



Heterogeneity of NSAID-Exacerbated Respiratory Disease: has the time come for subphenotyping?

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Purpose of review

NSAID-Exacerbated Disease (N-ERD) is a chronic eosinophilic inflammatory disorder of the respiratory tract occurring in patients with asthma and/or rhinosinusitis with nasal polyps, whose symptoms are exacerbated by NSAIDs. The purpose of this review is to provide an update on clinical characteristics, pathophysiology, and management of N-ERD, and to emphasize heterogeneity of this syndrome.

Recent findings

Growing evidence indicates that N-ERD, which has been considered a separate asthma phenotype, is heterogeneous, and can be divided in several subphenotypes varying in clinical characteristics. Pathophysiology of N-ERD is complex and extends beyond abnormalities in the arachidonic acid metabolism. Heterogeneity of pathophysiological mechanisms underlying development of airway inflammation seems to be associated with variability in response to both anti-inflammatory and disease-specific treatments (e.g., with aspirin after desensitization).

Summary

Progress in understanding of the pathophysiology of N-ERD leads to discovery and validation of new biomarkers facilitating diagnosis and predicting the response to treatment of the chronic inflammation underlying upper (CRSwNP) and lower airway (asthma) symptoms. Better characterization of the immunophysiopathological heterogeneity of N-ERD (identification of endotypes) may allow more personalized, endotype-driven approach to treatment in the future.

Keywords

Asthma-exacerbated respiratory disease, asthma, heterogeneity, NSAID-Exacerbated respiratory disease, rhinosinusitis

INTRODUCTION

NSAID-exacerbated respiratory disease (N-ERD), a clinical syndrome known for almost a century under various names (aspirin-triad, aspirin-sensitive asthma, Samter's/Vidal's Syndrome or aspirin-exacerbated respiratory disease) [1–3], has been recently defined by international panel of experts as 'a chronic eosinophilic inflammatory disorder of the respiratory tract occurring in patients with asthma and/or rhinosinusitis with nasal polyps, whose symptoms are exacerbated by NSAIDs, including aspirin' [4]. The incidence of N-ERD in western hemisphere varies from 7 to 14% in mild asthmatic patients and up to 24% in patients with severe asthma [5,6]. Although N-ERD has been one of the best defined asthma phenotypes, growing evidence indicates that it is not homogenous, instead can be further divided into several subphenotypes [7]. The purpose of this review is to describe recent developments in immunopathophysiology, diagnostic approaches, and treatment

modalities for N-ERD with special reference to heterogeneity of this syndrome.

TYPICAL PRESENTATION OF NSAID-EXACERBATED DISEASE PHENOTYPE

Hypersensitivity reaction in N-ERD patients develops usually within 1–2 h after intake of aspirin or other NSAID and is manifested with nasal congestion and rhinorrhea followed by dyspnea and progressing airway obstruction [8]. However, a heterogeneity in clinical reactions induced by

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KEY POINTS

- N-ERD is a heterogeneous asthma phenotype complicated by chronic rhinosinusitis (with nasal polyposis; CRSwNP) and cross-reactive type of hypersensitivity to NSAIDs.
- Pathogenesis of chronic airway inflammation involves specific abnormalities in arachidonic acid metabolism and activation of the innate immune response.
- Management of N-ERD in addition to anti-inflammatory treatment should include endotype-specific approaches (e.g., treatment with aspirin after desensitization).
- Discovery of new biomarkers and development of N-ERD endotype-specific treatment modalities, including targeted biological treatment, could be expected in the future.

NSAIDs has been observed, with up to one-third of patients manifesting cutaneous symptoms (rash and erythema or even urticarial wheals) in parallel to respiratory symptoms [9,10]. Chronic rhinosinusitis with nasal polyps (CRSwNP) runs protracted course, and is difficult to control. The recurrence rate for nasal polyps in N-ERD patients after standard polypectomy, but also after Endoscopic Sinus Surgery (EES), is several times higher than in NSAIDs-tolerant asthmatic patients [11]. A typical patient with N-ERD suffers from moderate to severe asthma with tendency to frequent exacerbations, despite chronic treatment with inhaled glucocorticoids, combined with long-acting beta-2 receptor agonist (LABA) [12]. Relatively new is the observation that up to 75% of N-ERD patients report respiratory symptoms (nasal congestion, rhinorrhea, and/or wheezing) following consumption of alcohol [13].

