

# NSAID Hypersensitivity (Respiratory, Cutaneous, and Generalized Anaphylactic Symptoms)

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## KEYWORDS

- Angioedema • Aspirin • Asthma
- Nonsteroidal anti-inflammatory drugs • Urticaria

Adverse reactions to drugs have been classified as predictable (related to the pharmacologic actions of the drug) and unpredictable (related to the individual's immunologic response or genetic susceptibility). The term "drug hypersensitivity" refers to the symptoms or signs initiated by an exposure to a drug at a dose normally tolerated by nonhypersensitive persons. "Drug allergy" refers to immunologically mediated drug hypersensitivity reactions, which may be either Immunoglobulin E (IgE)-mediated (immediate) or non-IgE-mediated (delayed). "Nonallergic hypersensitivity reactions" refer to adverse drug reactions that are not mediated by immunologic mechanisms.<sup>1</sup>

Nonsteroidal anti-inflammatory drugs (NSAIDs) are a group of substances of variable chemical composition that antagonize inflammation by interfering with the function of cyclooxygenases (COXs). COXs are enzymes that participate in the conversion of arachidonic acid (AA) into prostaglandins (PGs) and thromboxanes, which are strong mediators of the inflammatory process. This inhibition results in the shunting of AA metabolism toward the 5-lipoxygenase pathway, resulting in the increased release of cysteinyl leukotrienes (**Fig. 1**).

There are 2 isoforms of COXs: constitutive and inducible. COX-1 is the constitutive form present in all cells, whereas the inducible isoenzyme COX-2 is expressed

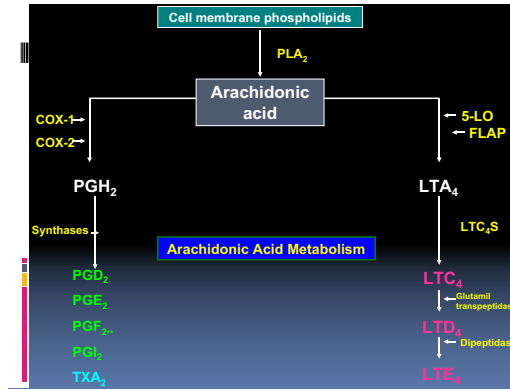
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**Fig. 1.** Metabolic pathways of arachidonic acid. 5-LO, 5-lipoxygenase; FLAP, 5-LO activating protein;  $LTA_4$ , leukotriene  $A_4$ ;  $LTC_4$ , leukotriene  $C_4$ ;  $LTC_4S$ , leukotriene  $C_4$  synthase;  $LTD_4$ , leukotriene  $D_4$ ;  $LTE_4$ , leukotriene  $E_4$ ;  $PGD_2$ , prostaglandin  $D_2$ ;  $PGE_2$ , prostaglandin  $E_2$ ;  $PGF_{2\alpha}$ , prostaglandin  $F_{2\alpha}$ ;  $PGH_2$ , prostaglandin  $H_2$ ;  $PGI_2$ , prostaglandin  $I_2$ ;  $PLA_2$ , phospholipase  $A_2$ ;  $TXA_2$ , thromboxane  $A_2$ .

exclusively in inflammatory cells after stimulation by cytokines, growth factors, bacterial lipopolysaccharide, tumor promoters, and other factors. While acetylsalicylic acid (ASA), also known as aspirin, and the classic NSAIDs inhibit both isoforms of COX, the new, selective COX-2 inhibitors are devoid of COX-1 inhibition and therefore have less ability to decrease gastric PG  $E_2$  ( $PGE_2$ ), producing less gastric irritation and ulceration (Table 1).

NSAIDs induce allergic and nonallergic hypersensitivity reactions. The second group of reactions is commonly described in medical literature as intolerant, pseudoallergic, or idiosyncratic reactions. In this article, the current knowledge on hypersensitivity reactions to NSAIDs is discussed.

