Zoonotic Threat of Anaplasmosis

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ABSTRACT

Anaplasmosis, a vector-borne zoonotic disease caused by various Anaplasma spp., poses significant threats to both human and animal health globally. A. phagocytophilum and A. marginale are notable pathogens, causing human granulocytic anaplasmosis and affecting livestock, particularly cattle. Transmitted through tick bites, the diseases exhibit a broad geographical distribution, with recent concerns arising in regions like North Africa and the Middle East. Despite advancements in understanding Anaplasma life cycles and their impact, challenges persist, necessitating further research for improved disease control and diagnostic methods. The complex life cycle involves ticks as vectors and mammalian hosts, contributing to the bacteria's wide dissemination. Clinical manifestations vary, with human cases showing acute symptoms resembling other febrile illnesses. Diagnostic methods include PCR and serological assays targeting specific antigens. Tetracyclines, particularly doxycycline, are the primary treatment, but challenges include antibiotic resistance. Control measures encompass vector management, biosecurity, and vaccination trials, notably targeting conserved antigens like A. phagocytophilum MSP4. Public health implications and zoonotic potential underscore the need for a One Health approach. Challenges in treatment, vector control, and economic considerations demand collaborative efforts for effective disease management. The interconnectedness of human, animal, and environmental health is emphasized, necessitating vigilance in surveillance, clinical awareness, and collaborative strategies to minimize public health risks associated with Anaplasma infections.

Keywords: Anaplasmosis, Zoonotic disease, Tick-borne pathogens, Diagnosis, One Health

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1. INTRODUCTION

Anaplasmosis is a vector-borne zoonotic disease caused by the Anaplasma spp. This group of bacteria includes several species that are notable for their impact on human and animal health, such as Anaplasma (A.) phagocytophilum and Anaplasma marginale (Parvizi 2021). A. phagocytophilum is known to cause human granulocytic anaplasmosis, a condition that results from the bacteria infecting white blood cells (Glatz et al. 2014). On the other hand, A. marginale is a well-known pathogen in livestock, particularly cattle. This species is prevalent in various regions around the globe, with particularly high prevalence rates noted in areas like Ghana (Heylen et al. 2023). The diseases caused by Anaplasma are transmitted to humans and animals through the bites of ticks. The role of ticks as vectors for these diseases highlights the importance of controlling tick populations to prevent the spread of Anaplasma (Madesh 2021). Furthermore, the importance of understanding and addressing these diseases is underscored by their broad geographical distribution and the wide range of animals that can serve as hosts. While a lot of attention has been focused on anaplasmosis in North America and Europe, a recent study have noted the presence of this disease in regions like North Africa and the Middle East (Parvizi 2021). While much progress has been made in understanding the life cycle of Anaplasma species and their effects on human and animal health, there remain many opportunities for further research. These include developing more effective strategies for disease control and prevention, and improving diagnostic methods for detecting infections (Suarez and Noh 2011).

Anaplasmosis, caused by several species of Anaplasma bacteria, has significant implications as a zoonotic disease, impacting both veterinary medicine and public health worldwide. These bacteria are recognized as important tick-borne pathogens (Wei et al. 2020). Species like A. phagocytophilum and A. marginale are of particular significance due to their broad distribution and the potential harm they cause to livestock and humans (Atif 2015). A. platys, another species within this genus, was initially detected in a dog from Florida and is now recognized as a causative agent of canine infectious cyclic thrombocytopenia and granulocytic anaplasmosis, both are zoonotic diseases (Atif et al. 2021). Apart from dogs, Anaplasma species have been reported in a variety of hosts, including cats, goats, and small ruminants, increasing the zoonotic potential of these diseases (Yang et al. 2017; Schäfer and Kohn 2020; Wei et al. 2020).

