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Diagnosis and management of NSAID-Exacerbated Respiratory Disease (N-ERD)—a EAACI position paper*

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Abstract

NSAID-exacerbated respiratory disease (N-ERD) is a chronic eosinophilic, inflammatory disorder of the respiratory tract occurring in patients with asthma and/or chronic rhinosinusitis with nasal polyps (CRSwNP), symptoms of which are exacerbated by NSAIDs, including aspirin. Despite some progress in understanding of the

Abbreviations: ASA, acetylsalicylic acid; ATAD, aspirin treatment after desensitization; COX, cyclooxygenase; CRSsNP, chronic rhinosinusitis without nasal polyps; CRSwNP, chronic rhinosinusitis with nasal polyps; LTMD, leukotriene-modifying drugs; N-ERD, NSAID-exacerbated respiratory disease; NSAIDs, non-steroidal anti-inflammatory drugs.

*The panel members dedicate the document to the memory of Andrew Szczeklik (1938-2012)

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pathophysiology of the syndrome, which affects 1/10 of patients with asthma and rhinosinusitis, it remains a diagnostic and therapeutic challenge. In order to provide evidence-based recommendations for the diagnosis and management of N-ERD, a panel of international experts was called by the EAACI Asthma Section. The document summarizes current knowledge on the pathophysiology and clinical presentation of N-ERD pointing at significant heterogeneity of this syndrome. Critically evaluating the usefulness of diagnostic tools available, the paper offers practical algorithm for the diagnosis of N-ERD. Recommendations for the most effective management of a patient with N-ERD stressing the potential high morbidity and severity of the underlying asthma and rhinosinusitis are discussed and proposed. Newly described sub-phenotypes and emerging sub-endotypes of N-ERD are potentially relevant for new and more specific (eg, biological) treatment modalities. Finally, the document defines major gaps in our knowledge on N-ERD and unmet needs, which should be addressed in the future.

KEYWORDS

AERD, asthma, asthma treatment, drug allergy, ENT (rhinitis, sinusitis, nasal polyps…), sinusitis

1 | INTRODUCTION

NSAID-exacerbated respiratory disease (N-ERD), originally referred to as aspirin-induced asthma, is a clinical syndrome that typically includes hypersensitivity to aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs), nasal polyposis, and asthma. It was clinically described by Samter and Beers[1] fifty years ago, and its non-allergic pathomechanisms were elucidated by Andrew Szczeklik in 1975,[2] but it still remains a diagnostic and therapeutic challenge. N-ERD affects approximately 1/10 of adults with asthma or with chronic rhinosinusitis and nasal polyps.[3] From the allergist's perspective, it is a specific type of NSAID hypersensitivity, from the perspective of the respiratory physician, it represents a phenotype of difficult to treat asthma, and for the ENT surgeon, the recurrent nasal polyposis typical for N-ERD is a difficult challenge.[3,4] Despite the morbidity from the syndrome and its relatively high prevalence, the initial cause and the underlying mechanisms remain incompletely explained. In order to provide evidence-based recommendations for the diagnosis and management of on N-ERD, a panel of experts was called by the EAACI Asthma Section and included also representatives of the EAACI ENT and Drug Hypersensitivity Section. In addition, internationally renowned experts, representing the non-European perspective on N-ERD, have been invited to the panel.

1.1 | Nomenclature and definitions

The panel of experts endorses EAACI recommendations[5] that *the term "NSAID" is a more inclusive term to replace "aspirin" in descriptions of this subtype of hypersensitivity to drugs that inhibit cyclooxygenase.* Accordingly, it is recommended that NSAIDs-exacerbated respiratory disease (abbreviated as N-ERD) is a more proper term to describe the syndrome of respiratory hypersensitivity to NSAIDs associated with asthma and chronic rhinosinusitis with nasal polyposis. Previously used names (e.g, aspirin-exacerbated respiratory disease, aspirin-induced asthma, and aspirin triad) should be abandoned.

BOX 1 Definitions and abbreviations

- NSAID-exacerbated respiratory disease (N-ERD) is a chronic eosinophilic inflammatory disorder of the respiratory tract occurring in patients with asthma and/or rhinosinusitis with nasal polyps, which symptoms are exacerbated by NSAIDs, including aspirin.
- NSAID challenge (NC) is an in vivo diagnostic procedure used to confirm or exclude suspected hypersensitivity to a culprit drug.
- NSAID Tolerance Test (NTT) is an in vivo diagnostic procedure used to confirm patient's oral tolerance to alternative NSAID.
- Aspirin desensitization (AD) is a procedure when tolerance of aspirin is induced in a hypersensitive patient by increasing doses of aspirin given orally or intranasally in short time intervals. The term aspirin desensitization should not apply to chronic treatment with aspirin after the tolerance has been achieved.
- Aspirin Treatment After Desensitization (ATAD) is a therapeutic (usually long-lasting) procedure when aspirin is given orally or intranasally after the tolerance has been achieved during aspirin desensitization procedure.