## HYPERSENSITIVITY REACTIONS TO NSAIDS

According to the temporal pattern of reactions, hypersensitivity to NSAIDs is classified as acute reactions occurring immediately or hours after exposure to the drug and delayed reactions, which manifest after more than 24 hours of administration of the drug.<sup>2</sup> Acute reactions are far more frequent and are the focus of this article. The

**Table 1**  
Classification of NSAIDs according to their selectivity for COX isoenzymes

Selectivity	Drugs
Weak COX inhibitors	Acetaminophen, salsalate
Inhibitors of COX-1 or COX-2	Piroxicam, indomethacin, sulindac, tolmetin, ibuprofen, naproxen, fenoprofen, meclofenamate, mefenamic acid, diflunisal, ketoprofen, diclofenac, ketorolac, etodolac, nabumetone, oxaprozin, flurbiprofen
Preferential COX-2 inhibitors	Nimesulide, meloxicam
Selective COX-2 inhibitors	Celecoxib, rofecoxib, valdecoxib, etoricoxib, parecoxib, lumiracoxib

following 2 groups of patients with underlying disease and 2 groups of patients without obvious underlying disease are included:

1. NSAID-exacerbated respiratory disease, presently designated as aspirin-exacerbated respiratory disease (AERD).
2. NSAID-exacerbated cutaneous disease, in particular, urticaria and angioedema in patients with chronic idiopathic urticaria (CIU). In analogy to AERD, it could be called NSAID- or aspirin-exacerbated cutaneous disease (AECD).
3. Multiple NSAID-triggered urticaria, angioedema, and anaphylaxis in patients without other underlying disease.
4. Urticaria, angioedema, and anaphylaxis induced by a single NSAID.

### ***Respiratory Reactions: AERD***

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#### ***Definition***

AERD was previously known as ASA triad, asthma triad, Fernand Widal syndrome, Samter syndrome, and aspirin-intolerant asthma. More recently, a denomination of AERD has been proposed to emphasize that the condition evolves independently of administration of aspirin or NSAID, although these drugs will provoke asthmatic attacks in affected individuals.

#### ***Prevalence***

AERD has been estimated to be prevalent in the range of 4.3% to 11% in adult asthmatics and in about 25% of patients who have asthma and nasal polyposis. One study reported a prevalence between 11% and 20% determined through a questionnaire, 3% through a medical record, and 21% through an oral provocation test.<sup>3</sup> AERD has similar effects on women and men.

#### ***Clinical picture***

The classic ASA triad consists of chronic rhinosinusitis, nasal polyposis, persistent asthma, and aspirin or NSAID hypersensitivity. The triad of symptoms may develop stepwise over years, and occasionally only 2 of the 3 main symptoms are present. Intake of aspirin or any other NSAID causes, within a few minutes to approximately 120 minutes, symptoms such as a flush reaction in the face and upper thorax, rhinitis, conjunctivitis, feeling of blocked nose, and an often severe exacerbation of asthma with severe breathlessness, which may require emergency treatment. The underlying asthma is generally severe and steroid dependent, and it may be life threatening. The exacerbation due to NSAID intake is clearly dose dependent and probably also dependent on the potency of the COX inhibition of the particular NSAID. The threshold for aspirin doses for asthma exacerbations ranges between 3 and 100 mg and rarely more than 100 to 600 mg. In consequence, such patients may also react to an aspirin dosage given for cardioprotective purposes (100 mg/d).

#### ***Pathogenesis***

The COX hypothesis proposed by Szczeklik<sup>4</sup> states that inhibition of COX-1, resulting in increased production of leukotrienes and decreased synthesis of PGE<sub>2</sub> (a modulator of mast cell mediator release), is responsible for airway inflammation, rhinosinusitis, and asthma observed in patients with AERD. Multiple observations support this theory, including increased urinary leukotriene (LT) E<sub>4</sub> (LTE<sub>4</sub>) levels, and increased expression of the enzyme LT C<sub>4</sub> synthase (LTC<sub>4</sub>S) and LT receptors in this patient population.<sup>5,6</sup>

A genetic predisposition for the development of AERD has been proposed, and various genes seem to be involved, including some HLA alleles, single nucleotide

polymorphisms in cysteinyl LT receptor 1 (CysLTR1) and CysLTR2 receptors, LTC<sub>4</sub>S, thromboxane receptors (TBXA<sub>2</sub>R), high-affinity receptor for IgE (FcεR1b), T-box transcription factor TBX21, PGE receptor (EP2 type), and tumor necrosis factor  $\alpha$  promoter.<sup>7</sup> However, none of these genes are strongly associated with AERD.

