REVIEW

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# Preventing herpes zoster in immunocompromised patients: Current concepts

## ABSTRACT

Herpes zoster (HZ) incidence is much higher in immunocompromised individuals than in immunocompetent individuals. HZ also occurs at a younger age and is often more severe in immunocompromised persons. Preventive strategies center around the recombinant zoster vaccine (RZV), which is approved for immunocompromised adults age 19 and older. Identifying those at greatest risk is critical. For those considering vaccination, evidence gaps regarding vaccine efficacy, toxicity, length of protection, and potential effects on underlying conditions may complicate shared and informed decision-making. Recent data have filled some of these gaps, with several societies issuing recommendations regarding vaccination. Remaining gaps are currently addressed by expert opinion.

## KEY POINTS

Patients who are immunocompromised are at increased risk for HZ and its complications.

The RZV is highly effective for preventing HZ. It is approved for immunocompromised patients age 19 and older.

The immunocompromised population is complex and heterogeneous. Hence, appraising individual risk and weighing the risks and benefits of the RZV can be challenging.

Filling knowledge gaps about HZ can help clinicians individualize shared and informed decision-making, leading to risk reduction.

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Herpes zoster (HZ), also known as shingles, occurs due to reactivation of latent varicella-zoster virus (VZV) and generally presents as a painful cutaneous eruption. VZV is typically first acquired during a primary infection (chickenpox), but may also be acquired via live, attenuated virus vaccines (Varivax or ProQuad).[1] HZ is common in the general population, with about 1 million cases reported annually in the United States.[1] Incidence increases with age, especially after age 50.[2]

HZ most often is a self-limiting disease, commonly accompanied by severe pain with loss of productivity, but in its most severe form can be life-threatening.[1,2] Patients who are immunocompromised due to an underlying disease (eg, cancer, transplantation, primary or acquired immunodeficiency states, immune-mediated inflammatory diseases) or exposure to immunosuppressive drugs are at increased risk for uncomplicated HZ as well as HZ-related complications.[3] This review discusses clinically important aspects of preventing HZ in immunocompromised patients, focusing primarily on vaccination: identifying at-risk populations, weighing the risks and benefits of a recombinant zoster vaccine (RZV), and using best practices for administering RZV and monitoring patients afterwards.

## REACTIVATION MORE LIKELY IN IMMUNOCOMPROMISED PATIENTS

VZV is the etiologic agent for chickenpox (varicella). The classic cutaneous lesions in

**TABLE 1**
**Complications of herpes zoster**

| Complications | Comment |
|---|---|
| Postherpetic neuralgia | Most common complication of herpes zoster<br>Manifests as persistent pain beyond 90 days of rash |
| Herpes zoster ophthalmicus | Vision-threatening complication from involvement of ophthalmic division of cranial nerve V<br>High risk of vision loss if antiviral therapy is not promptly initiated |
| Acute retinal necrosis | Necrotic infection of the retina that often leads to profound vision loss<br>Caused by herpes viruses, most often by herpes zoster or varicella |
| Ramsay Hunt syndrome (herpes zoster oticus) | Major otologic complication of herpes zoster from viral reactivation within the geniculate ganglion, with potential spread to cranial nerves V, VII, VIII, IX, and X<br>Often manifests as the triad of facial palsy, ear pain, and otic vesicular lesions |
| Miscellaneous neurologic complications | Stroke syndromes, motor neuropathy, myelitis, encephalitis, central nervous system vasculitis |
| Disseminated infection | Disseminated varicella infection with potential for visceral target organ involvement with possible widespread cutaneous involvement |

Based on information from references 1 and 2.

chickenpox result from dissemination of the virus during the viremic phase of the illness. As the infection resolves, cell-free virus is believed to infect sensory nerves in the skin, travel in a retrograde fashion, and establish lifelong latency in regional ganglia along the entire neural axis.[4,5] Cell-mediated immunity appears to be central to maintaining viral latency. Disruption of cell-mediated immunity, most commonly observed as a function of aging and immunosenescence, increases the likelihood of viral reactivation.[6] Once VZV is reactivated within sensory ganglia, it can spread neuronally in an antegrade fashion, often accompanied by inflammation and necrosis in a dermatomal distribution.

