV, highlighting adverse drug reactions (ADRs) associated with each. Furthermore, it proposes an innovative treatment approach involving a combination of polyethylene glycol (PEG) and pyrazomycin as a potential alternative to current therapies. The rationale for this combination stems from the structural similarities between pyrazomycin and ribavirin, suggesting potential efficacy in HPV treatment. Supporting evidence from the literature underscores the antiviral properties of pyrazomycin and its compatibility with PEG, emphasizing the need for further investigation into this promising treatment avenue. The review concludes by advocating for informed decision-making in healthcare practices and public health policy, offering new possibilities for enhanced HPV care through the exploration of alternative treatment strategies.

I. INTRODUCTION:

Human Papillomavirus (HPV) stands as a critical public health concern due to its widespread prevalence and its association with various health risks, including cervical cancer and other malignancies. With over 100 different types, some of which are categorized as high-risk, HPV infections pose a significant global burden.

Understanding the implications of HPV is vital for public health initiatives, as it not only affects individuals but has broader societal implications.

Human papillomavirus (HPV) is a small, non-enveloped deoxyribonucleic acid (DNA) virus that infects skin or mucosal cells. The circular, double-stranded viral genome is approximately 8-kb in length. The genome encodes for 6 early proteins responsible for virus replication and 2 late proteins, L1 and L2, which are the viral structural proteins. At least 13 of more than 100 known HPV genotypes can cause cancer of the cervix and are associated with other anogenital cancers and cancers of the head and neck. The two most common "high-risk" genotypes (HPV 16 and 18) cause approximately 70% of all cervical cancers. HPV was estimated to cause almost half a million cases and 250,000 deaths from cervical cancer in 2002, of which about 80% occurred in developing countries. Two "low-risk" genotypes (HPV 6 and 11) cause genital warts, a common benign condition of the external genitalia that causes significant morbidity. HPV is highly transmissible, with peak incidence soon after the onset of sexual activity, and most persons acquire infection at some time in their lives.

HPV refers to a group of related viruses, some of which are sexually transmitted and can infect various parts of the body, including the genital area, mouth, and throat. It is the most common sexually transmitted infection (STI) globally. HPV infections are usually transient, but persistent infections, especially with high-risk types, can lead to the development of various cancers, such as cervical, anal, and oropharyngeal cancers.

Objectives of the Review:

1. Comprehensive Overview: Provide a detailed examination of HPV, covering its types, transmission, and associated risk factors, to establish a foundational understanding.

2. Causes and Mechanisms: Explore the underlying causes and mechanisms of HPV infections, shedding light on the virological aspects and host-related factors.
3. Treatment Strategies: Investigate the current approaches to treating HPV infections, including antiviral medications, surgical interventions, and emerging therapeutic options.
4. Market Analysis: Assess the available treatments in the market for HPV, outlining their efficacy and safety, with a focus on Adverse Drug Reactions (ADR).
5. Public Health Implications: Discuss the broader implications of HPV on public health, emphasizing preventive measures, vaccination programs, and awareness campaigns.

Types of HPV:

HPV is classified into low-risk and high-risk types based on their association with cancer. Low-risk types can cause warts, while high-risk types are linked to the development of cancer. Notable high-risk types include HPV 16 and 18, which are responsible for a significant proportion of cervical cancers.

Global Prevalence:

HPV is highly prevalent worldwide. According to global health organizations, the majority of sexually active individuals will be infected with at least one type of HPV at some point in their lives. The prevalence varies across regions and age groups, with a higher incidence among younger populations.

	LOW RISK	HIGH RISK
HPV TYPES	1,6,10,11,32,42,44	16,18,31,33,35,39,45,51,52,56,58,59,66,68
Associated Disease	Anogenital warts Cutaneous warts Recurrent respiratory Papillomatosis	Intraepithelial neoplasia Invasive carcinoma HNSCC, Cervical cancer, Anogenital cancer, Non-melanoma skin cancer

Context:

Understanding the diverse types of HPV and its global prevalence is crucial for appreciating the impact it has on public health. The subsequent sections will delve into the modes of transmission, risk factors, causes, and treatment options for HPV, providing a comprehensive view to inform healthcare practices and public health interventions.