### Diagnosis

The diagnostic approach for AERD is based on the clinical picture of chronic rhinosinusitis and moderate to severe asthma, with exacerbations occurring when NSAIDs are taken. Aspirin hypersensitivity is confirmed by single-blind oral provocation, which is commonly used in the United States.<sup>8</sup> The test should be performed when asthma is stable (forced expiratory volume in the first second of expiration [FEV<sub>1</sub>] >70%, with diurnal variability <10%). In Europe, inhalation or nasal challenges with lysine-aspirin are used.<sup>9</sup> All these tests bear the risk of severe asthma exacerbations, and should be done only by trained specialists with easily available equipment and medication for the treatment of acute asthma attacks if they develop.

In vitro assays measuring sulfidoleukotriene release, such as basophil activation tests and the 15-hydroxyeicosatetraenoic acid generation assay (Aspirin Sensitive Patient Identification Test), are still under study and need further validation at this time.<sup>6</sup>

Multiple protocols for oral ASA provocation are used in different centers,<sup>8–10</sup> and some provocation tests are immediately followed by desensitization.<sup>10</sup> Examples are presented in **Tables 2** and **3**.

### Management

Patients with AERD are advised to avoid all COX-1 inhibitors, including aspirin and the classic NSAIDs, to prevent serious asthma exacerbations. For the treatment of pain and inflammation, NSAIDs that do not inhibit (or weakly inhibit) COX-1, such as acetaminophen in doses less than 1000 mg, and COX-2 inhibitors are recommended. It is advisable to challenge these alternatives under supervision to exactly define the tolerated dose, because approximately 10% of patients with AERD also react to acetaminophen, at least in higher doses (>500–800 mg). It is also advisable to strictly instruct the affected patients to use only the controlled alternative drugs, if needed. A list of available and forbidden NSAIDs should be explained and given to the patients, as well as an emergency card (bracelet).

Aspirin desensitization is useful for patients who require continuous therapy, such as those with ischemic heart disease or chronic arthritis.<sup>10</sup> Persistent asthma and rhinosinusitis should be treated with the approaches given by international guidelines such as the Global Initiative for Asthma and European Position Paper on Rhinosinusitis and Nasal Polyps.<sup>11,12</sup>

Time	Day 1	Day 2	Day 3
7 AM	Placebo	ASA, 30 mg	ASA, 100–150 mg
10 AM	Placebo	ASA, 45–60 mg	ASA, 150–325 mg
1 PM	Placebo	ASA, 60–100 mg	ASA, 325–650 mg

Positive if FEV<sub>1</sub> decreases greater than or equal to 20% and/or a prominent naso-ocular reaction.

Data from Stevenson DD. Aspirin desensitization in patients with AERD. Clin Rev Allergy Immunol 2003;24:159–67. (Stevenson DD, Scripps Clinic and the Scripps Research Institute, La Jolla, CA).

Day 1	Day 2
Placebo	ASA, 27 mg
Placebo	ASA, 44 mg
Placebo	ASA, 117 mg
—	ASA, 312 mg

Doses administered every 1.5 to 2 hours.

Positive if FEV<sub>1</sub> decreases greater than or equal to 20% or symptoms (which are bronchial, in the upper airways, ocular, cutaneous, gastrointestinal) occur.

*Abbreviations:* EAACI, European Academy of Allergy and Clinical Immunology; GA<sup>2</sup>LEN, Global Allergy and Asthma European Network.

*Data from* Nizankowska-Mogilnicka E, Bochenek G, Mastalerz L, et al. EAACI/GA2LEN guideline: aspirin provocation tests for diagnosis of aspirin hypersensitivity. *Allergy* 2007;62(10):1111–8.