Definitions used in this document and recommended for use with respect to the N-ERD are listed in Box 1.

1.2 | Methods—search strategy

Evidence for the recommendations was collected by electronic literature searches of the MEDLINE and EMBASE databases, using these primary key words: NSAID-exacerbated respiratory disease, aspirin-exacerbated respiratory disease, aspirin-sensitive asthma, aspirin-induced asthma, Samter's triad, aspirin triad, and Widal's triad, with extra key words as appropriate for each specific section. Each article was reviewed for suitability and the recommendations were evidence graded by two members of the panel using the SIGN criteria. Where evidence was lacking, during the panel meetings a consensus was reached among the experts.

2 | PREVALENCE AND RISK FACTORS

The prevalence of N-ERD is unknown and varies from 1.8% to 44%, depending on the population and diagnostic criteria used. Respiratory symptoms following NSAID intake have been reported by 1.8% of the general European population and by 10%-20% of patients with asthma.[6,7] A recent meta-analysis concluded that N-ERD has been diagnosed among 5.5% to 12.4% of adult asthmatics (the mean prevalence, 7.1%), but the prevalence rises to 21% when NSAID hypersensitivity is determined by provocation.[6,8] The prevalence of N-ERD increases with the severity of the underlying airway disease, reaching 14.9% among patients with severe asthma[3] and up to 24% in patients admitted to the intensive care unit (ICU) with an asthma exacerbation.[9]

Risk factors include family history of N-ERD, presence of CRSwNP, and/or asthma. In contrast to earlier reports, recent studies show a high prevalence of atopy among N-ERD patients.[10,11]

3 | CLINICAL PRESENTATION OF N-ERD

3.1 | Acute reaction to NSAIDs

In patients with N-ERD, the clinical reaction to aspirin or other NSAID is manifested by upper and/or lower airway symptoms, which develop within 30-180 min. The reaction usually starts with nasal congestion and/or rhinorrhea, followed by wheezing, coughing, and shortness of breath. In patients with unstable asthma, the symptoms may appear much faster, progressing rapidly to severe bronchospasm or even leading to death.[12] A subgroup of N-ERD patients will develop pronounced flushing, urticarial, and/or gastrointestinal symptoms.[13] Both the onset and severity of the reaction, in a given patient, are dose-related and the lowest dose provoking a reaction (threshold dose) for individual patients varies between 10 and 300 mg, but 60 mg of ASA would induce symptoms in a majority of patients.[14,15]

3.2 | Natural history of N-ERD

In the majority of patients, the first respiratory symptoms after intake of a NSAID, including aspirin, develop during the course of chronic airway disease (asthma and/or CRSwNP). In some, NSAID hypersensitivity may occur prior to the onset of obvious respiratory disease, marking usually the beginning of asthma/CRSwNP. The syndrome is usually diagnosed in the 3-4th decade of life, with most patients reporting upper airway symptoms occurring 1-5 years prior to asthma. Despite avoidance of NSAIDs, patients continue to suffer from chronic airway symptoms with loss of smell and asthma and need for repeated sinus surgery[4]. Increased prevalence of respiratory symptoms (nasal and bronchial) after consuming alcoholic beverages has been reported among N-ERD patients develop.[16]

3.3 | Clinical presentation of asthma

The majority of N-ERD patients suffer from moderate to severe asthma, although some patients may present with a mild asthma phenotype. The prevalence of severe asthma among N-ERD patients (15%) is approximately twice the general asthma population.[17] In the ENFUMOSA study, a history of aspirin hypersensitivity emerged as an independent risk factor for severe asthma.[18] In an European cohort, 51% of patients with NSAID hypersensitivity were on inhaled and oral corticosteroids, and 30% were on high doses of inhaled corticosteroids4. In the GA2LEN multicentre population study, patients with respiratory symptoms after NSAIDs have been hospitalized more often for asthma (11.8% vs. 2.4%), had more current asthma symptoms within last 12 months (22% vs. 3.4%), and were more frequently taking medications for asthma (26.1 vs. 5.6%)7. The risk of uncontrolled asthma in N-ERD patients is increased twofold, severe asthma and asthma attacks increase by 60%, emergency room visits by 80%, and asthma hospitalization by 40%8. The atopic aspirin-sensitive group experienced impaired quality of life and more frequent exacerbations.[19]

3.4 | Clinical presentation of chronic rhinosinusitis

Upper airway disease (CRSwNP) in N-ERD patients is dominated by symptoms such as nasal blockage, nasal congestion or stuffiness, facial pain or pressure, and nasal discharge/postnasal drip. Partial loss of smell or even anosmia occurs more frequently in N-ERD patients, and loss of smell may be considered a clinical marker to identify N-ERD patients.[20] On average, upper respiratory symptoms are worse, and recurrence of nasal polyps after surgery is more frequent in N-ERD than in NSAIDs-tolerant CRSwNP patients.[11]