NSAID-EXACERBATED DISEASE IMMUNOPATHOPHYSIOLOGY

The mechanism of NSAID-induced reactions in asthmatic patients has been related to pharmacological properties of acetylsalicylic acid; aspirin (ASA) and other NSAIDs, namely to cyclooxygenase-1 (COX-1) and prostaglandin synthesis inhibition [14,15] with subsequent activation of a biochemical cascade leading to release of mast-cell and eosinophil-derived mediators, including enhanced production of cysteinyl leukotrienes and PGD₂ [10]. The pathogenesis of chronic eosinophilic inflammation in the airway mucosa and of nasal polyps in NSAID-intolerant patients is not fully understood, but is not related to exposure to aspirin or other NSAIDs. Chronic airway inflammation in N-ERD patients is characterized by predominate expression of type 2

cytokines, although mixed type 2/1 cytokines patterns have also been found in the upper airway mucosa [16–18]. Distinctive features of chronic airway inflammation (increased airway and blood eosinophilia, platelet-adherent leukocytes and mast cell activation with abundant production of cysteinyl leukotrienes, and prostaglandin D₂) have been explained by the inherited abnormalities in arachidonic acid metabolism [19,20].

Although a large majority of N-ERD patients are atopic, very little is known on the contribution of immunoglobulin E (IgE)-mediated mechanisms to the pathogenesis of the airway inflammation in this population of asthma. More recently, it has been shown that a group 2 innate lymphoid cells (ILC2s) may contribute to the production of type 2 cytokines, specifically in response to environmental stimuli including viral infections [21]. A Boston research group suggested that eosinophilic inflammation and mast cell activation in N-ERD are largely driven by innate type 2 immunity, initiated by epithelium-derived innate cytokines TSLP and IL-33 [22,23]. Along these lines, White and coworkers [24[■],25] documented that in N-ERD patients ILC2s were recruited to the nasal mucosal in response to COX-1 inhibitor and numbers of nasal ILC2s correlated with symptom scores, urinary LTE₄ and PGD₂ metabolites increases during reactions. However, it is not clear whether ILC2-driven type 2 inflammation is characteristic to all N-ERD patients or to a subpopulation.

Genetic studies identified numerous genetic polymorphisms within target genes (lipid mediators and inflammatory responses) associated with distinct pathogenetic pathways of N-ERD [26–28]. Hence, substantial genetic heterogeneity among N-ERD patients may further add to the heterogeneity of clinical characteristics and underline observed variability in the response to treatment.

NSAID-EXACERBATED DISEASE SUBPHENOTYPES AND SUBENDOTYPES

N-ERD with clinically typical characteristics, which include asthma with more than average severity, and chronic rhinosinusitis (CRS) characterized by hyperplastic rhinosinusitis (often with nasal polyposis), has been considered as one of the best characterized asthma phenotypes [29]. However, in clinical practice, a large heterogeneity in patients' clinical profiles has been observed pointing to existence of several subphenotypes. Two recent studies, one from Poland and the second from Korea, both conducted in relatively large groups of patients, documented clinical and pathophysiological heterogeneity among N-ERD patient populations [30,31[■]]. Bochenek *et al.* [30], employing latent class analysis, distinguished four

classes (disease subphenotypes) within the N-ERD phenotype: class 1 (18.9% of the study population) was characterized by asthma with moderate course, but intensive upper airway symptoms; class 2 (34.8% of patients) included mild and relatively well controlled asthmatic patients. In contrast, asthmatic patients in class 3 (41.3% of patients) and class 4 (5%) had severe and poorly controlled disease. Thus, in contrast with popular believes, over 50% of the N-ERD patients in this study presented with moderated and relatively well controlled asthma. In a more recent study by a Korean group [31²²] applying a two-step cluster analysis, patients were also distinguished four phenotypic clusters (subtypes), but with different clinical characteristics than in the Polish cohort. Among the four subtypes, distinguished according to the presence of urticaria, atopy, and CRS, significant differences were found with respect to antiasthmatic medication requirement, asthma exacerbation rate, and baseline forced expiratory volume (FEV₁)1%.