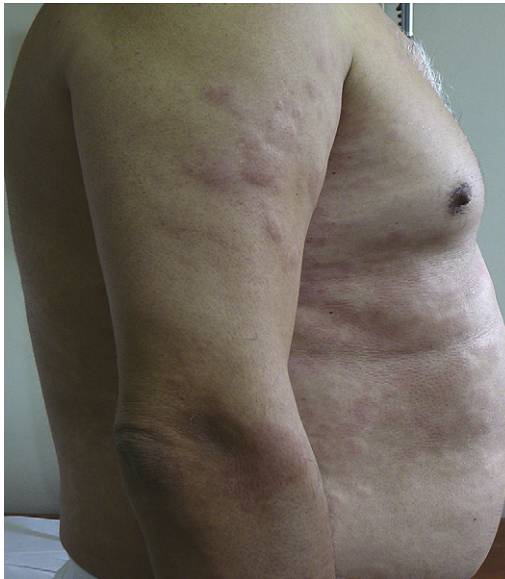
### ***NSAID-Exacerbated Urticaria and Angioedema in Patients with Chronic Urticaria***

#### ***Prevalence and clinical picture***

Reactions to NSAIDs are responsible for 21% to 25% of all adverse reactions to drugs and occur in 0.5% to 1.9% of the general population. Exacerbations of a preexisting urticaria or angioedema after taking aspirin or classic NSAIDs are observed in up to one-third of patients with controlled chronic urticaria and up to two-thirds of patients with active CIU (**Fig. 2**).<sup>13</sup> Analogous to AERD, an NSAID-exacerbated cutaneous disease or AECD could be considered.

#### ***Pathogenesis***

Mastalerz and colleagues<sup>14</sup> observed that patients with chronic urticaria and aspirin intolerance had increased basal urinary LTE<sub>4</sub> when compared with patients with



**Fig. 2.** CIU exacerbated by aspirin.

CIU tolerant to aspirin. Further increases of  $\text{LTE}_4$  occurred in the first group but not in ASA-tolerant individuals when patients from both groups were challenged with aspirin. These results suggest that exacerbations of urticaria induced by aspirin in patients with CIU are mediated by inhibition of COX-1.

Asero<sup>15</sup> has recently observed the positive results from autologous serum skin tests and autologous plasma skin tests in more than 90% of patients with chronic urticaria and NSAID intolerance. This observation would suggest a possible association among CIU, autoimmunity, and aspirin hypersensitivity.

### **Diagnosis**

In general, patients have a history of recurrent urticaria without a known precipitating factor, and they may provide, spontaneously or after questioning, information on the aggravation of cutaneous symptoms when exposed to NSAIDs. Some patients may have had only a generalized pruritus with scarce urticarial wheals (eg, after pressure), but NSAID intake may have caused a generalization and aggravation of their urticaria and first manifestation of angioedema. Confirmation by oral challenge may be necessary in some patients (see later discussion on multiple NSAID-triggered urticaria).

### **Management**

Patients with CIU who do not tolerate ASA or NSAIDs should avoid all inhibitors of COX-1. Alternative drugs such as acetaminophen (tolerated by about 89% of these patients) or COX-2 inhibitors may be used after single-blinded oral challenge.<sup>16,17</sup> Compared with patients with AERD, most patients exhibiting cutaneous symptoms caused by multiple NSAIDs need higher doses, for example, of aspirin (approximately 300 mg), to cause an exacerbation of their disease.

The treatment of chronic urticaria is done with nonsedating antihistamines alone or combined with other drugs, as recommended by recent guidelines.<sup>18</sup>

### **Multiple NSAID-Triggered Urticaria, Angioedema, and Anaphylaxis in Patients Without Other Underlying Disease**

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#### **Definition and prevalence**

In the cases of patients who do not have chronic urticaria and experience urticaria and/or angioedema after treatment with COX-1 inhibitors of various chemical groups, the drugs more frequently involved depend on the prescription pattern predominant in the area. A heteroaryl group of NSAIDs (such as naproxen, diclofenac, ibuprofen) has been more often incriminated.<sup>19,20</sup>

Although no history of underlying disease is obtained, the authors have observed that these reactions occur more often in atopic individuals with rhinitis and/or asthma.<sup>21</sup> ASA and NSAIDs are the 2 major causes of anaphylaxis.<sup>22-24</sup> Cutaneous reactions to COX-2 inhibitors in hospitalized patients are observed in 0.008% of treated subjects,<sup>25</sup> about 50% less frequently than reactions to classic NSAIDs (with a relative risk 0.96 vs 1.77).<sup>26</sup>

#### **Pathogenesis**

The mechanisms of multiple NSAID reactions in this patient subpopulation are not known. The observation that urticaria and angioedema are provoked by drugs that share a common pharmacologic mechanism of action would suggest that COX-1 inhibition is involved. On the other hand, it is puzzling that some patients seem to tolerate certain NSAIDs (eg, ibuprofen), but react to others (eg, aspirin, diclofenac, and naproxen).