Transmission of HPV:

1. Sexual Contact: The primary mode of HPV transmission is through intimate skin-to-skin contact, typically during vaginal, anal, or oral sex. Even without visible symptoms, the virus can be transmitted.
 2. Vertical Transmission: HPV can be passed from an infected mother to her newborn during childbirth, although this is relatively uncommon.
 3. Non-Sexual Transmission: While less common, non-sexual transmission can occur through close personal contact, such as shared towels or surfaces.
- Risk Factors Associated with HPV Infection:**
1. Sexual Activity: Engaging in sexual activity, especially at a younger age or with multiple partners, increases the risk of HPV exposure.
 2. Immune System Health: A weakened immune system, either due to a medical condition or immunosuppressive medications, can heighten susceptibility to HPV infections.
 3. Smoking: Tobacco use, particularly smoking, is linked to a higher risk of persistent HPV infections and progression to cervical cancer.
 4. Genital Warts: Having a history of genital warts or other sexually transmitted infections (STIs) may increase the likelihood of acquiring or transmitting HPV.
 5. Gender and Age: Certain age groups, particularly adolescents and young adults, are more susceptible to HPV infections. Additionally, females generally face a higher risk of HPV-related complications.
- Understanding these modes of transmission and associated risk factors is crucial for implementing effective prevention strategies and targeted interventions to reduce the incidence of HPV infections.

Causes of HPV:

Viral Factors:

1. HPV Genotypes: Different genotypes of HPV exist, categorized as low-risk and high-risk. High-risk types, such as HPV 16 and 18, have a greater potential to lead to cancer.

2. **Viral Persistence:** Persistent infection with high-risk HPV types is a key factor in the development of HPV-related cancers.

Host-Related Factors:

1. **Sexual Behavior:** Early onset of sexual activity and having multiple sexual partners increase the risk of exposure to HPV.
2. **Immune System:** A compromised immune system, whether due to immunosuppressive medications, diseases like HIV, or other factors, can hinder the body's ability to clear the virus.
3. **Genetic Predisposition:** Some individuals may be genetically predisposed to a higher susceptibility to persistent HPV infections and the development of associated cancers.



How HPV Infections Occur:

1. **Transmission:** HPV is primarily transmitted through direct skin-to-skin contact, most commonly through sexual activity. The virus can infect genital, anal, and oral areas.
2. **Micro abrasions:** Even small cuts or abrasions on the skin can serve as entry points for the virus. Mucous membranes in the genital, anal, and oral regions are particularly vulnerable.
3. **Asymptomatic Transmission:** HPV infections can occur without noticeable symptoms, making it possible for individuals to transmit the virus unknowingly.

Understanding the interplay between viral factors and host-related factors provides insight into the complexity of HPV infections. The persistent nature of high-risk HPV infections, combined with certain host vulnerabilities, contributes to the development of HPV-related cancers. This comprehension is crucial for developing targeted prevention strategies and effective management approaches.

Additional Factors Influencing HPV Infections:

1. **Behavioral Factors:** Certain behaviors, such as smoking and a history of multiple sexual partners, can increase the risk of persistent HPV infections and the progression to cancer.
2. **Oral Contraceptives:** Long-term use of oral contraceptives has been associated with an increased risk of developing persistent HPV infections, particularly in women.
3. **Pregnancy:** Pregnancy-related changes in the immune system may contribute to increased susceptibility to HPV infections.
4. **Male Circumcision:** Studies suggest that male circumcision may reduce the risk of HPV transmission and infection.
5. **Coinfection with Other STIs:** Concurrent infection with other sexually transmitted infections, such as herpes simplex virus (HSV) or Chlamydia, can impact the course and persistence of HPV infections.
6. **Nutritional Factors:** Some studies suggest that certain nutritional deficiencies may affect the immune response to HPV, influencing infection outcomes.

Understanding the multifaceted nature of HPV infections involves considering a range of factors, both viral and host-related, as well as behavioral and environmental influences. This holistic perspective is crucial for developing comprehensive prevention and management strategies in the context of public health initiatives.