2. HISTORY

In Uruguay, the history of research and control efforts for anaplasmosis (alongside babesiosis) has been associated with the tick species *Rhipicephalus microplus* (Miraballes and Riet-Correa 2018). Similarly, the epizootiology and control strategies for anaplasmosis have also been studied extensively in South Africa (Potgieter 1979). In Iran, detection and diagnosis of *A. marginale* in cattle have been crucial, with several herds having a history of acute anaplasmosis (Noaman et al. 2009; Noaman 2013). Meanwhile, in Northeastern Brazil, there's a recorded clinical history of babesiosis and anaplasmosis in dairy farms, indicating enzootic stability for anaplasmosis (Souza et al. 2013). A decade-long seroepidemiological study in Belgium also highlighted the relevance of anaplasmosis in humans, especially in those with a history of tick bites and febrile illnesses (Cochez et al. 2011).

In terms of geographical distribution, anaplasmosis has been identified in a wide range of regions. For example, a significant prevalence of bovine anaplasmosis was confirmed in Egypt, with implications for public health, veterinary practice, and the livestock industry (Parvizi et al. 2020). Studies also point to the relevance of this disease in North American countries such as Canada, where human granulocytic anaplasmosis (HGA) is considered as a major emerging zoonotic disease (Kulkarni et al. 2015). In Africa, the significance of *Anaplasma* species is underscored by their detection in cattle populations in Nigeria and Ethiopia. Furthermore, anaplasmosis is prevalent in small ruminants in China, where the identification of a novel *Anaplasma* species has raised concerns about potential public health implications (Yang et al. 2017).

3. LIFE CYCLE

The life cycle of *Anaplasma* is complex and involves both an arthropod vector, usually a tick, and a mammalian host. This life cycle is initiated when a tick that carries *Anaplasma* bacteria feeds on a mammalian host, injecting the bacteria into the host's bloodstream along with the tick's saliva (Atif 2015). This can happen when ticks, in the quest for blood meals, attach themselves to various mammalian hosts including humans, livestock, and pets. Upon entering the mammalian host, *Anaplasma* bacteria show a marked affinity for certain types of white blood cells, particularly the granulocytes. The bacteria utilize an array of specialized proteins, including Asp14, to facilitate attachment and subsequent invasion into the host cells (Kahlon et al. 2013). This invasion process is crucial for the bacteria to establish infection as it provides a protective environment against the host's immune responses and allows the bacteria to replicate unhindered. Inside the host cells, the bacteria manipulate host cellular processes to survive, grow, and multiply, creating unique cellular structures known as morulae. The infected cells eventually rupture, releasing the new bacteria which can then infect other cells, thus perpetuating the infection within the host (Rikihisa 2010). Simultaneously, ticks feeding on these infected hosts can ingest the bacteria during their blood meal, and consequently become carriers, ready to transmit the bacteria to other hosts in their future blood meals. This ensures the continuation of the bacteria's life cycle and its propagation across a wide range of hosts and geographical locations. Additionally, the movement of mammalian hosts, particularly birds and migratory mammals, contributes significantly to the spread of *Anaplasma* bacteria. These hosts can carry the bacteria over long distances, increasing its range and the possibility of encountering new potential host species (Stuen et al. 2013). The entire events involved in the life cycle are shown in Fig. 1.

4. CLINICAL SIGNS AND SYMPTOMS

Clinical manifestations of *Anaplasma* infections exhibit variability based on the particular species involved and the mammalian host affected. Notably, in the case of human granulocytotropic anaplasmosis (HGA), which is attributed to *A. phagocytophilum*, the disease typically manifests with a set of acute and nonspecific symptoms. Individuals afflicted with HGA often experience fever, accompanied by chills, headache, muscle aches, and a general sense of malaise. This clinical presentation frequently mirrors the symptomatology of other febrile illnesses, underscoring the challenge of distinguishing HGA solely based on clinical grounds (Bakken and Dumler 2006). Pro-inflammatory immune responses have been associated with clinical signs and symptoms of human anaplasmosis, indicating the involvement of the host's immune system in the disease presentation. The clinical signs of anaplasmosis in cattle and other mammalian hosts can also vary widely, presenting a complex diagnostic challenge. An outbreak of clinical anaplasmosis in dairy cattle was characterized by primary signs such as fever, anemia, jaundice, and lethargy, demonstrating the impact of *A. marginale* infections on livestock. These symptoms can lead to significant production losses, affecting both milk yield and reproductive efficiency (Schotthoefer et al. 2017).
In Turkey, laboratory-confirmed clinical cases of bovine anaplasmosis caused by *A. phagocytophilum* were identified, further highlighting the potential severity of anaplasmosis in livestock. These instances revealed that the disease could be both acute and chronic in nature, depending on factors such as the host's immune system, age, and the specific strain of *Anaplasma* involved. The geographical spread of anaplasmosis is also of significant concern. Environmental factors, vector distribution, and livestock management practices all contribute to the epidemiology of the disease, making it a considerable threat to both commercial farming and smallholder systems. Efforts to control anaplasmosis must include regular