Rhinoscopy or nasal endoscopy findings of edema/mucosal obstruction, and or nasal polyps, and/or mucopurulent discharge, primarily from the middle meatus, are usually present in N-ERD patients helping to the diagnosis of CRS.[21,22] On a upper CT scan, which is the gold standard for imaging, N-ERD patients have a more severe sinus opacification and extension than CRSwNP patients without N-ERD.[23]

3.5 | N-ERD in children

NSAID hypersensitivity has been diagnosed in up to 5% of children with asthma, which, in addition to respiratory, frequently manifests extra-pulmonary symptoms, such as urticaria/angioedema, or diarrhea and abdominal pain after NSAIDs.[5,24-26] Asthma usually develops first and CRS with/without nasal polyps later asthma severity varies from mild-moderate to severe-persistent asthma.[24,26]

4 | PATHOGENESIS OF N-ERD

4.1 | Pathomechanisms of NSAID-induced reactions

Ground-breaking experiments performed by Andrew Szczeklik et al[2] four decades ago demonstrated that the capacity of individual NSAIDs to trigger clinical symptoms in asthmatics was related to the drug's potency to inhibit the production of prostaglandins. Upon discovery of the cyclooxygenase enzymes, it became evident that the NSAID-induced reactions result from inhibition of COX-1 (but not of COX-2). It has been hypothesized inhibition of PGE_2 biosynthesis in a hypersensitive patient triggers activation of inflammatory cells including mast cells, basophils, eosinophils, and potentially platelets,[27] leading to release of cysteinyl leukotrienes, PGD_2, histamine, tryptase, and other mediators responsible for development of clinical symptoms (Figure 1). However, the mechanism underlying this specific activation of inflammatory cells is debatable; it may involve increased susceptibility of COX-1 to inhibition with NSAIDs, intrinsic deficiency of PGE_2 production by COX-2, and/or abnormal function of PGE_2 receptors in N-ERD patients.

4.2 | Pathogenesis of chronic inflammation

Both upper airway pathology and lower airway pathology in N-ERD patients are characterized by chronic and extensive eosinophilic mucosal inflammation. This chronic eosinophilic airway inflammation in patients with N-ERD seems to be related to abnormalities of both cyclooxygenase- and lipoxygenase-derived arachidonic acid metabolism. Basal levels of leukotriene E4, the stable end-metabolite of cysteinyl leukotrienes, are elevated in the urine of N-ERD patients and further increases are noted upon aspirin challenge. Increased numbers of cells expressing the $CysLT_1R$ have been found in their bronchi and nasal polyps.[28] A relative PGE_2 deficiency in the airways is accompanied by reduced expression of prostaglandin EP_2 receptor, pointing to a functional deficiency of this prostaglandin.[29] PGD_2, primarily derived from mast cells, is also abundant in N-ERD airways.[30] Decreased production of the anti-inflammatory lipoxin A4 has been found in peripheral blood leukocytes and in nasal polyp tissue from N-ERD patients, suggesting a protective role for 15-LO metabolites.[31] Increased numbers of tissue eosinophils have been linked to a distinctive profile of cytokine expression, which represents a mixed Th1/Th2 type of inflammation. More recently, the innate immune responses, involving innate lymphoid cells (ILC 2), and heralded by increased expression of IL-33 and TSLP have been implicated.[30,32] A role for respiratory viral infections, antibodies, or staphylococcal enterotoxins (SAEs) acting as super antigens in development of airway inflammation in N-ERD patients has also been suggested.[31] Contribution of genetic and epigenetic polymorphisms has been also investigated suggesting a permissive, genetic predisposition for N-ERD.[33]