Social and Economic Factors:

1. **Socioeconomic Status:** Individuals with lower socioeconomic status may face barriers to accessing preventive healthcare, including HPV vaccination and regular screenings.
2. **Education:** Limited education and awareness about sexual health practices and preventive measures can contribute to higher HPV infection rates.
3. **Healthcare Disparities:** Disparities in healthcare access and utilization can affect the likelihood of early detection and treatment of HPV infections, impacting outcomes.

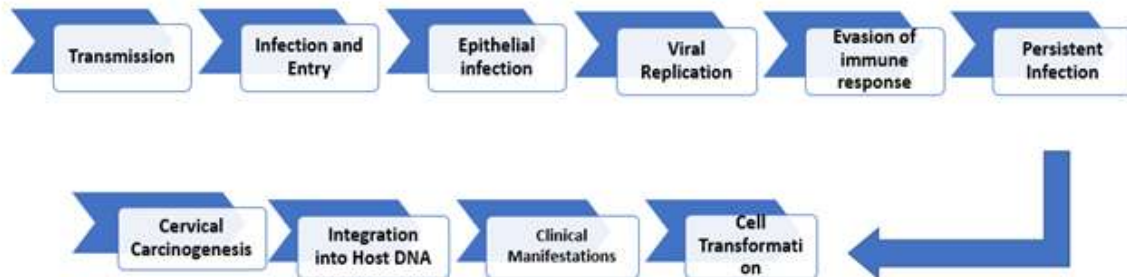


Fig1. PATHOPHYSIOLOGY OF HPV

Pathophysiology of HPV:

The pathophysiology of Human Papillomavirus (HPV) involves the virus's interaction with host cells, leading to various clinical manifestations. Here is an overview of the key aspects of HPV pathophysiology:

1. **Transmission:** HPV is primarily transmitted through direct skin-to-skin contact, most commonly during sexual activity. It can also be transmitted from an infected mother to her newborn during childbirth or through non-sexual close personal contact.

2. **Infection and Entry:**

- The virus enters the host through microabrasions or small cuts in the skin or mucous membranes, providing access to basal cells.

3. **Epithelial Infection:**

- HPV primarily infects the squamous epithelial cells of the skin and mucous membranes. The virus targets the basal cells, which are actively dividing and provide a suitable environment for viral replication.

4. **Viral Replication:**

- The virus undergoes a complex life cycle involving early and late gene expression. Early genes are involved in viral replication and evasion of host defenses, while late genes contribute to the formation of viral particles.

5. **Evasion of Immune Response:**

- HPV has evolved mechanisms to evade the host immune response. For example, it can inhibit the function of immune cells, modulate cytokine production, and avoid detection by the host's immune system.

6. **Persistent Infection:**

In many cases, the immune system successfully clears HPV infections. However,

persistent infection with high-risk HPV types, particularly HPV 16 and 18, is a key factor in the development of HPV-related cancers.

7. **Cell Transformation:**

Persistent infection with high-risk HPV types can lead to cellular changes, including dysplasia and transformation of infected cells into precancerous or cancerous cells. This is especially relevant in the context of cervical cancer.

8. **Clinical Manifestations:**

HPV infections can result in various clinical manifestations, including common warts, genital warts, respiratory papillomatosis, and HPV-associated cancers such as cervical, anal, and oropharyngeal cancers.

9. **Integration into Host DNA:**

In some cases, high-risk HPV types may integrate their genetic material into the host cell's DNA. This integration can disrupt cellular regulatory mechanisms and contribute to oncogenesis.

10. **Cervical Carcinogenesis:**

In the case of cervical cancer, the prolonged presence of high-risk HPV types contributes to the progression from low-grade squamous intraepithelial lesions (LSIL) to high-grade squamous intraepithelial lesions (HSIL) and ultimately to invasive carcinoma.

Understanding the pathophysiology of HPV is crucial for developing preventive measures, early detection strategies, and targeted therapeutic interventions to manage HPV-related diseases effectively.

General Approaches of Treating HPV Infections:

1. Watchful Waiting: In many cases, especially for low-risk HPV infections without symptoms, a watchful waiting approach may be recommended. The immune system can often clear the infection over time.