Immunocompromised individuals are more vulnerable to loss of viral control and development of HZ and its complications than those who are in generally good health. Complications of HZ include more severe local-regional tissue inflammation and destruction as well as widespread viral dissemination.[4] Implicit in this pathogenic framework is the fact that immunocompromised patients often have far more severe deficits of immunologic function that may occur at any age. In contrast, healthy individuals' major risk for loss of virologic control is immunosenescence.

## COMPLICATIONS MORE COMMON, SEVERE IN IMMUNOCOMPROMISED PATIENTS

HZ is a disease with significant morbidity that disproportionally affects immunocompromised patients.[3] It most commonly manifests as an acute neuritic rash that is generally diagnosed clinically based on the presence of a unilateral, usually painful, vesicular eruption with a well-defined dermatomal distribution. In immunocompromised individuals, the appearance of the vesicles can be atypical, and unroofing and swabbing the vesicles may be necessary to make a diagnosis. In typical cases, new vesicles continue to form over 3 to 5 days, after which the rash progressively dries and scabs over, usually healing in 2 to 4 weeks.

Although HZ is self-limiting in most cases, its clinical severity should not be underestimated. It often has adverse effects on health-related quality of life, primarily loss of function and productivity.[6] The pain associated with HZ is often severe and has been described by patients as feeling like a severe electric shock or a blowtorch.[2]

The complications of HZ can be serious (**Table 1**).[1,2] Postherpetic neuralgia, the persistence of pain, often

severe, lasting beyond 3 months, is the most common. Postherpetic neuralgia occurs in about 10% to 15% of all HZ cases in the general population,[1,2] and immunocompromised patients are at increased risk for this complication.[3]

Other complications include zoster paresis with motor impairment of involved nerves, disseminated infection resulting in VZV meningitis, central nervous system vasculitis or vasculopathy,[7] other end-organ involvement, and death.[2,3] Ocular involvement may manifest as keratitis or acute retinal necrosis, which can lead to uveitis, retinal detachment, and blindness, particularly in immunocompromised individuals.[2,4,8] In general, while all of these complications are observed in the general population, they are more common and more severe in the immunocompromised population.[3]

Best practices for diagnosis and treatment of uncomplicated and complicated forms of HZ have been reviewed elsewhere.[1,2]

## EPIDEMIOLOGY

### General population

An estimated 1 million cases of HZ are reported in the United States each year.[9] Over a lifetime, the cumulative risk of developing HZ is about 1 in 3, with rates increasing with age, a phenomenon generally ascribed to age-related weakening of the immune system.[1] The incidence is higher in women and lower in Black adults.[1,4] Between 1% and 6% of otherwise healthy individuals will experience a second episode of HZ over a lifetime.[3,10] The risk for recurrent HZ is higher in immunocompromised patients.

### Immunocompromised population

Given the importance of a well-functioning, integrated immune system in maintaining a state of lifelong viral latency, it is logical that patients who are immunocompromised are at increased risk of developing HZ, having a more severe episode, and having complications such as postherpetic neuralgia and a range of complex end-organ manifestations that could lead to severe disability and death.[3] Recurrent HZ is also a concern in this patient population.

Unfortunately, determining who is immunocompromised, and to what degree, is complex. Estimates suggest that around 3% to 6% of the US general population are immunocompromised.[11] However, these data likely do not adequately reflect the number of patients on immunosuppressive therapies, including the rapidly expanding class of biologic agents being employed for a growing list of indications.[12,13]

**TABLE 2**
**Patient groups identified as immunocompromised by the Centers for Disease Control and Prevention**

| |
|---|
| Patients with primary immunodeficiency states |
| Patients with hematopoietic stem cell transplant |
| Patients with solid-organ transplant |
| Patients with malignancies |
| Patients living with human immunodeficiency virus infection |
| Patients with immune-mediated disease states |
| Patients taking immunosuppressive medications |

Based on information from reference 12.

The Centers for Disease Control and Prevention (CDC) has identified 7 groups as immunocompromised based on underlying conditions or use of immunosuppressive therapies (**Table 2**).[12] The CDC notes that the list of immunocompromised groups is not limited to these discrete categories and that consultation between patient and clinician may be necessary.

