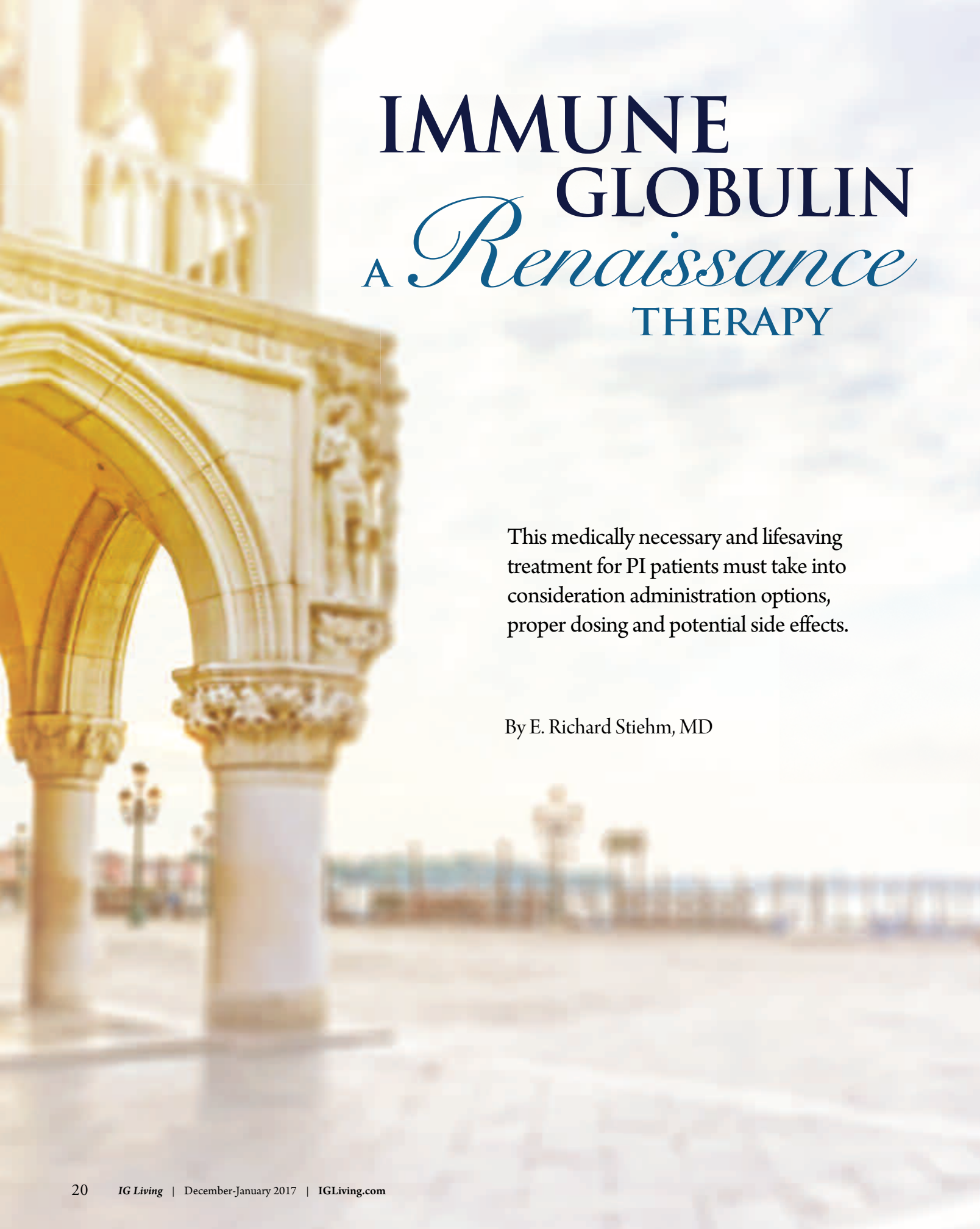

IMMUNE GLOBULIN A *Renaissance* THERAPY

This medically necessary and lifesaving treatment for PI patients must take into consideration administration options, proper dosing and potential side effects.

By E. Richard Stiehm, MD

HUMAN IMMUNE GLOBULIN (IG) is a true renaissance drug — the Benvenuto Cellini of the pharmacopeia because of its multiple forms, uses, mechanisms and, sadly, side effects. It is, with the exception of corticosteroids, used in more diseases than any other drug or biologic. Indeed, entire volumes and symposia discuss its therapeutic use, as do 14,000 articles cited in PubMed.[1]

Antibody therapy dates back to the 1890s, when Emil von Behring used horse antibodies to tetanus and diphtheria toxins to save the lives of infected children, thus garnering him the first Nobel Prize in Medicine.[2] Shortly thereafter, antisera from immunized animals or plasma from convalescing patients were used to prevent or treat a variety of infections.