### **Clinical picture**

Facial angioedema is the most common clinical manifestation (**Fig. 3**).<sup>27</sup> Up to 37% of patients may develop chronic urticaria in the future.<sup>28</sup> Some patients with multiple NSAID hypersensitivity exhibit an increased risk for developing oral mite anaphylaxis (pancake syndrome).<sup>29</sup>

### **Diagnosis**

The medical history discloses the presence of episodes of urticaria or angioedema occurring after exposure to various COX-1 inhibitors of unrelated chemical groups. If necessary, confirmation by means of single-blind oral provocation as depicted in **Table 4** is performed.

### **Management**

Patients are advised to avoid COX-1 inhibitors. Acetaminophen and COX-2 inhibitors are alternative drugs suitable for analgesia and treatment of pain and inflammation in this group of subjects (**Fig. 4**). At present, COX-2 inhibitors are not recommended for chronic use because of the increased risk of cardiovascular accidents, especially in people with a history of coronary or cerebrovascular disease.

### **Urticaria, Angioedema, and Anaphylaxis Induced by a Single NSAID**

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#### **Definition and prevalence**

Reactions to a single NSAID class are seen more often in patients treated with pyrazolones,<sup>30,31</sup> but they have been reported for many other NSAIDs (mainly diclofenac, and also rarely for others such as acetaminophen, aspirin, ibuprofen, ketorolac, indomethacin, sulindac, zomepirac, fenoprofen, meclofenamate, naproxen, piroxicam, tolmetin, and celecoxib).<sup>32</sup>

These reactions constitute about 30% of all cases of NSAID hypersensitivity, and about 30% of patients have concomitant chronic urticaria. An increased prevalence of atopy has been reported.<sup>21</sup>

### **Clinical picture**

Any of the following clinical manifestations may be observed: urticaria, angioedema, laryngeal edema, systemic anaphylaxis, generalized itching, rhinitis, and bronchospasm.



**Fig. 3.** Facial (periorbital) edema induced by ibuprofen in a 15-year-old female patient with multiple NSAID-triggered angioedema.

<b>Table 4</b>			
<b>Oral provocation with aspirin for patients with urticaria and angioedema</b>			
<b>Day 1</b>	<b>Day 2</b>	<b>Day 3</b>	<b>Day 4</b>
Placebo	ASA, 100 mg	ASA, 325 mg	ASA, 650 mg
Placebo	ASA, 200 mg		

On days 1 and 2, doses given every 2 hours.

Skin scores recorded every 2 hours.

In patients with active chronic urticaria, rule of nines (as calculated in cases of patients having burns) may be used.

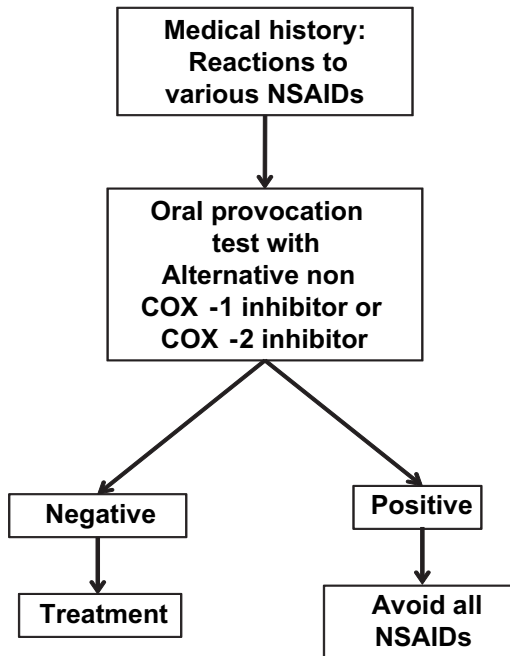
In Europe, the recommended consecutive doses of ASA are 71 mg, 117 mg, 312 mg, and 500 mg.<sup>9</sup>