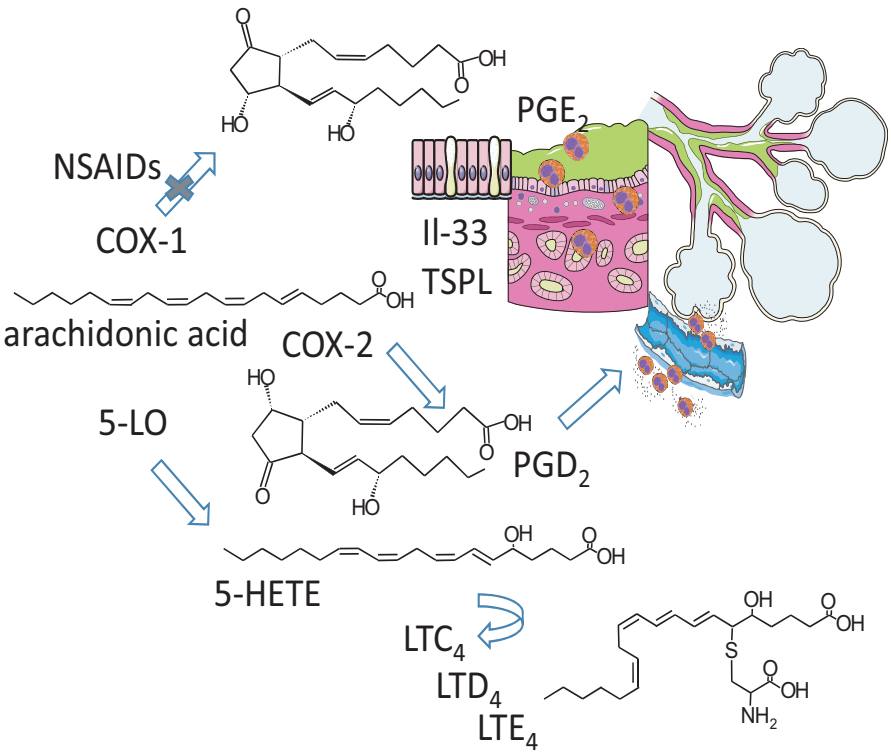

FIGURE 1 Pathomechanisms of N-ERD. In response to non-specific, unknown factors, respiratory epithelium overproduces innate immunity type 2 mediators (e.g, interleukin-33 (IL-33), thymic stromal lymphopoietin-TSPL) attracting eosinophils. Inhibition of cyclooxygenase-1 (COX-1) by NSAIDs decreases biosynthesis of prostaglandin E_2 (PGE2) from arachidonic acid. Deficiency of this anti-inflammatory mediator is not compensated by the inducible isoenzyme COX-2, which produces chemoattractant prostaglandin D_2 (PGD_2). Excess of arachidonate substrate is metabolized by 5-lipoxygenase (5-LO) to leukotrienes (LTC_4, LTD_4, and LTE_4), potent pro-inflammatory mediators. Eosinophils and possibly granulocyte-platelet aggregates accumulate at the bronchi perpetuating these specific alterations in the lipid mediators of asthma

4.3 | Heterogeneity of the N-ERD: sub-phenotypes and sub-endotypes

N-ERD has been considered as a separate asthma phenotype defined by clinical characteristics including presence of severe CRSwNP and hypersensitivity to aspirin. At the same time, the syndrome represents a distinct endotype with specific biological mechanisms involving arachidonic acid metabolism abnormalities and upregulated type 2 inflammation.[34,35] However, increasing evidence indicates that N-ERD is heterogeneous with respect to both clinical presentations (N-ERD sub-phenotypes) and possibly to the pathogenetic mechanism involved (N-ERD sub-endotypes). A Polish study distinguished four N-ERD phenotypes varying in clinical characteristics: asthma control and severity, intensity of upper airway symptoms, severity of airway obstruction, and healthcare use. Furthermore, these phenotypes differed in blood eosinophilia and urinary LTE_4.[36] Similarly, a Korean study reported four phenotypes which differed in atopic status, presence of CRS and chronic urticaria, as well as in baseline FEV1%, incidence of asthma exacerbations and anti-asthmatic medication requirement.[37] Significant differences between groups were found in the serum total IgE levels, eosinophil counts, and urinary LTE_4 levels. Another study reported a group of patients with asthma and rhinitis, who presented with respiratory reactions to a single NSAID (including paracetamol) and good tolerance to aspirin.[38] Similarly, heterogeneity of N-ERD phenotypes has also been reported among children with N-ERD with 32% of the cases presenting with a combination of respiratory and cutaneous symptoms after aspirin challenge.[39] These studies document a wider than currently appreciated spectrum of N-ERD phenotypes and/or presence of sub-phenotypes, pointing at the necessity for re-evaluation of clinical criteria for the diagnosis of N-ERD. Furthermore, heterogeneity of the underlying pathophysiological mechanism (presence of sub-endotypes) may have critical implications for the development of sub-endotype-specific treatment approaches, potentially increasing the effectiveness of aspirin treatment after desensitization (ATAD), treatment with leukotriene modifiers or biologicals in patients with N-ERD.

5 | DIAGNOSIS

A clear history of multiple reactions developed within 1-2 hours after ingestion of an NSAID manifesting with respiratory symptoms in a patient with adult-onset asthma and recurrent nasal polyposis may be sufficient to diagnose N-ERD. However, the reliance exclusively on a history may result in either underdiagnosing or overdiagnosing of NSAIDs hypersensitivity.[40,41] In certain cases, a challenge test with aspirin or culprit drug is necessary to establish the diagnosis.