Human IG (16%), prepared from pooled human plasma, was used during World War II to prevent transfusion hepatitis and later to prevent measles and polio. In 1952, Dr. Ogden Carr Bruton reported the first case of agammaglobulinemia in a boy he treated with weekly intramuscular injections of 16% IG.[3] But, because these painful injections were insufficient to normalize the patient's immunoglobulin G (IgG) level, he and most other antibody-deficient patients continued to have frequent infections. In 1974, a 5% human IG free of high molecular weight complexes and, thus, safe for intravenous (IV) use was shown to be equally effective in preventing infections in immunodeficient patients, with the added advantages of providing larger doses of IG at monthly intervals by the less painful IV route.[4]

IVIG products are associated with many systemic side effects, usually mild but sometimes severe. In the 1970s, Swedish investigators infused IG subcutaneously at weekly intervals to duplicate the total dose of IgG given monthly,[5] which resulted in a much lower frequency of adverse effects. Today, there are 10% and 20% subcutaneous IG (SCIG) products.

IG Products

All 13 IG products in the U.S. are licensed to treat patients with primary immunodeficiencies (PIs). Yet, therapy for PIs accounts for less than half of its use. IVIG is also approved for Kawasaki disease, chronic lymphocytic leukemia, kidney and bone marrow transplants, immune thrombocytopenic purpura, pediatric HIV infection, chronic inflammatory demyelinating polyneuropathy and multifocal motor neuropathy.[6] Medicare and Aetna recognize 23 other neurologic, hematologic and dermatologic disorders in which IVIG may be beneficial. In a recent text on IgGs, more than 100 uses of IVIG are discussed.[1]

IG products for use in the U.S. are derived from large pools of plasma from U.S. donors screened for viral diseases, including HIV and Zika. The final products must have protective antibody titers to tetanus, diphtheria and one or more strains of poliovirus. All have a similar profile of antibodies to common bacterial and viral pathogens, so they are therapeutically interchangeable. Yet, each product differs slightly in its method of purification and viral inactivation, as well as stabilizers, pH, sodium content, sugars and proteins, including IgA levels, albumin, isoagglutinin titers (anti-A, anti-B), HLA antigens and HLA antibodies. Some products are associated with side effects, including renal failure due to high sucrose levels and thrombosis due to trace amounts of procoagulant factors.[7]

IG is expensive (approximately $100 per gram), meaning an adult weighing 70 kg receiving 400 mg/kg every four weeks incurs a cost of $3,000 per month plus infusion fees. Indeed, IG is the second-largest annual expenditure for the University of California, Los Angeles pharmacy. This emphasizes the importance of getting insurance approval prior to starting IG therapy.

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In addition to standard IGs discussed in this article, there are several hyperimmune human IVIGs with high viral antibody titers to cytomegalovirus, hepatitis B, rabies, vaccinia and varicella zoster, as well as high titers to botulinum toxin (for infantile botulism) and RhD erythrocytes (for prevention of Rh hemolytic disease or the treatment of immune thrombocytopenic purpura).

Antimicrobial Properties of IG

Following an IG infusion, half of the IgG remains in the bloodstream, and half enters the extracellular tissues, including the alveoli of the lung. At these sites, IgG antibodies neutralize bacterial toxins and superantigens, lyse bacteria (with the help of complement) and coat (opsonize) bacteria to facilitate their

phagocytosis by circulating granulocytes and tissue macrophages, especially those in the spleen. IG also neutralizes viruses, forms viral immune complexes that are cleared from the circulation and coats viral-infected cells for lysis by antibody-dependent cellular cytotoxicity mediated by natural killer lymphocytes. These antibodies also prevent pathogens from entering adjacent tissues such as nerve roots and the central nervous system. The nonantibody Fc portion of the IgG molecule may bind to tissues and certain organisms such as protein A of Staphylococcus to provide nonspecific defenses.

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Very little of the infused IG enters the external secretions (e.g., tears, saliva, breast milk) or the mucosa surfaces of the respiratory or gastrointestinal tracts, which are protected by secretory IgA antibodies produced locally. Patients with profound antibody defects (e.g., agammaglobulinemia) do not make secretory IgA antibodies. However, measurable quantities of IgG in these areas are rarely achieved with the standard dose of IG. This fact is exemplified by the common complaint that PI patients with chronic conjunctivitis have a flare of their symptoms two or three weeks after their monthly IVIG therapy as their serum IgG decreases. This also explains why most patients, despite therapeutic IG doses, still get respiratory infections, yet are protected against major infections associated with bacteremia, including pneumonia.