As discussed above, N-ERD has been associated with several immunopathophysiological abnormalities specific for this phenotype, for example, overproduction of urinary cysteinyl leukotrienes and PGD₂ or local PGE₂ or lipoxins deficiency, which allowed to consider N-ERD as a separate asthma endotype [32]. Both Polish and Korean study identified significant differences in pathophysiological features, for example, blood eosinophilia or urinary concentrations of cysteinyl leukotrienes, among distinguished N-ERD subphenotypes. Among patients with this, by definition, eosinophilic asthma phenotype, a subgroups with both high and of low eosinophilia could be distinguished, and patients with particularly intensive upper airway symptoms had the highest levels of blood eosinophilia and the highest concentrations of urinary LTE₄ [30], suggesting a presence of different endotypes with potentially different mechanisms underlying airway inflammation. Further studies are needed to characterize potential endotypes of N-ERD, for example, subgroups with low eosinophilia (class 2 in the Polish study and subtype 3 in the Korean study), which may have different pathogenesis of airway inflammation. Presence of subphenotypes and subendotypes may have a potential implication for understanding the heterogeneity in the responses to treatment observed in N-ERD patients [33] (Fig. 1).

BIOMARKERS AND NOVEL APPROACHES TO DIAGNOSIS OF NSAID-EXACERBATED DISEASE

N-ERD is diagnosed based on the presence of typical triad in a patient: bronchial asthma, chronic

rhinosinusitis with nasal polyps, and a hypersensitivity reaction to aspirin or other cross-reacting NSAID. A convincing history of NSAID-induced adverse reactions (usually to two or more cross-reactive NSAIDs) may be sufficient to make a diagnosis, but in some patients, confirmation by an aspirin challenge is necessary [4³,34]. Oral aspirin challenge, when performed in a controlled setting with adequate expertise is safe [35²³], and can reliably confirm the diagnosis, but nasal or bronchial provocation with lysine-ASA, may offer alternative diagnostic tools [36]. There are no validated in-vitro tests which could distinguish NSAID-tolerant from NSAID-hypersensitive individuals, although recently, several biomarkers to identify N-ERD patients have been proposed [32]. In a study by Kim *et al.* [37], serum periostin levels were significantly elevated in N-ERD patients and associated with phenotypic characteristics and disease severity. Wardzyńska *et al.* [38] could not differentiate N-ERD patients from NSAID-tolerant based on periostin levels in serum or in exhaled breath condensate, but were able to distinguish N-ERD subgroups. They reported that N-ERD patients with skin manifestation of NSAIDs hypersensitivity had higher serum periostin levels as compared to N-ERD patients with no skin symptoms potentially representing a subphenotype/subendotype of N-ERD.

Although on average N-ERD patients have elevated urinary levels of LTE₄ (uLTE₄), substantial individual variability has been observed across patients, which precluded the potential diagnostic value of this biomarker so far. Ban *et al.* [39] compared metabolomic profiles of serum from N-ERD, NSAID-tolerant asthmatic patients and healthy controls, analyzed with the ultra-high-performance liquid chromatography (UHPLC)/Q-ToF MS system. Serum levels of LTE₄ and LTE₄/PGF₂ α ratio before and after the Lys-ASA BPT were significantly higher in patients with N-ERD than in control asthmatic patients, and urine baseline levels of these two metabolites were significantly higher in patients with N-ERD. Although authors suggest that serum level of LTE₄ and LTE₄/PGF₂ α ratio could serve as potential in vitro diagnostic biomarkers for N-ERD, sophisticated technology used in this study may be difficult for implementing in routine diagnosis. Hagan *et al.* [40] who reviewed literature in order to assess the diagnostic testing accuracy of uLTE₄ as a biomarker of N-ERD concluded that uLTE₄ is a reliable biomarker of NSAID hypersensitivity in patients with asthma. However, the diagnostic performance of uLTE₄ measurement to determine NSAID intolerance in subjects with asthma varied significantly depending on the methodology used. When two-enzyme immunoassays, mass spectrometry, and radioimmunoassay