Statements and recommendations[41-47]

- N-ERD should be considered in patients suffering from asthma and chronic rhinosinusitis whose symptoms exacerbate after ingestion of aspirin and other COX-1 inhibitors (Grade 4 D).
- Lack of history of respiratory reactions to NSAIDs in a patient with asthma and CRS with nasal polyposis does not exclude the presence of hypersensitivity (Grade 3 C).
- Challenge tests (oral, inhalation, or intranasal), which involve the administration of increasing doses of aspirin in fixed time intervals, if performed according to described protocols, are reliable methods to confirm hypersensitivity to NSAIDs in a patient with suspected N-ERD (Grade 3 C). (Box 2)
- Challenge tests with aspirin should be performed only according to established indications (Grade 4 D). (Table 2)
- Oral aspirin challenge is considered to be the gold standard for diagnosing hypersensitivity to NSAIDs, as it mimics natural exposure to the drug (Grade 4 C).
- Inhalation challenge with lysine–aspirin is as sensitive as oral one (Grade 3 C), but safer and faster to perform (Grade 4 C)
- Intranasal aspirin challenge, although less sensitive when compared with oral (Grade 3 C), is safer, quicker and may be a good diagnostic alternative for patients in whom oral or inhaled challenge is contraindicated (Grade 4 D)
- Intranasal aspirin challenge can be used initially to diagnose the most sensitive subjects safely, leaving the less sensitive ones to be challenged orally (Grade 3 C)
- Intranasal challenge with ketorolac is less sensitive and cannot substitute for oral aspirin challenge (Grade 3 C)
- Patients undergoing oral or inhalation challenge with aspirin should be in a stable clinical condition and their baseline FEV_1 should be at least 70% of the predicted value (Grade 4D)
- Contraindications for performing aspirin challenges, different with respect to the type of the test, should be followed (Grade 4 D). (see Box 3)

BOX 2 Indications for performing aspirin challenge tests in N-ERD

Indications for oral aspirin challenge:
- confirmation (or exclusion) of hypersensitivity to NSAIDs in patients with ambiguous history
- verification of negative results of inhalation or intranasal tests
- assessment of provocation dose of aspirin before oral desensitization
- research purposes

Indications for inhalation aspirin challenge:
- diagnosis of hypersensitivity to NSAIDs
- research purposes.

Indications for intranasal aspirin challenge:
- diagnosis of hypersensitivity to NSAIDs in patients with contraindications to oral or inhalation tests
- diagnosis of N-ERD in patients with upper airways symptoms of hypersensitivity to NSAIDs
- research purposes.

BOX 3 Contraindications for aspirin challenge tests

Oral or inhalation aspirin challenge tests:

- a history of anaphylactic reactions precipitated by aspirin or other NSAIDs (alternatively, intranasal challenge test should be considered),
- uncontrolled asthma,
- FEV_1 <70% of the predicted value,
- history of chronic renal failure or gastrointestinal bleeding,
- respiratory tract infection or exacerbation of asthma within 4 weeks prior to the test,
- pregnancy, and
- current treatment with β-receptor blocker.

Nasal challenge test:

- pathology of the nasal cavity which interferes with nasal challenge and
- upper respiratory tract infection within 4 weeks prior to the test.

- Oral and inhalation tests should be performed in a specialized clinical setting (either outpatient or hospital) by experienced physicians and trained nurses. After completion of the test, the patient should stay in the office for few hours to one day, depending on clinical assessment (e.g, severity of the reaction) (Grade 4 D).
- Several protocols for aspirin challenges can be used and Table 2 describes the protocol recommended by the panel.
- In vitro tests that have been proposed to confirm aspirin hypersensitivity (e.g, sulfidoleukotrienes release assay; 15-HETE generation assay (ASPITest); or basophil activation test (BAT)) cannot substitute for aspirin challenges and are not recommended for routine diagnosis (GRADE 3 C).

5.1 | Algorithm for diagnosis of N-ERD

N-ERD should be suspected if a patient reports respiratory symptoms occurring after ingestion of aspirin or other NSAIDs. The following algorithm for diagnosis of N-ERD is recommended by the panel (Figure 2).

Step 1 Ask about respiratory symptoms after intake of any NSAID, including aspirin.

Step 2. Verify if the reported history of NSAID-induced respiratory reaction is reliable. The reliability increases if, for example more than one reaction occurred, reactions to two or more different NSAIDs have been reported or the latest reaction occurred within last 5 years. Note that respiratory symptoms may be accompanied by skin and gastrointestinal symptoms.

Step 3. Ask about underlying chronic respiratory disorders (CRS with NP and/or asthma). The following clinical characteristics increase probability of N-ERD diagnosis: high recurrence of NP, loss of smell, moderate to severe asthma, intolerance of alcohol, and blood eosinophilia.

If answers at step 2 and 3 are positive: N-ERD can be diagnosed with high probability.

If answer to one of the above questions is negative or uncertain, go to steps 4-6.

Step 4. When the history of respiratory symptoms is not convincing, ask about non-respiratory symptoms after intake of the NSAIDs and check other potential triggers of reported reactions.