A recent systematic review of HZ and its complications in patients with hematopoietic cell transplant, cancer, human immunodeficiency virus (HIV) infection, or solid-organ transplant revealed incidence rates 6 to 11 times higher than in the adult general population in the United States.[3] Among the 16 immunocompromised groups examined, hematopoietic stem cell transplant recipients had the highest risk. Incident risk in other groups varied widely, but increased rates were noted, not surprisingly, in patients with solid tumors receiving chemotherapy and patients with solid-organ transplants.[3] HIV infection traditionally has been associated with an increased risk of HZ. Although this risk has declined since antiretroviral therapy became available, HZ incidence remains greater in patients living with HIV than in the general population.[14]

The data are less clear regarding the risks associated with immune-mediated conditions and their therapies and with primary immunodeficiency diseases, especially those with humoral immune deficiency states. In these populations, risk is highly influenced by the immunologic pathways affected and the severity of the defect. For those with immune-mediated diseases like rheumatoid arthritis, inflammatory bowel disease, multiple sclerosis, and psoriasis, the risk for HZ is primarily related to the intensity and duration of the immunosuppressive regimens and the specific immunosuppressive therapy employed (eg, biologic agents,

kinase inhibitors, antimetabolites, glucocorticoids).[15] These variables are discussed separately below.

## PREVENTION FOCUSES ON VACCINATION

There are 2 strategies for preventing HZ in the immunocompromised population: vaccination and antiviral prophylaxis. By far the most comprehensive and effective modality is vaccination, which in the United States is currently limited to RZV, a subunit vaccine composed of a surface glycoprotein and a potent adjuvant.

RZV was introduced in 2017 as a 2-dose series administered 2 to 6 months apart to prevent HZ in adults age 50 or older, and was shown to be 90% effective at preventing HZ incidence over a 4-year period.[16,17] RZV replaced a live, attenuated vaccine for HZ prevention first introduced in 2006 that is no longer available in the United States (but is available in other countries). In 2021 the Advisory Committee on Immunization Practices recommended RZV for adult patients age 19 and older who are or will be immunodeficient or immunosuppressed because of disease or therapy.[18]

Antiviral prophylaxis, generally with low-dose valacyclovir, may be considered in select immunocompromised patients who are not candidates for RZV or who have had recurrences despite full immunization.

## RZV EFFICACY AND TOXICITY

RZV has proven to be highly effective and durable in the general population. In 2 large randomized controlled trials with a combined 7 years of follow-up, ZOE-50 (Zoster Efficacy Study in Adults 50 Years of Age or Older)[16] and ZOE-70 (Zoster Efficacy Study in Adults 70 Years of Age or Older),[17] a regimen of 2 vaccine doses administered at baseline and 2 to 6 months later had an efficacy against HZ incidence of 97.2% in adults age 50 and older and 91.3% in adults 70 and older. In these studies, RZV was also shown to be highly effective in preventing postherpetic neuralgia.[19]

Evidence for the efficacy of RZV in immunocompromised patients remains limited, however. Data from 2 randomized controlled trials[20,21] formed the basis of the recommendation for administering RZV in immunocompromised patients age 19 and older.[18] These studies have recently been summarized.[6] Bastidas et al[20] evaluated the efficacy of RZV in patients who underwent autologous hematopoietic stem transplantation, and reported an efficacy of 68.2%. Dagnew et al[21] evaluated RZV use in patients with hematologic malignancies receiving immunosuppressive therapy, and reported an efficacy of 87.2%.

Local and systemic reactogenicity are common in RZV recipients, with 1 in 10 reporting systemic reactogenicity that limits activity.[16,17] The safety profile of RZV appears to be similar in the general and immunocompromised populations, with primarily reactogenicity-type responses like fever, myalgias, headache, and injection-site reactions and few serious adverse effects.[6]

The biology, efficacy, and toxicity of RZV have been thoroughly reviewed elsewhere.[19]

## SPECIAL CONSIDERATIONS IN IMMUNOCOMPROMISED PATIENTS

A number of unique questions and challenges arise when considering strategies for preventing HZ in immunocompromised patients. These include concerns regarding vaccine administration, patient education, and patient selection. The responses to the following questions are based on varying levels of clinical evidence,[22] including expert opinion (identified as such) in areas where there is particular uncertainty.