2. Topical Treatments: For external genital warts caused by certain HPV strains, topical treatments such as creams or solutions containing imiquimod or podophyllotoxin may be prescribed.

3. Surgical Interventions:

- Cryotherapy: Freezing warts using liquid nitrogen.

- Electrosurgery: Using an electrical current to remove warts.

- Laser Therapy: Using laser light to destroy warts.

4. Interferon Therapy: In some cases, especially with recurrent or persistent warts, injections of interferon may be used to boost the immune response.

Antiviral Medications:

1. Cytotoxic Drugs: Medications like trichloroacetic acid (TCA) or podophyllin may be applied directly to warts to destroy infected cells.

2. Antiviral Medications: Although there is no specific antiviral medication to cure HPV, certain drugs like cidofovir or interferon may be considered in severe cases.

3. Immunotherapy: Therapies aimed at boosting the immune response, such as systemic interferon or intralesional immunomodulators, are areas of ongoing research.

It's important to note that while treatments can address symptoms, they may not eliminate the virus entirely. Additionally, there is a strong emphasis on preventing HPV infections through vaccination, especially for high-risk types associated with cancer. The effectiveness of treatments can vary, and the choice of approach depends on factors such as the type of HPV, location of warts, and individual health considerations. Regular screenings and early detection remain crucial for managing HPV-related conditions.

Existing Treatments for HPV and Associated Adverse Drug Reactions (ADRs):

1. Podophyllotoxin:

- Overview: Topical treatment for external genital warts.

- ADR: Local irritation, burning, pain, erythema. Should not be used during pregnancy.

- Efficacy: Effective for external warts; limited use due to potential side effects.

2. Imiquimod:

- Overview: Topical cream stimulating the immune system.

- ADR: Local skin reactions (redness, itching, burning). Generally well-tolerated.

- Efficacy: Effective for external genital warts; also used for some precancerous lesions.

3. Cryotherapy:

- Overview: Freezing warts using liquid nitrogen.

- ADR: Pain, blistering, local irritation. Rarely, scarring.

- Efficacy: Effective for various types of warts; may require multiple sessions.

4. Electrosurgery:

- Overview: Using an electrical current to remove warts.

- ADR: Pain, scarring, risk of infection.

- Efficacy: Effective for various warts; may require local anesthesia.

5. Interferon-alpha:

- Overview: Boosts the immune system's antiviral response.

- ADR: Flu-like symptoms, fatigue, headache. Injection site reactions.

- Efficacy: Used for recurrent or persistent warts; limited by side effects.

6. Cidofovir:

- Overview: Antiviral medication inhibiting DNA replication.

- ADR: Nephrotoxicity (kidney damage), local irritation.

- Efficacy: Limited use due to potential kidney toxicity; considered for severe cases.

7. 5-Fluorouracil (5-FU):

- Overview: Inhibits DNA synthesis and cell division.

- ADR: Local irritation, redness, peeling.

- Efficacy: Used for certain types of genital warts; requires careful application.

8. Trichloroacetic Acid (TCA):

- Overview: Destroys infected cells by chemical coagulation.

- ADR: Local irritation, burning, scarring.
- Efficacy: Used for localized warts; requires careful application.

Limitations and Considerations:

Treatment effectiveness may vary based on the type and location of warts. Recurrence is possible after treatment, and multiple sessions may be required. Treatments focus on symptom management and may not eliminate the virus entirely. Some treatments are not recommended during pregnancy due to potential harm to the fetus. Individual responses to treatment can vary, and the choice of therapy depends on factors such as wart type, location, and patient preferences. Regular follow-ups with healthcare providers are essential for monitoring treatment outcomes and addressing any adverse reactions.

9. Surgical Excision:

- Overview: Surgical removal of warts using a scalpel or laser.
- ADR: Pain, scarring, risk of infection.
- Efficacy: Effective for various warts; may require local or general anesthesia.

10. Laser Therapy:

- Overview: Using laser light to destroy warts.
- ADR: Pain, redness, swelling. Rarely, scarring.
- Efficacy: Effective for certain types of warts; may require multiple sessions.