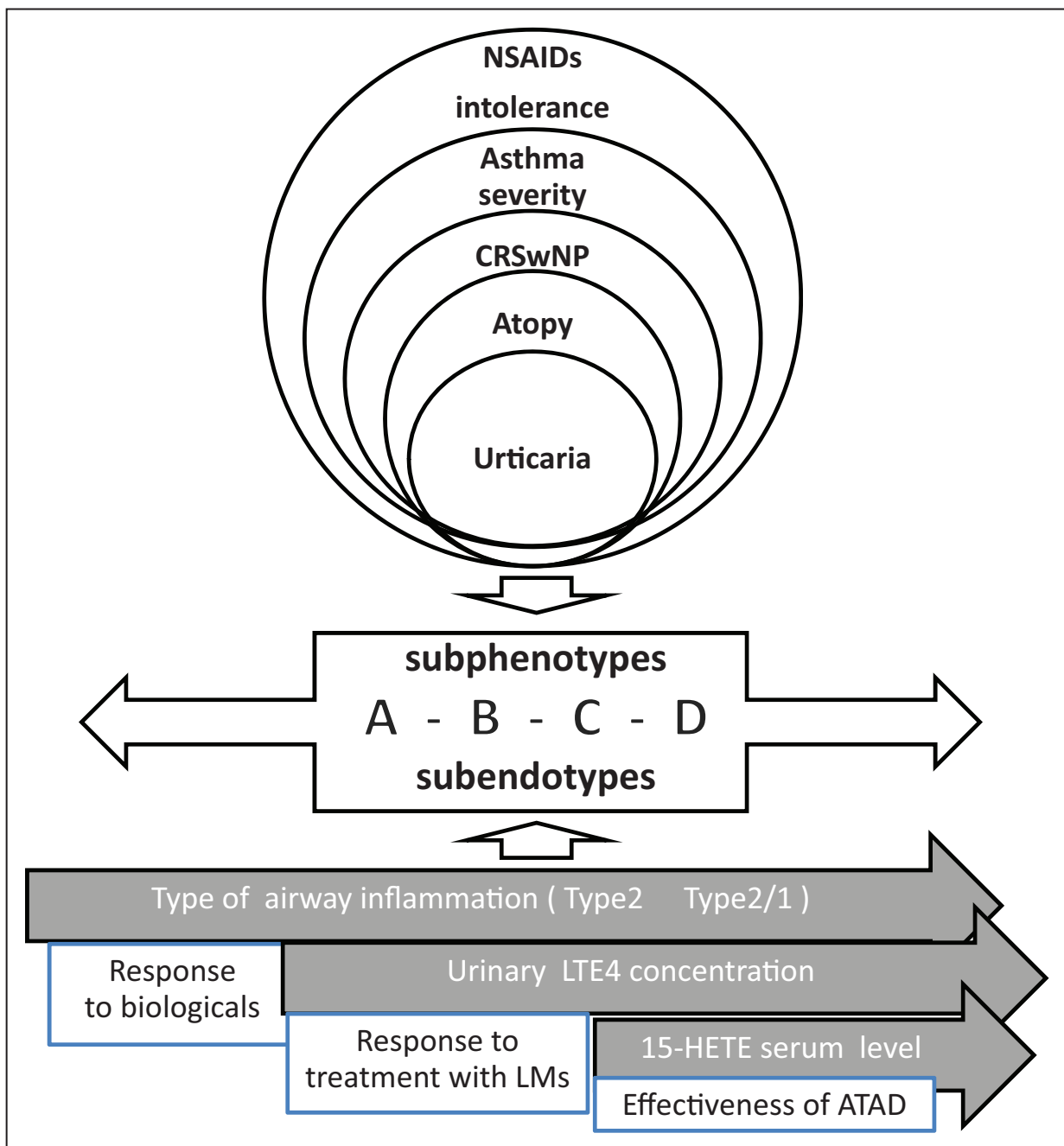


FIGURE 1. Potential characteristics of emerging N-ERD subphenotypes and subendotypes. CRSwNP – chronic rhinosinusitis with nasal polyps; LM leukotriene modifiers; ATAD – aspirin treatment after desensitization.

were compared; the radioimmunoassay was shown to have the best performance. The authors concluded that due to observed significant interindividual variability in urinary levels, uLTE₄ measurement alone cannot be not recommended as a diagnostic tool. Such conclusion has been supported by the observation of Bochenek *et al.* [41^{***}] who studied a large group of N-ERD patients, and documented that a set of typical clinical parameters (nasal polyps, upper airway symptoms, nasal corticosteroid treatment,

asthma exacerbations, FEV₁ predicted, and age of asthma onset) had a superior accuracy for N-ERD diagnosis than the measurement of uLTE₄ concentration alone.

NOVEL ASPECTS OF NSAID-EXACERBATED DISEASE MANAGEMENT

Management of asthma and rhinosinusitis in the NSAID-intolerant patient is similar to treatment of

other forms of asthma and rhinosinusitis, but several important additional treatment modalities could be considered when N-ERD is diagnosed [42]. Topical steroids are quite effective in controlling symptoms of rhinosinusitis and may slow down the recurrence of nasal polyps, but surgical procedures (polypectomy, endoscopic sinus surgery, or ethmoidectomy) are usually needed to relieve symptoms at certain stage of the disease, and remove hyperplastic tissue. In contrast to earlier studies, which suggested that N-ERD patients responded less well to surgical intervention [43], more recent studies demonstrate good clinical effects of endoscopic sinonasal surgery (ESS) in this group of patients. Interestingly, Miglani *et al.* [44[•]] reported that N-ERD patients not only experienced clinically meaningful reduction in postoperative (median follow-up of 28 months) sinonasal symptom scores (SNOT-22), but also had low revision ESS rates, similar to other types of CRS.