Recommendations for administering the RZV in immunocompromised groups are summarized in **Table 3**.[23–28]

### What are the risks of RZV in general and in terms of flaring an underlying immune-mediated disease?

The adverse event profile of RZV, including reactogenicity, is similar in immunocompromised patients age 18 and older and those 50 and older who are not immunocompromised.[6] Patients should be counseled accordingly, keeping in mind that there are no head-to-head clinical trials addressing this question.[6]

A significant concern when using any adjuvanted vaccine in patients with immune-mediated diseases is the potential to flare the underlying disease. Several studies that examined the potential for disease flare in patients with autoimmune and inflammatory diseases have recently been reviewed.[29] Rheumatologic disorders have been the most extensively evaluated, and it appears that flares after RZV vaccination are uncommon. When they do occur, they are mostly self-limited and do not require therapy.[30,31] There are currently no high-quality data on the risk of post-vaccine flares in neurologic diseases like multiple sclerosis.

### What is the potential for diminished efficacy of RZV?

The efficacy of RZV in immunocompromised patients is based in part on data from Bastidas et al[20] in the hematopoietic transplantation population. During the 21-month median follow-up, the reduction in incident

**TABLE 3**
**Summary of recommendations for recombinant zoster vaccine in immunocompromised groups**

| Group (recommendation source) | Recommendations |
|---|---|
| Hematopoietic transplantation (CDC)[23] | Autologous: wait at least 3 months after transplant<br>Allogeneic: wait at least 6 months after transplant<br>Initiate RZV about 2 months before discontinuation of antiviral therapy[a] |
| Solid-organ transplantation (CDC)[23] | Administer RZV prior to transplant (if possible) or 6–12 months after transplant when graft stable on maintenance immunosuppression[a] |
| Malignancy (CDC)[23] | Administer RZV before to treatment (if possible) or when the immune system is not acutely suppressed or is likely to be most robust[a] |
| Rheumatic inflammatory and musculoskeletal diseases (American College of Rheumatology)[24] | Administering RZV is strongly recommended for patients with rheumatic and musculoskeletal diseases age > 18 who are taking immunosuppressive medication |
| Inflammatory bowel disease (American College of Rheumatology)[24] | All patients receiving Janus kinase inhibitor therapy should receive RZV<br>Risk of herpes zoster should be considered with combinations of other immunosuppressive[b] therapies |
| Psoriasis (Medical Board of the National Psoriasis Foundation)[25] | RZV should be given to all patients with psoriasis and psoriatic arthritis > age 50 and to patients < age 50 on tofacitinib, systemic corticosteroids, or combination systemic therapy[b] |
| Primary immunodeficiency diseases | No formal recommendations from societies as of now; per package insert RZV is indicated in adults age 18 and older who are or will be at increased risk of herpes zoster due to immunodeficiency or immunosuppression caused by known disease[26] |
| HIV (CDC)[27] | Patients with HIV ≥ age 18 should receive 2 doses of RZV at 0 and 2 to 6 months<br>Consider delaying vaccination until the patient is virologically suppressed on antiretroviral therapy or until the CD4 count is > 200 cells/mm$^3$ to ensure a robust vaccine response<br>Patients with HIV ≥ age 18 should receive RZV regardless of previous history of herpes zoster or previous receipt of live zoster vaccine (no longer available) or therapy |

[a]Recommendations vary somewhat among societies; expert opinion was recently summarized.[28]

[b]Systemic immunosuppression refers to current treatment with prednisone (> 20 mg/day for more than 14 days), azathioprine (> 2.5 mg/kg/day), mercaptopurine (> 1.5 mg/kg/day), methotrexate (> 0.4 mg/kg/week), cyclosporine, tacrolimus, infliximab, adalimumab, golimumab, certolizumab, ustekinumab, or tofacitinib.

CDC = Centers for Disease Control and Prevention; HIV = human immunodeficiency virus; RZV = recombinant zoster vaccine

HZ was significant, with an incidence rate ratio of 0.32 (95% confidence interval 0.22–0.44, $P < .001$), equivalent to a vaccine efficacy of 68.2%. This study also showed reductions in the incidence of postherpetic neuralgia and overall HZ-related pain.[6,20] Although this is well below the durable reduction in HZ demonstrated in the pooled analysis of the pivotal ZOE-50 and ZOE-70 trials,[16,17] which showed RZV efficacy of 91.3% for HZ incidence and 88.8% for postherpetic neuralgia incidence,[19] such reductions are still clinically meaningful.