11. HPV Vaccination (Preventive):

- Overview: Gardasil 9 and Cervix are vaccines targeting high-risk HPV types.
- ADR: Mild reactions like pain at the injection site; serious side effects are rare.
- Efficacy: Highly effective in preventing infection with targeted HPV types; most effective when administered before exposure to the virus.

12. Intralesional Immunotherapy:

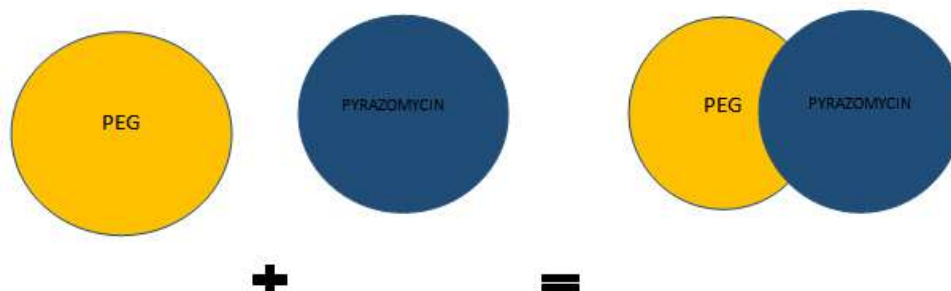
- Overview: Injecting substances like interferon directly into warts.
- ADR: Flu-like symptoms, pain at the injection site.
- Efficacy: Used for resistant or recurrent warts; limited by potential side effects.

Limitations and Considerations:

- No single treatment is universally effective for all cases.
 - Efficacy can vary based on the type, location, and size of warts.
 - Recurrence is a common challenge, especially in cases of persistent infections.
 - Treatment decisions should consider individual health, preferences, and potential side effects.
- It's important to note that while treatments aim to manage symptoms and reduce the risk of complications, none guarantee complete eradication of the virus. Prevention through vaccination, safe sexual practices, and regular screenings remains crucial in managing the overall impact of HPV on public health. Individualized treatment plans should be developed in consultation with healthcare professionals based on a thorough assessment of each patient's specific condition and needs.

Treatment Approach for HPV: Exploring PEG and Pyrazomycin Combination

Introduction: Human Papillomavirus (HPV) poses a significant health challenge, necessitating innovative treatment strategies for improved outcomes. Current treatments, including the use of PEG and ribavirin, exhibit limitations, warranting exploration of alternative approaches.



Current Treatment Landscape:

PEG and ribavirin have been employed in specific cases for HPV, as reported in studies such as [cite research paper]. However, challenges persist, prompting a reevaluation of treatment options.

Proposal for Treatment Optimization:

This review proposes optimizing HPV treatment by considering alternatives to ribavirin. Notably, pyrazomycin emerges as a promising candidate due to its structural similarities with ribavirin.

Ribavirin

- Overview: Ribavirin is a broad-spectrum antiviral medication with activity against RNA and DNA viruses, but its role in treating HPV is not well-established.
- Administration: Usually administered orally or through inhalation, depending on the specific medical condition.
- ADRs (Adverse Drug Reactions): Potential side effects include anemia, fatigue, rash, and gastrointestinal disturbances. Severe adverse effects are rare but may include hemolytic anemia and teratogenicity (harmful effects on the fetus during pregnancy).
- Efficacy for HPV: Research on the specific efficacy of ribavirin for treating HPV is limited. It is not considered a primary treatment for HPV infections, and its use may be explored in specific cases where other treatments are not suitable.
- Mechanism of Action: Ribavirin inhibits the replication of RNA and DNA viruses, including some strains of HPV.
- Administration: Typically used as an oral medication.
- Use in HPV: While ribavirin has demonstrated antiviral activity against various viruses, its efficacy against HPV is not well-established. Research on its specific role in treating HPV infections is limited.

Pyrazomycin

- Overview: Pyrazomycin is an antibiotic with antimicrobial activity. Its role in treating HPV is not well-documented.
- Administration: Administered orally or intramuscularly, depending on the specific medical condition.
- ADRs (Adverse Drug Reactions): Limited information is available on the adverse effects of pyrazomycin. As with any medication, potential

side effects may include gastrointestinal disturbances, allergic reactions, or other systemic effects.