Confirming the Diagnoses

Starting PI patients on IG therapy is a serious decision because of its inconvenience, expense, commitment to long-term therapy and effect on insurability, employment, athletic participation and mobility. Further, once IG therapy is started, making a diagnosis of antibody deficiency using IgG levels or antibody titers is impossible because the infused product normalizes them.

IG must be started on patients with proven agammaglobulinemia, common variable immunodeficiency (with very low levels of IgG, IgM and IgA) or with a well-defined combined immunodeficiency such as Wiskott-Aldrich syndrome or severe combined immunodeficiency. In these patients, IG therapy is essential for their future well-being.

The decision is more difficult in hypogammaglobulinemic patients with somewhat low IgG levels (400-600 mg/dl) and near-normal IgG and IgA levels. Starting IG is also a difficult decision for those with selective antibody deficiency, selective IgA deficiency and children with prolonged transient hypogammaglobulinemia of childhood. Many of these patients have had only respiratory infections and coexistent allergies, and they respond to intensive allergy and antibiotic therapy. In these patients, it is important to document decreased antibody function by vaccine titers and get insurance company approval for IG therapy reimbursement.

Because of its great expense, many hospitals have a pharmacy committee that must approve IG use to validate its need for each patient.

Infusion Considerations

Most PI patients are initially treated with IVIG, even if they plan to switch to SCIG. See the advantages and disadvantages of SCIG in Table 1.

Table 1. Advantages and Disadvantages of SCIG

Advantages

- Fewer adverse systemic reactions, even in those with prior reactions with IVIG
- Venous access is unnecessary
- More stable trough levels, avoiding recurrent symptoms prior to the next IVIG infusion
- Home treatment and self-administration is easier

Disadvantages

- More frequent dosing is necessary
- More frequent local reactions
- Delay in achieving a stable trough level unless preceded by IVIG
- Rarely used for autoimmune and inflammatory disorders

The first IVIG infusion should be given at a medical facility with persons equipped to handle an adverse event. The usual initial dose for PI is 400 mg/kg, given slowly with premedication and careful monitoring. Since half of the IgG goes into the tissues, a second loading dose is often given two days to seven days later, after which infusions are given every four weeks.

For patients who have one or more risk factors for adverse reactions (Table 2), a lower initial dose should be considered. If this is well-tolerated, subsequent doses can be increased.

IgG trough levels (the level just before the next infusion) should be monitored every two months until a stable level is achieved. If patients are doing well, this dose and schedule should be continued. If patients have continued infections and/or feel run-down toward the end of the infusion period, the IVIG dose can be increased by infusing every three weeks. The aim is to achieve a trough level 400 mg/dl to 500 mg/dl above the pre-infusion IgG level.

Table 2. Risk Factors for IVIG Adverse Effects

Infusion Factors
- No premedication
- Prior history of infusion reaction
- First infusion or switch to a new IVIG brand
- Large dose
- Rapid dose
- No pre-infusion or post-infusion hydration

Patient Factors
- Fever/infection at time of infusion
- Autoimmunity
- Older age
- Immobility/air travel
- Hypertension
- Present or past cardiovascular disease
- Diabetes
- High lipids/cholesterol
- Elevated serum proteins/gammopathy
- Smoking
- Prior/current thrombosis
- Estrogen use
- Hereditary hypercoagulable state (factor V Leiden; prothrombin mutations; protein C, S or antithrombin III deficiencies)
- Permanent indwelling venous catheter (i.e., portacath)

Stopping IG infusions is an option for some patients previously diagnosed with an antibody deficiency.

If patients continue to have repeated serious infections, the IVIG dose can be gradually increased. Since IgG levels are associated with fewer infections, the maintenance dose is that which controls patients' infections.[8,9] IgG levels, blood counts and chemistries should then be checked every six months.

If PI patients are switched to SCIG therapy, the same monthly dose of IG is prescribed. However, because the dose given subcutaneously at one site is limited, infusions are usually given weekly, or in some cases biweekly, in multiple sites. Alternatives are small daily subcutaneous injections (termed rapid-push SC) or monthly SCIG infusions using hyaluronidase to accelerate tissue update (termed hyaluronidase-facilitated SCIG).[10] (See "Hyaluronidase-Facilitated SCIG" on page 28.)

IG Reactions

Adverse reactions to IG may be local (at the infusion site) or systemic, involving the whole body.[7]

Local reactions to IVIG are rare. They include local pain, bleeding or bruising that typically occurs when venous access is difficult or if the medication leaks into the tissue during the infusion.

By contrast, local reactions to SCIG are common. Because tiny needles are used, there is minimal pain with needle insertion. However, 75 percent of infusions are associated with some pain, swelling and redness at the infusion site. These reactions usually subside within 12 hours to 24 hours, and they may decrease with subsequent infusions, making it unnecessary to rotate infusion sites.