The duration of protection in the immunocompromised population, while currently unknown, is likely less than that in the general population. Long-term, real-life studies are underway. Serial assessment of immune responses to RZV has shown good but diminished humoral responses to RZV in immunocompromised adults.[32] The interpretation of such data is problematic, however, because there is no agreed-upon ex vivo correlate of protection.[33] The results of ongoing studies on the duration of clinical effectiveness in a variety of immunocompromising conditions are eagerly awaited.

### Do certain immunosuppressive drugs and regimens pose a higher risk for incident HZ?

Individuals with immune-mediated diseases being treated with immunosuppressive drugs (eg, glucocorticoids, antimetabolites and related agents, biologics, targeted therapies such as kinase inhibitors) are the most rapidly expanding group of immunocompromised patients, spanning all ages. The attendant risks vary with the intensity of the immunosuppressive regimen, its duration, and, in particular, the use of agents known to increase HZ risk based on mechanism of action.

Glucocorticoids are the most commonly prescribed class of drugs with immunosuppressive potential. Doses greater than 20 mg per day of prednisone or equivalent are considered high-dose[12] and are associated with an increased HZ risk compared with low-dose regimens. Risk for HZ is elevated, but modestly, with many biologic agents, including tumor necrosis factor inhibitors, interleukin-6 inhibitors, B-cell–depleting agents, and T-cell co-stimulatory inhibitors.[15]

The most commonly used therapies associated with the highest risk of HZ are Janus kinase (JAK) inhibitors, which are now approved for numerous rheumatic,[34] dermatologic,[35] and inflammatory bowel[36] indications, potentially affecting millions of patients. The toxicity of JAK inhibitors has recently been reviewed.[15,37] Even within this class, the risk for HZ varies considerably for specific agents and with concomitant immunosuppressive therapies. In general, HZ risk appears to be increased with concomitant glucocorticoid therapy.[26] Also, the risk of HZ in patients on JAK inhibitors does not diminish over time, and a previous history of HZ is a strong risk factor for a second episode.[37] The risk for recurrent HZ is relatively low, however.[38] Collectively, these observations should serve to make patients on JAK inhibitors a high priority for prevention.

The type 1 interferon inhibitor anifrolumab, approved for the treatment of systemic lupus, is also associated with a significant risk of HZ.[39] This is not surprising given the centrality of type 1 interferon in antiviral defense. Unlike the risk of HZ associated with JAK inhibitors, the risk with anifrolumab appears greatest in the first year and diminishes sharply for those who continue taking it.[39]

Awareness of the changing landscape of risks associated with immune-based therapy is critical to risk-mitigation strategies.

### Should patients with humoral immunodeficiency states receive RZV?

The spectrum of primary immunodeficiency disorders is rapidly expanding, with 485 genetic disorders identified and approximately 1% of the global population affected.[40] Primary humoral immunodeficiency accounts for more than half of these patients. Immunoglobulin replacement therapy is often indicated in patients with humoral deficiency, and while anti-VZV antibodies are present in pooled immunoglobulin, the quantity is not standardized or validated across formulations or lots. Furthermore, data on the incidence of HZ in patients with humoral immunodeficiency states are limited.[41]

The CDC currently recommends RZV for patients age 19 or older with immunodeficiency conditions that increase the risk of VZV reactivation. Although humoral deficiency is not clearly defined in these recommendations, patients with such deficiencies may be candidates. There are currently no formal society guidelines regarding the use of RZV in this sizable subset of patients with primary immunodeficiency. We currently recommend RZV for such patients with a history of remote HZ. Decisions on the use of RZV in the remaining segment of this patient population are made on an individual basis. More data are needed to further define the epidemiology and risks of HZ in this highly heterogeneous group.

### What are the recommendations for timing?

The spectrum of immunocompromise is broad among patients with cancer, immunodeficiency states, transplantation, and immune-mediated diseases. Hence the need for and timing of vaccine administration varies widely. In general, it is best to administer all vaccines at least 2 weeks before planned immunosuppression to allow time for optimal response.[22] This is frequently not feasible, and therefore vaccination during active immunosuppression is still recommended.