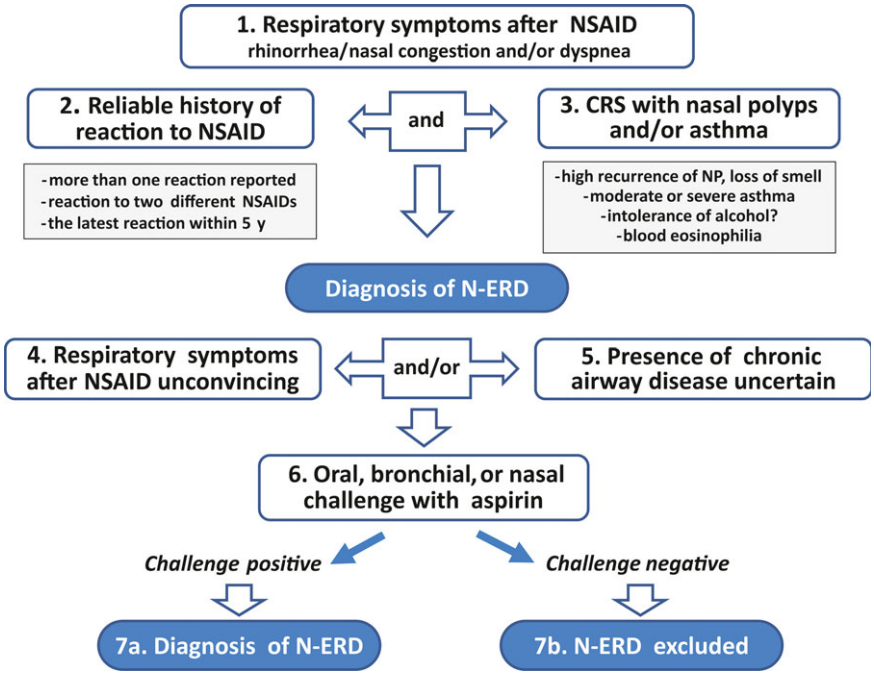

FIGURE 2 Algorithm for diagnosis of N-ERD (description in the text)

Step 5. Exclude/confirm the presence of CRS (ENT consultation; sinus imaging) and asthma (respiratory function test, assessment of non-specific bronchial hyper reactivity).

Step 6. Perform oral, inhaled or intranasal aspirin challenge

Step 7a. If aspirin challenge is positive → N-ERD is diagnosed, go to management

Step 7b. If aspirin challenge is negative → N-ERD can be excluded with high probability; follow-up the patient if necessary (*)

(*) if aspirin challenge is negative, but there is concern that concomitant medications (leukotriene modifier drugs or monoclonal antibodies) might have led to a false negative challenge → consider withholding concomitant medications and repeat the challenge.

TABLE 1 NSAID classes according to their pharmacological action against cyclooxygenase

Strong COX-1 inhibitors Piroxicam, indomethacin, sulindac, tolmetin, ibuprofen, naproxen, naproxen sodium, fenoprofen, oxazoprin, mefenamic acid, flurbiprofen, diflunisal, ketoprofen, diclofenac, ketorolac, etodolac, nabumetone, and acetylsalicylic acid
Weak COX-1 inhibitors Paracetamol and salsalate
Preferential COX-2 inhibitors at low doses and weak COX-1 inhibitors at high doses Nimesulide and meloxicam
Selective COX-2 inhibitors Celecoxib, etoricoxib and parecoxib.

6 | MANAGEMENT OF PATIENTS WITH N-ERD

Management of a patient with N-ERD includes both pharmacological and non-pharmacological measures and requires a close collaboration among several specialists (allergist, respiratory physician, and ENT surgeon). Pharmacological management of asthma and CRSwNP in N-ERD patients should follow general guidelines focusing on underlying mucosal eosinophilic inflammation of the respiratory tract. However, several distinct pathophysiological mechanisms associated with this syndrome suggest that more specific treatments referring to syndrome-specific pathways/targets should be considered in the future.

6.1 | Management of NSAID hypersensitivity

The management options are essentially based on strict avoidance of the culprit drug and cross-reactive drugs. Patient's education is important, since NSAIDs respiratory symptoms are not limited to a specific drug, but they may appear after the intake of other, cross-reacting NSAIDs as well.

Statements and recommendations[2,47-51]

- The likelihood of cross-reactivity between NSAIDs in patients with N-ERD is directly related to their power of COX-1 inhibition (Grade 1A).
- A patient must avoid not only the single drug responsible for his/her symptoms, but also all the other molecules which are strong COX-1 inhibitors (Table 1) (Grade 1A).
- Selective COX-2 inhibitors (celecoxib and etoricoxib) are well tolerated by most N-ERD patients (Grade 2B)
- NSAIDs with weak inhibitory action toward COX-1 (i.e, paracetamol <1000 mg) (Grade 2B) and preferential COX-2 inhibitors (i.e, nimesulide and meloxicam)(Grade 1B), given at pharmacological doses, do not usually cross-react with other NSAIDs.
- Tolerance tests with alternative NSAID should be performed in the office before the drug is prescribed (Grade 4B).
- Although low salicylate diet has been reported to significantly improve sinonasal symptoms, quality of life and endoscopic scores, as well as asthma control in N-ERD patients, at present stage of evidence additional studies are needed to confirm its efficacy (Grade 4D).
- Alcohol avoidance should be advised to N-ERD patients (Grade 3C).
- Written information, including lists of potentially cross-reactive and alternative safe medications, should be always provided to N-ERD patients (Grade 4D).
- Patients should carry with them information about their drug hypersensitivity (Grade 4D).