For controlling asthma symptoms and underlying airway inflammation inhaled glucocorticosteroids in relevant doses, often in combination with long acting beta-2 agonists are effective in most patients [45]. Leukotriene modifiers (LM), as add on therapy, may be effective in relieving symptoms and improving respiratory function, but the degree of improvement is similar in NSAID-sensitive and tolerant asthmatic patients [46]. However, heterogeneity of response to LM has been observed, with N-ERD patients bearing variant C allele of *LTS4* synthase and HLA *DRB1**301 allele responding better to treatment [47]. It may suggest a potential benefit from pharmacogenetic approaches to treatment of this apparently heterogeneous population of asthmatic patients.

Having in mind possible heterogeneity of pathomechanisms underlying airway inflammation in N-ERD patients and potential existence of endotypes, targeted therapy with monoclonal antibodies rises new hopes for effective management. Omalizumab, an anti-IgE antibody, decreased asthma exacerbation and hospitalization rates, while lowering the urinary concentration of LTE4 and PGD2 in atopic patients with N-ERD; however, more studies are needed to proof benefit over standard therapies [48]. Eosinophilic airway inflammation with Type 2 molecular phenotype characterized by tissue and blood eosinophils and type 2 cytokines typical for N-ERD patients is considered to be particularly prone to new targeted treatment such as anti-IL-5 or anti-IL-13 antibodies [49]. Few studies with mepolizumab, a monoclonal antibody that inhibits IL-5, included subsets of N-ERD patients and reported overall improvement in CRS and nasal polyposis [50,51]. However, until now, no anti-IL5

monoclonal antibody has been studied specifically in N-ERD patients to assess efficacy in management of both upper and airway symptoms.