- Efficacy for HPV: Research on the efficacy of pyrazomycin for treating HPV is sparse, and it is not considered a standard or recommended treatment for HPV infections.
- Mechanism of Action: Pyrazomycin is an antibiotic with antimicrobial activity.
- Administration: Administered orally or intramuscularly.
- Use in HPV: Pyrazomycin is not a commonly studied or recommended treatment for HPV infections. Research on its effectiveness against HPV is limited, and it is not a standard part of current HPV treatment guidelines.

Both ribavirin and pyrazomycin have been explored for their antiviral properties, but their specific roles in treating HPV are not firmly established. As with any potential treatment, it's crucial to rely on evidence-based practices, and currently, the primary focus for HPV management involves established antiviral medications, surgical interventions, and immunotherapies.

Considerations:

Both ribavirin and pyrazomycin have primarily been studied and used for different viral infections, and their roles in HPV management are not well-defined. The choice of antiviral medication for HPV treatment is generally based on established treatments such as topical agents, surgical interventions, and immunotherapies. Consultation with a healthcare professional is crucial for determining the most appropriate and evidence-based treatment options for HPV infections based on individual circumstances. It's important to note that ongoing research may provide more insights into the potential roles of various antiviral medications in managing HPV infections. As of my last knowledge update in January 2022, specific evidence for the use of ribavirin and pyrazomycin in HPV treatment was limited, and newer findings may have emerged since then. Always rely on the latest medical literature and consult with healthcare professionals for the most up-to-date information.

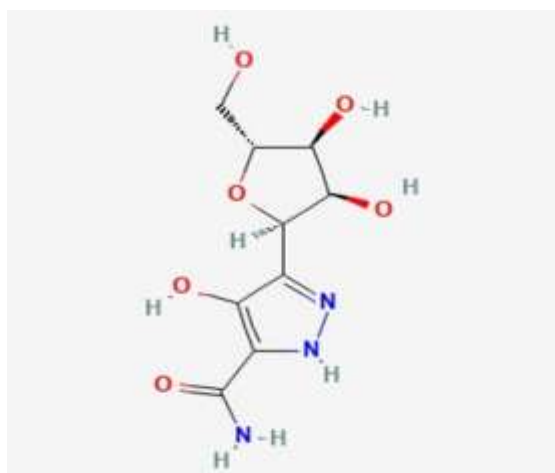


Fig. 2. Structure of Pyrazomycin

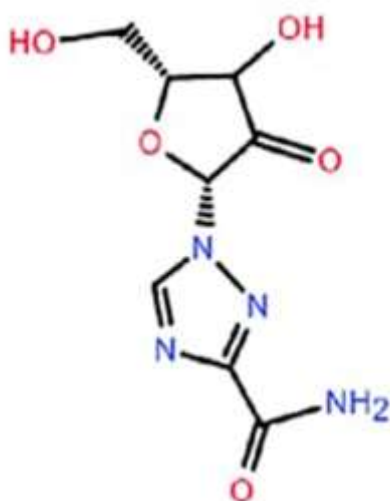


Fig.3. Structure of Ribavirin

Rationale for PEG and Pyrazomycin Combination:

Pyrazomycin shares chemical structures with ribavirin, suggesting potential efficacy in HPV treatment. The combination with PEG is anticipated to enhance treatment response while minimizing side effects.

Supporting Evidence:

Literature supports the antiviral properties of pyrazomycin, indicating its potential as a viable treatment option. Studies discussing response rates and side effect profiles further endorse the proposed combination.

Safety Considerations:

Acknowledging the side effects associated with ribavirin and pyrazomycin, the review

considers the overall safety profile of the proposed treatment. Striking a balance between efficacy and safety is imperative for successful HPV management.

II. CONCLUSION:

This review aims to contribute to the understanding of HPV from various perspectives, fostering informed decision-making in healthcare practices and public health policy. In conclusion, the exploration of a treatment approach involving PEG and Pyrazomycin presents a compelling avenue for optimizing HPV management. While not claiming definitive outcomes, the shared chemical structures and potential synergies between these agents provide a rationale for further investigation. This proposed strategy aims to offer a potentially effective and safer alternative to current treatments, suggesting new possibilities for enhanced HPV care.

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