Many studies show the safety and maintained effectiveness with co-administration of adult vaccines, with rare exceptions. The CDC and Advisory Committee on Immunization Practices advise that RZV can be co-administered with any other adult vaccine, provided the vaccines are given at different injection sites.[18] Concomitant administration of vaccines is often recommended, and even encouraged, to improve vaccine uptake. Practically speaking, however, given the potential for reactogenicity with the RZV series, many experts opt to separate RZV from other vaccines if the patient is able and amenable to receiving vaccines on different days. If a patient receives more than 1 vaccine at the same time and has an adverse event or significant reactogenicity, how can you determine which vaccine is the culprit? This experience may dissuade the patient from getting vaccines in the future.

Regardless of whether patients receive RZV alone or with other vaccines, reactogenicity counseling is key.

### Is antiviral prophylaxis warranted as a strategy to prevent HZ?

RZV is the primary strategy to prevent HZ and its complications in immunocompromised patients. However, vaccination is not always possible or, more commonly, is not effective, with some patients experiencing vaccine breakthrough. Data for the efficacy of antiviral prophylaxis in most settings are limited. It is recommended, however, in patients who have undergone hematopoietic transplantation; in these patients, efficacy has been demonstrated for up to 2 years, with the incidence of HZ increasing when prophylaxis is discontinued.[42]

More common is the scenario of HZ breakthrough in patients fully vaccinated with RZV but facing treatments likely to induce either extreme immunosuppression or that include drugs linked to incident HZ described above. Recommendations in this scenario are mostly limited to expert opinion. We currently offer antiviral prophylaxis to such patients.

### What changes in practice can enhance HZ prevention in immunocompromised patients?

Vaccination with RZV is essential to HZ prevention efforts. Reaching out to immunocompromised patients in a process of shared and informed decision-making, especially regarding RZV, is equally important. Offering and administering all appropriate vaccines to immunocompromised patients is complex, as the Infectious Diseases Society of America showed in their practice guideline more than a decade ago.[43] While new vaccines have emerged since this publication, the principles of collaboration between patients, their primary care physician, and the specialist who cares for the condition that contributes to their state of immunocompromise remain at the core of this process. All too often patients are caught in the middle of well-meaning clinicians struggling to figure out who will take the lead to approach them regarding the increasingly complex landscape of old and new vaccines. Unfortunately, the guidance document provided annually by the CDC[18] has become increasingly complex and ponderous, leaving many clinicians uncertain themselves regarding which patients are eligible candidates and when to administer the increasing array of available vaccines. Helping immunocompromised patients understand their increased risks of developing HZ, the significant burden of symptoms they may incur, the increased risk of complications, and the risks and benefits of RZV (including how to prepare for the strong likelihood of reactogenicity balanced by the extremely low incidence of serious adverse events) are key to this discussion.

## CONCLUSION AND FUTURE DIRECTIONS

HZ is a serious illness in the general population, and more so in the immunocompromised population. Effective prevention through administration of RZV to vulnerable patients age 19 and older is currently recommended. The vaccine has been demonstrated to be both safe and effective in this group. Numerous questions remain, however, regarding how to identify immunocompromised patients and what the long-term efficacy of RZV in the immunocompromised will be. For now, sufficient data exist to aggressively engage vulnerable patients in a process of shared and informed decision-making regarding vaccination.

## DISCLOSURES

Dr. Cassandra Calabrese has disclosed consulting with Astra Zeneca, Lilly, and Pfizer, and consulting, teaching, and speaking for Sanofi-Regeneron. Dr. Kirchner has disclosed consulting with Janssen Pharmaceuticals, Lilly, and Pfizer; teaching and speaking for RhAPP; and acting as an advisor or review panel participant for Boehringer Ingelheim, Horizon Pharma, and UCB. Dr. Fernandez has disclosed teaching and speaking for Baxalta. Dr. Leonard Calabrese has disclosed consulting for Abbvie Pharmaceuticals, GSK, Genentech/Roche, Janssen, Novartis, Sanofi Aventis, and UCB; teaching and speaking for Astra Zeneca, Genentech-Roche, Janssen, and UCB; and acting as an advisor or review panel participant for Genentech/Roche.

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