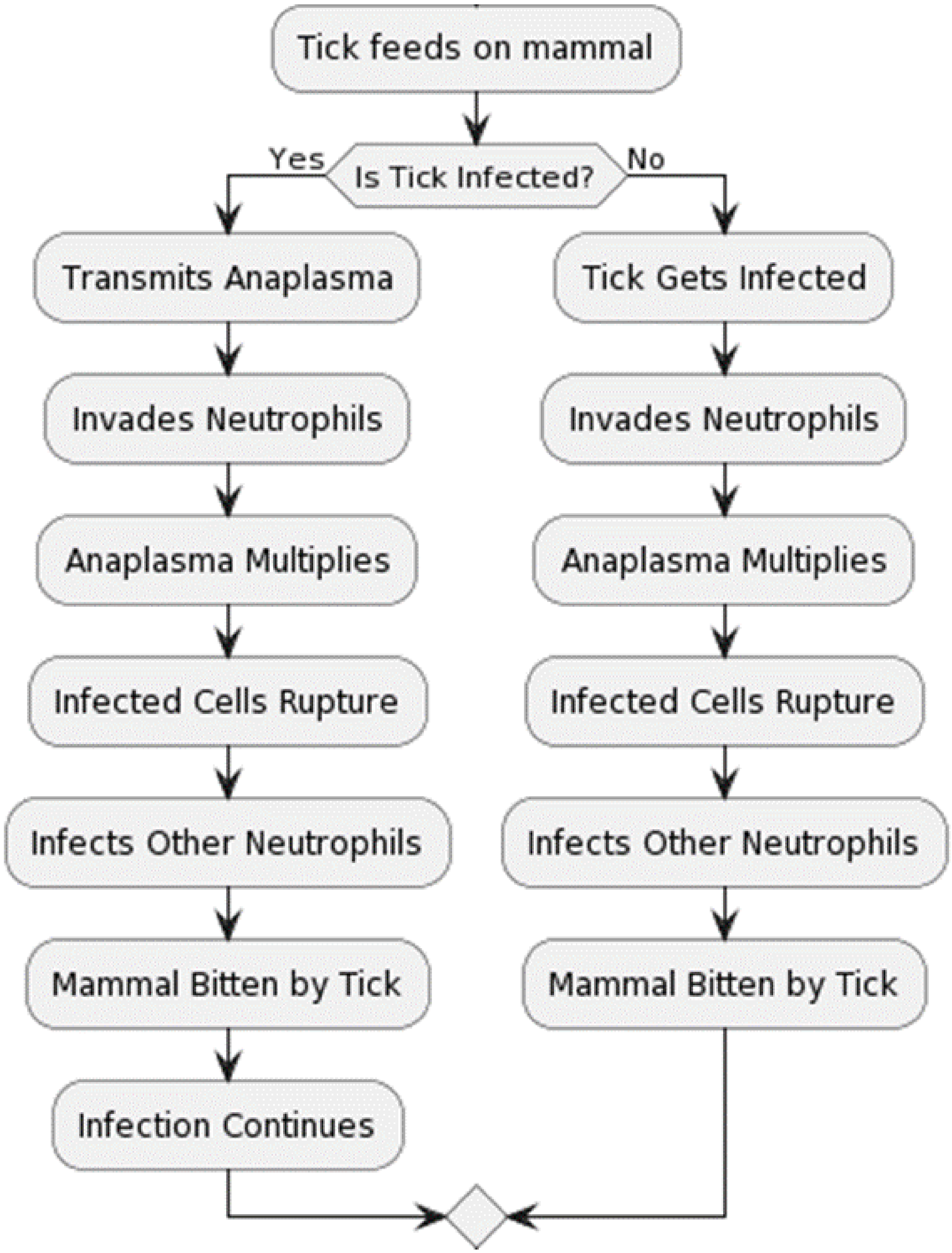

Fig. 1: Life cycle of *Anaplasma* spp.

monitoring, efficient diagnostic methods, and effective treatment protocols. Vaccination, where available, and vector control measures are essential components of a comprehensive prevention strategy. Collaboration between veterinary authorities, farmers, and researchers is crucial to develop and implement policies that address the complexities of anaplasmosis in different regions and livestock populations (Aktas and Özübek 2017). Additionally, transfusion-transmitted *A. phagocytophilum* cases have been reported, emphasizing the importance of considering *Anaplasma* infections as potential complications in blood transfusion recipients (Annen et al. 2012).

5. DIAGNOSIS

The swift and accurate diagnosis of anaplasmosis is a paramount endeavor in ensuring effective treatment and preventing further transmission. Anaplasmosis has garnered increasing attention due to its impact on both human and animal health. As such, the development of robust diagnostic methods has become essential for timely intervention and disease control. One of the key challenges in diagnosing anaplasmosis lies in its nonspecific clinical manifestations. The symptoms exhibited by infected individuals or animals often overlap with those of other febrile illnesses, making it challenging to pinpoint the causative agent solely based on clinical grounds.

Therefore, diagnostic approaches rely on a combination of clinical evaluation, laboratory tests, and advanced techniques to unravel the presence of *Anaplasma* pathogens. A significant stride in the diagnosis of human granulocytotropic anaplasmosis (HGA) was the identification of *A. phagocytophilum* as the responsible agent. HGA was first recognized in 1990, shedding light on a previously unidentified pathogen that infiltrates neutrophils and elicits acute, nonspecific symptoms in infected individuals (Bakken and Dumler 2006). The clinical diagnosis of HGA is further complicated by its similarity to other tick-borne illnesses. This