6.2 | Management of asthma

In most N-ERD patients standard, step-wise approach to asthma treatment following GINA/US guidelines is effective. Combination therapy with inhaled corticosteroid and long acting beta-2 agonists is sufficient to control asthma in the majority of N-ERD patients; however, in some patients more specific measures should be considered. Overexpression of 5-LO pathways of AA and overproduction of cysteinyl leukotrienes seem to provide a rational for treatment with leukotriene-modifying drugs (LTMD) in N-ERD patients.[52,53] Prospective, placebo-controlled studies with montelukast[54] and zileuton[55] have both shown efficacy in N-ERD patients as measured by improved respiratory function, decreased use of rescue inhalers, and an increase in asthma quality-of-life measures. Zileuton may have superior efficacy in N-ERD since it blocks all leukotriene production by virtue of 5-LO inhibition, and based on patients' survey data, zileuton had a higher benefit in N-ERD patients.[56] A critical question is if LTMD are more effective in N-ERD patients as compared to NSAIDs-tolerant asthmatics, which could justify to consider LTMD as drug of choice in these patients. Two controlled studies compared efficacy of montelukast in the treatment of N-ERD and NSAIDs-tolerant patients, and both failed to show its superiority in N-ERD patients.[57,58]

Biologicals seem to be promising agents for the treatment of N-ERD, especially in difficult to treat asthmatics. N-ERD patients can benefit from the treatment with omalizumab, and its effectiveness has been described in several case reports. In a recent study of 21 patients with history of bronchial reactions after NSAIDs intake,

12 months therapy with omalizumab resulted in a reduction of the number of exacerbation and ameliorated respiratory symptoms which were accompanied by a significant reduction in urinary LTE_4 and PGD_2M levels.[59] Biologicals targeting eosinophilic inflammation (mepolizumab, reslizumab, and benralizumab), which is typical for most N-ERD patients, could be potentially beneficial. Mepolizumab was shown recently to be effective in nasal polyposis with co-morbid asthma in a trial in which N-ERD subjects were included.[60]

Statements and Recommendations[54-59]

- The management for the N-ERD patient should be individualized; however, the severity of asthma should be assessed early in the disease course and considered in treatment decisions.
- Standard, step-wise approach to the treatment of bronchial asthma symptoms in N-ERD patients is recommended. Combination therapy with inhaled corticosteroid and long acting beta2 agonists is effective as initial treatment for most N-ERD patients. For patients with more severe disease, oral corticosteroids should be implemented (Grade 4 D).
- The addition of a LTMD is effective in ameliorating asthma symptoms in N-ERD patients (Grade 1 A); thus, anti-leukotriene drugs can be considered as add-on therapy (Grade 1 A).
- LTMD are not more effective in N-ERD patients as compared to NSAIDs-tolerant asthmatics (Grade 3 B).
- Zileuton seems to be more effective as compared to montelukast in N-ERD patients (Grade 3 D)
- Anti-IgE (omalizumab) seems to be effective in improving asthma control in N-ERD patients with severe asthma (Grade 3 D)

6.3 | Management of chronic rhinosinusitis

The management of CRSwNP in patients with N-ERD is similar to that in patients without history of NSAIDs hypersensitivity and should follow international guidelines.[21] However, CRSwNP in patients with N-ERD is more resistant to pharmacological (Grade B) and surgical treatment (Grade B) and concomitant bronchial asthma may complicate the management.

Medical treatment[20,21,61-63]

According to current guidelines, medical treatment of CRS should be based on topical corticosteroids with dosing adjusted to the severity of symptoms (Grade A). Short courses of oral steroids (2-3 weeks) may be needed to control severe CRS symptoms and to improve the quality of life (QoL) (Grade A). Nasal saline irrigation, both isotonic and hypertonic, as well as short-term (before surgery) and long-term (after surgery) antibiotics may help to alleviate nasal symptoms (Grade A).

Surgical treatment[20,21,64]

Sinonasal surgery (polypectomy, functional endoscopic sinus surgery, and/or ethmoidectomy) is reserved for patients with severe or uncontrolled symptoms and for those with inadequate improvement despite intranasal and oral steroid therapy (a picture seen in a significant proportion of N-ERD patients) (Grade C).