### **Pathogenesis**

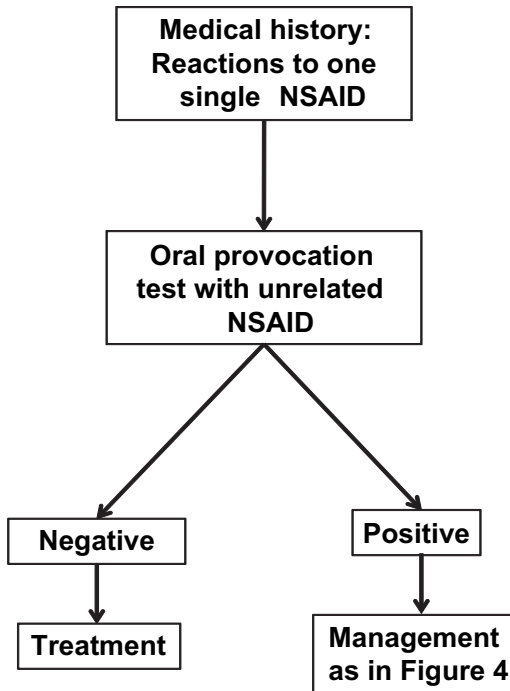
In some patients at least, an allergic sensitization mediated by drug-specific IgE to a certain NSAID is likely. Specific IgE can be demonstrated by means of prick or intradermal skin tests or in vitro by immunoassays,<sup>33</sup> which have been well documented for patients with hypersensitivity to pyrazolones and may also play a role in other reactions, although this is less well documented.<sup>34</sup>

### **Diagnosis**

In patients with a history of reaction to a single NSAID and no additional exposure to a second NSAID, skin testing is possible and may reveal a selective sensitization. IgE tests are not commercially available. It may be convenient to confirm the diagnosis by oral challenge, although this should be done cautiously because low concentrations of



**Fig. 4.** Algorithm for the management of patients with urticaria and angioedema triggered by multiple NSAIDs.



**Fig. 5.** Algorithm for the management of patients with urticaria and angioedema triggered by a single NSAID.

the drug may already cause symptoms. If the results are positive, another NSAID of a different chemical group should be tested to demonstrate single reactivity (**Fig. 5**). A history of systemic anaphylaxis would be a contraindication to perform the provocation tests with the incriminated substance.

Table 5 Chemical classification of NSAIDs	
Group	Drugs
Salicylic acid derivatives	Aspirin, sodium salicylate, choline magnesium trisalicylate, salsalate, diflunisal, salicylsalicylic acid, sulfasalazine, olsalazine
Para-aminophenol derivatives	Acetaminophen
Indole and indene acetic acids	Indomethacin, sulindac, etodolac
Heteroaryl acetic acid	Tolmetin, diclofenac, ketorolac
Arylpropionic acid	Ibuprofen, naproxen, flurbiprofen, ketoprofen, fenoprofen, oxaprozin
Anthranilic acid (fenamates)	Mefenamic acid, meclofenamic acid
Enolic acid	Oxicams (piroxicam, tenoxicam), pyrazoledinediones (phenylbutazone, oxyphentathrazone)
Alkanones	Nabumetone
Pyrazolic derivatives	Antipyrine, aminopyrine, dipyrone

### **Management**

Once the diagnosis of single drug reaction is confirmed, avoidance of the drug and other chemically similar NSAIDs should be advised. These patients can be treated with other non-cross-reacting NSAIDs (**Table 5**).

### **SUMMARY**

Reactions to NSAIDs are a major cause of hypersensitivity to drugs, occupying second place after reactions to antibiotics. The most common acute clinical manifestations involve the respiratory tract (rhinosinusitis and asthma), the skin (urticaria and angioedema), or are generalized (anaphylaxis). The affected patients often already have an underlying respiratory or cutaneous disease, and the intake of various NSAIDs can precipitate more severe symptoms. Early diagnosis and treatment, proper medical advice on drug use, and referral to an allergy specialist when indicated are of paramount importance to prevent unnecessary morbidity and the potential risk of death from these severe reactions.

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