underscores the importance of integrating laboratory findings with clinical presentation to establish a conclusive diagnosis. Laboratory testing constitutes a cornerstone in the diagnostic process for anaplasmosis. Techniques like polymerase chain reaction (PCR) have emerged as powerful tools for detecting the genetic material of *Anaplasma* pathogens in blood samples. This molecular approach enables the identification of the pathogen's DNA, offering a rapid and accurate means of diagnosis.

Similarly, serological assays play a pivotal role in detecting antibodies produced in response to *Anaplasma* infections. Enzyme-linked immunosorbent assays (ELISAs) have been developed to target specific antigens associated with *Anaplasma* species, aiding in serodiagnosis and serosurveillance. A noteworthy advancement in the diagnostic landscape is the utilization of major surface proteins (MSPs) as serodiagnostic markers. Genetic diversity among *Anaplasma* strains has prompted the exploration of MSPs as targets for serodiagnosis and vaccine development. The implications of these findings extend beyond diagnosis, potentially paving the way for preventive measures through vaccine strategies (Kocan et al. 2010).

Canine anaplasmosis, caused by *A. phagocytophilum*, presents diagnostic challenges akin to its human counterpart. In dogs, clinical manifestations can include various nonspecific symptoms, such as fever and lethargy. To facilitate diagnosis, observation of neutrophilic morulae, distinctive inclusions within neutrophils, has been employed (Lester et al. 2005). This microscopic finding contributes to a conclusive diagnosis of canine anaplasmosis and guides appropriate management. The diagnostic landscape for anaplasmosis continues to evolve. Emerging research highlights the potential of whole organism–based immunofluorescent assays (IFAs) for serologic diagnosis. These assays, which target antibodies against *Anaplasma* and other tick-borne pathogens, hold promise for accurate and comprehensive diagnostic evaluations (Qurollo et al. 2021).