Systemic reactions to IVIG are common and varied and may be immediate or delayed (Table 3). Immediate reactions occur in

5 percent to 15 percent of infusions, while delayed reactions are much less common. Immediate reactions occur shortly after the start of the infusion or within a few hours after the infusion. These include headache, malaise and muscle or back pain. Less common are fever, chills, nausea, flushing or urticaria. Some of these reactions may persist for several hours.

Table 3. Adverse Effects Associated with IVIG[7]

Mild Adverse Effects
(common, usually immediate*)
- Infusion site pain, swelling, erythema*
- Headache*
- Myalgia, back pain, arthralgia*
- Fever, chills, flushing*
- Anxiety, malaise, fatigue*
- Nausea, vomiting*
- Hypotension, hypertension, tachycardia*
- Hyponatremia**
- Neutropenia**
- Direct Coombs positivity**

Moderate Adverse Effects
(less common, usually delayed)**
- Persistent headache**
- Aseptic meningitis**
- Hemolytic anemia**
- Serum sickness/arthritis**
- Dermatologic complications**
- Interference with vaccine effectiveness and/or immunodiagnosis***

Severe Adverse Effects
- Anaphylactic/anaphylactoid reaction*
- Renal complications**
- Pulmonary complications**
- Thrombosis/embolism**
- Colitis**
- Bloodborne infectious diseases***

* Immediate reaction — within six hours from onset of infusion
** Delayed reaction — six hours to one week after infusion
*** Late reaction — weeks to months after infusion.

The most severe immediate reaction is an anaphylactic reaction sometimes associated with anti-IgA antibodies. These are treated like other anaphylactic reactions by stopping the infusion and giving epinephrine, antihistamines, steroids and fluids.

Delayed systemic reactions occur six or more hours after an infusion. The most common is persistent headache resembling a migraine. Other less-common delayed reactions include aseptic meningitis, renal failure, hemolysis and thrombosis. A variety of very rare delayed reactions have also been reported, involving nearly every system of the body.[7]

Reactions to IVIG are uncommon in patients doing well with a particular product. In these cases, switching brands is not recommended. Patients treated with IVIG who are doing well may be candidates for IVIG therapy at home by an infusion service or switching to home SCIG infusions. Switching to SCIG is especially attractive if patients are having systemic side effects from IVIG.

Delayed systemic reactions to SCIG infusions are rare. One report identified only 30 reactions in 3,232 infusions (less than 1 percent). Due to the infrequency of systemic reactions, premedication or close monitoring is usually unnecessary, making this route of administration ideal for home.

Discontinuing IG Infusions

Stopping IG infusions is an option for some patients previously diagnosed with an antibody deficiency. Most of these patients will have been diagnosed with mild hypogammaglobulinemia and normal IgM and IgA levels, mild respiratory infections and no serious infections. In addition, many of these patients will not have had antibody titers tested prior to starting IG infusions. In some cases, insurance carriers will request therapy be stopped to confirm the indication requiring the infusions.

Some patients who are candidates for discontinuing IG infusions have IgG levels of 800 mg/dl on standard IG doses. A good first step in such patients is to estimate their own endogenous IgG level by subtracting their monthly dose of IG in mg/kg from their IgG trough level in mg/dl. For example, a patient with an IgG trough level of 1,000 mg/dl on 400 mg/kg/month has an endogenous IgG level of 600 mg/dl. If the patient's endogenous IgG is over 400 mg/dl, the patient may not be immunodeficient.

Diagnosing an antibody deficiency while on IG therapy requires giving an antigen to which the IG does not have an antibody. Immunization with rabies vaccine, φχ phage and keyhole limpet hemocyanin have been used to measure antibody

function in these patients.[11] Alternatively, IG therapy must be stopped for four months, followed by immunizations for tetanus, H influenzae or pneumococci, with antibody response measured before and after four weeks.

Summary

Patients with PIs with or without a cellular immune deficiency require periodic infusions of IG to replace missing or non-functional IgG antibodies. A monthly IVIG dose of 400 mg/kg is the usual initial dose for these patients. A similar monthly dose of SCIG is used but must be administered in divided doses at more frequent intervals, usually weekly. Because of its expense, potential side effects and the frequent need for lifetime therapy, a firm diagnosis of immunodeficiency should be established prior to starting therapy. Mild systemic side effects with IVIG infusions (e.g., fever, chills, headaches, joint pain) are common, and serious side effects (aseptic meningitis, renal failure, hemolytic anemia and thrombosis) are occasionally encountered. Many patients treated with IVIG are switched to SCIG infusions because of its reduced side effects, ease of administration and suitability for self-administration.

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