The upper airway mucosa in a proportion of N-ERD patients is characterized by Type 2/1 mixed type of inflammation (potentially representing specific CRS endotype), and a recent study suggested differential mechanism of eosinophil recruitment in upper airway mucosa in these patients with possible role for IL-16 and TARC [19,52,53]. Thus, controlled clinical trials with newly emerging biologicals affecting Type 1 inflammatory pathways (e.g., anti-IL-17) should be tested for efficacy in N-ERD patients.

Laidlaw *et al.* [54^{••}] proposed a novel approach to treatment of patients with N-ERD referring to previously reported enhanced platelet activation in this patient population [20]. However, 4 weeks treatment with prasugrel blocking the type 12 purinergic (P2Y₁₂) receptor did not alleviate aspirin-induced symptoms, and failed to decrease the frequencies of platelet-adherent leukocytes or to diminish aspirin-induced mast cell activation. However, in a subpopulation of patients prasugrel completely inhibited aspirin-induced respiratory symptoms. These patients had on average greater baseline platelet activation and milder upper respiratory symptoms during aspirin-induced challenge, suggesting that they may represent a distinct subphenotype/subendotype, and pointing at the heterogeneity of response to the P2Y₁₂ receptor antagonist.

ASPIRIN TREATMENT AFTER DESENSITIZATION

Aspirin treatment after desensitization (ATAD) in majority of N-ERD patients may result in alleviation of chronic upper and lower airway symptoms, a significant reduction in asthma exacerbations and in the need for nasal/sinus surgery [55]. ATAD is usually recommended for patients with refractory chronic rhinosinusitis with nasal polyps requiring either frequent systemic steroids burst or repeated revision sinus surgeries. More recently, Glicksman *et al.* [56^{••}] reported that ATAD significantly improved alcohol tolerance in N-ERD patients. The clinical benefits of ATAD continue to be effective for several years; however, the safety of long-term treatment with aspirin has not been sufficiently documented [57[•]]. Walters *et al.* [58[•]] evaluated a group of N-ERD patients with long-lasting ATAD and reported that, a significant improvement in sense of smell, asthma, sinus, and rhinitis scores could be maintained during the average 15 years length of follow-up. The majority of patients did not require further sinus surgery, and no major side-effects have been reported. This study documented that ATAD

maintained over long period (10 years +) is safe and effective in majority of N-ERD patients.

Clinical improvement during ATAD can be achieved in some, but not all patients, and at present it is not possible to predict clinical response (no biomarkers have been identified) before the procedure is implemented. Jerschow *et al.* [59[■]] who investigated associations between clinical outcomes of ATAD and plasma eicosanoid levels found, that patients with symptom improvement had higher baseline plasma 15-hydroxyeicosatetraenoic acid (15-HETE) levels than did patients with symptom worsening ($P=0.0005$). Furthermore, baseline 15-HETE plasma levels positively correlated with the change in Asthma Control Test score ($r=0.61$, $P=0.001$) and in FEV₁ after 4 weeks of aspirin treatment ($r=0.49$, $P=0.01$), and inversely correlated with Rhinoconjunctivitis Quality of Life Questionnaire score ($r=-0.58$, $P=0.002$). Clinical usefulness of plasma 15-HETE levels as a biomarker for predicting outcome of ATAD should be tested in future studies.

CONCLUSION

N-ERD is a difficult to manage clinical syndrome involving moderate to severe bronchial asthma, chronic rhinosinusitis with recurrent nasal polyps (CRSwNP) and hypersensitivity to aspirin and other COX-1 inhibitors. Recently validated lipid biomarkers, combined with clinical evaluation may increase accuracy of N-ERD diagnosis and can potentially be used to predict outcome of aspirin treatment after desensitization. Better characterization of heterogeneity in clinical presentations and the underlying immunopathophysiological mechanisms may allow for more personalized approach to diagnosis and treatment of N-ERD in the future.

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Conflicts of interest

There are no conflicts of interest.

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