6. TREATMENT AND CONTROL

One of the primary goals in anaplasmosis management is the development of suitable treatment regimens. Tetracyclines, a class of antibiotics, have emerged as the treatment of choice for eliminating

Anaplasma infections. Notably, these antibiotics have shown efficacy against a spectrum of *Anaplasma* species, including both human and animal pathogens. The use of tetracyclines, such as doxycycline, has proven to be instrumental in mitigating clinical manifestations and reducing pathogen burden. This is particularly significant as *Anaplasma* infections can lead to serious health complications if left untreated. The symptoms of anaplasmosis can vary widely, ranging from mild fever and fatigue to more severe manifestations like organ failure. The effectiveness of tetracyclines in treating *Anaplasma* infections can be attributed to their broad-spectrum antimicrobial activity. They inhibit the synthesis of bacterial proteins by binding to the ribosomal subunits, thereby preventing the growth and multiplication of the bacteria. This makes them highly effective in targeting various strains of *Anaplasma*. However, the use of tetracyclines is not free of challenges. Resistance to these antibiotics has been reported in some cases, necessitating ongoing research and development to identify alternative treatment options or to enhance the existing ones. Additionally, the administration of tetracyclines must be carefully monitored, as overuse or misuse can lead to side effects such as gastrointestinal disturbances or photosensitivity (Dantas-Torres and Otranto 2017).

Anaplasmosis control, however, extends beyond treatment to encompass preventive measures. The concept of endemic stability comes to the fore, emphasizing the need to maintain *Anaplasma*-free herds. This entails meticulous breeding practices, robust biosecurity protocols, and identification of carriers to prevent the transmission of the pathogen within the herd (Atif 2015). The role of vectors, such as ticks, in anaplasmosis transmission underscores the significance of vector control strategies. The use of acaricides and tick control measures assumes paramount importance to curb the spread of pathogen. These measures, aimed at breaking the transmission cycle, prove pivotal in managing the disease. Vaccination offers a promising avenue for anaplasmosis control, an approach that has gained momentum in recent years with advances in research and technology. The identification of specific antigens, such as *A. phagocytophilum* Major Surface Protein 4 (MSP4), has opened new vistas for vaccine development, bringing hope to livestock industries across the globe. Vaccination trials targeting MSP4 have demonstrated potential in conferring protection against *Anaplasma* infections, reflecting an innovative approach to disease control. These trials have been conducted both in the laboratory and in field settings, with results showing significant reductions in clinical symptoms and transmission rates among vaccinated animals. The utilization of MSP4 as a key component in vaccines represents a targeted and refined strategy that addresses the unique characteristics of *Anaplasma* pathogens. This protein has shown to be highly conserved among different *Anaplasma* species, thereby increasing the potential for cross-protection against various strains of the bacteria (Miraballes and Riet-Correa 2018).

Collaborative efforts between researchers, veterinary scientists, and pharmaceutical companies are essential to further refine the vaccine, ensuring safety, efficacy, and scalability for commercial use. Challenges such as the adjuvant selection, dosage optimization, and delivery methods must be carefully addressed to develop a vaccination protocol that can be widely adopted. Public-private partnerships may also play a vital role in accelerating the development and deployment of the vaccine, ensuring that it reaches the farmers and regions where it is most needed. Education and training programs for farmers and veterinary professionals will also be crucial in maximizing the effectiveness of the vaccine, enhancing understanding of when and how to administer it, and monitoring its impact on herd health (de la Fuente et al. 2022).

7. PUBLIC HEALTH IMPACT AND ZOONOTIC POTENTIAL

The interplay between human-animal interaction necessitates a one health approach to anaplasmosis control. The potential zoonotic implications of *Anaplasma* infections further accentuate the importance of cross-species disease management. Strategies that address animal reservoirs and vector control in tandem with human preventive measures will be pivotal in halting the progression of the disease. The management of anaplasmosis is critical to both veterinary and public health due to the potential economic losses in livestock and the zoonotic nature of certain *Anaplasma* species. Developing effective strategies for treatment and control is imperative to mitigate the impact of the disease. Early diagnosis and treatment are essential for effectively managing anaplasmosis. Administering antibiotics, particularly tetracyclines like doxycycline, plays a crucial role in treating the disease. Doxycycline's mechanism of inhibiting bacterial protein synthesis hinders the proliferation of *Anaplasma* organisms within host cells (Atif et al. 2021).

Vector Control is a pivotal aspect of anaplasmosis control due to the reliance of *Anaplasma* pathogens on vectors like ticks for transmission. Implementing efficient tick control measures disrupts the transmission cycle, protecting animals from infection and reducing the risk of transmission to humans (Waruri et al. 2021). Identifying carriers and isolating infected individuals helps to prevent the disease's spread within the herd. Strategies like culling or treating carriers are necessary to achieve and sustain endemic stability (Abdisa 2019). Challenges in treatment and control persist. The emergence of antibiotic-resistant strains of *Anaplasma* underscores the need for continuous research and innovative solutions. The complex behavior of vectors and the evolving nature of the disease demand adaptable strategies. Economic Considerations highlight the benefits of diagnostic testing. Accurate diagnosis enables timely treatment, reducing the severity of the disease and minimizing economic losses. Analyzing the cost-effectiveness of diagnostic testing provides valuable insights into managing anaplasmosis (Railey and Marsh 2021).

The zoonotic potential of anaplasmosis extends to the canine population, with diseases like canine infectious cyclic thrombocytopenia and granulocytic anaplasmosis being of particular concern. The detection of *A. platys* in dogs from Florida underscores the close relationship between animals and humans, necessitating a thorough understanding of these zoonotic diseases for effective prevention (Atif 2015). Genetic genotyping of *Anaplasma* strains offers valuable insights into their impact on public health. Continual discovery of novel tick-associated microbes with zoonotic potential has global implications for public health. As these discoveries reshape our understanding of zoonotic diseases, they underscore the need for surveillance and effective management strategies (Yang et al. 2017).

Equine granulocytic anaplasmosis (EGA), caused by *A. phagocytophilum*, is a tick-borne equine disease with zoonotic implications. EGA's veterinary and public health significance highlights the importance of comprehensive control measures to mitigate its impact. Similarly, the detection of *A. phagocytophilum* in olive baboons and vervet monkeys in Kenya raises concerns about the role of wildlife reservoirs in zoonotic pathogen transmission, necessitating effective management strategies (Masika et al. 2021). The transmission of zoonotic *Anaplasma* species across various host types, such as dogs, horses, and ruminants, emphasizes the need for coordinated efforts to minimize public health risks. The interconnectedness of human, animal, and environmental health is underscored by the impact of vector-borne zoonotic diseases like *A. phagocytophilum*, highlighting the importance of a one health approach that addresses both veterinary and public health concerns (Kulkarni et al. 2015).

Clinical awareness and surveillance play a critical role in managing zoonotic diseases like *A. phagocytophilum* infection in cats, serving to detect and manage these diseases in various animal species to prevent transmission to humans and promote overall health. Integrating regular veterinary check-ups, diagnostic testing, and public education helps in early identification and containment of the disease. Collaboration between veterinarians, healthcare providers, and public health authorities fosters a comprehensive approach, ensuring that both pet owners and professionals are informed and equipped to deal with the challenges of zoonotic infections. This alignment of efforts is crucial in safeguarding animal and human health (Schäfer and Kohn 2020).

8. CONCLUSION

The complex landscape of anaplasmosis, characterized by its diverse species, global distribution, intricate life cycle, clinical manifestations, and zoonotic potential, demands a comprehensive and collaborative approach for effective control and prevention. The intricate interplay between Anaplasma species, arthropod vectors, mammalian hosts, and the environment underscores the need for a One Health perspective that integrates veterinary and public health efforts.

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