Statements and recommendations

- Saline irrigation is important in CRS of all kinds and should be used daily
- Intranasal corticosteroid drops are most effective and constitute the first line of pharmacological treatment for CRS with nasal polyps in patients with N-ERD (Grade A)
- In N-ERD patients, treatment with maximal doses of intranasal corticosteroids is often needed (Grade B)
- Short courses of oral steroids are necessary when maximal doses of intranasal corticosteroids are not able to control CRS severity (Grade A).
- LTMD have moderate effects in relieving nasal symptoms and nasal polyps size in some N-ERD patients (for montelukast—Grade B; for zileuton—Grade C).
- LTMD are not more effective in N-ERD patients as compared to NSAIDs-tolerant patients with CRSwNP (Grade B).
- Macrolides (for 3 months) show a moderate effect on QoL (but not symptoms) in patients with CRSsNP (Grade A). There is no separate evidence for a course of macrolides to be recommended in severe cases of CRSwNP in N-ERD (Grade D).
- Anti-IgE/omalizumab is equally effective in N-ERD and NSAIDs-tolerant patients in relieving nasal symptoms (Grade A) but without evidence of preventing polyp recurrence after surgery (Grade D).
- Other biological drugs affecting eosinophilic, Th2 pathway of inflammation (e.g, mepolizumab and dupilumab) are effective for the treatment of eosinophilic CRSwNP, typical of N-ERD patients (Grade A).
- In N-ERD patients, endoscopic sinus surgery improves nasal symptoms (Grade D) quality of life (Grade D), nasal endoscopy, and CT scores (Grade D).
- Endoscopic sinus surgery may reduce bronchial symptoms (Grade D) and the requirement for asthma medications (Grade D) in N-ERD patients.
- N-ERD patients respond less well to surgical interventions and are more likely to undergo repeated interventions as compared to NSAIDs-tolerant subjects (Grade D).
- Ocular complications are more likely in N-ERD nasal polypectomies (Grade B)
- In N-ERD patients, a more extensive endoscopic surgery (Lothrop technique) may improve the clinical outcomes (Grade D).
- For nasal surgery, N-ERD patients should be referred to the most experienced ENT centers (Grade D).
- Follow-up and medications, including nasal and oral corticosteroids, are recommended after surgery (Grade A).

6.4 | Aspirin treatment after desensitization (ATAD)

Following the original report of Stevenson et al,[65] it has been well documented that aspirin given after desensitization may improve CRS and asthma course in N-ERD patients. The efficacy of ATAD

has been confirmed in observational studies and in placebo-controlled double-blind trials.[66-68] Protocols for desensitization are usually extension of ASA-provocation protocols; however, a "silent" desensitization (i.e, without evoking adverse reaction) is possible.[69,70] Patients for ATAD should be carefully selected and monitored during treatment to assess the efficacy and to reduce the prevalence of adverse effects associated with aspirin intake.

Statements and recommendations[65-68]

- Aspirin treatment after desensitization is an option in the management of patients with N-ERD (Grade 1B) (Box 4)
- Desensitization procedure can be performed in both outpatient and hospital setting and should be supervised by experienced physician (Grade 4D)
- To secure safety and effectiveness of desensitization, the panel recommends that one of well-established protocols is followed with gradual dose increase with at least 90-120 min intervals between doses (Grade 4 D) (Table 2)
- In the majority of N-ERD patients, ATAD is associated with a decrease in CRS symptoms (Grade 1 A), decrease in intranasal corticosteroid use (Grade 2 B), reduction in recurrence of nasal polyps (Grade 2B), and decrease in the need for revision surgery (Grade 2 B)
- In a subset of N-ERD patients, ATAD may result in decreased asthma symptoms and improved asthma control (Grade 1 B)
- The overall effect of ATAD on asthma seems to be less favorable as compared to the effect on the course of CRS (Grade 4 D)
- Effective oral maintenance dose of aspirin ranges from 300 to 1300 mg (Grade 3 C)
- ATAD is associated with adverse effects (mostly gastrointestinal), and the incidence of adverse symptoms related to aspirin intake ranges from 0% to 34%.
- In order to reduce the prevalence of adverse effects associated with aspirin treatment, appropriate preventive measures (Helicobacter pylori eradication, PPI, and H_2blockers) should be introduced and continued during the treatment (Grade 4 D)

BOX 4 Indications for treatment with aspirin after desensitization (ATAD) in N-ERD patients

- rhinosinusitis symptoms (e.g, loss of smell) not responding to pharmacological treatment
- highly recurrent nasal polyposis/hypertrophy
- prevention of nasal polyps after sinus surgery
- asthma symptoms difficult to control with standard therapy
- need to reduce the dose or withdraw chronic oral corticosteroids
- need for anti-platelet treatment with aspirin of ischemic heart disease or stroke
- need for chronic anti-inflammatory treatment (e.g, in rheumatoid arthritis)

TABLE 2 Recommended oral aspirin challenge/desensitization protocol (modified from A. White and DD Stevenson IACNA 2013[71])

Time	Day 1	Day 2
9:00 AM	20-40 mg	100-160 mg
11:00 AM	40-60 mg	160-325 mg
01:00 PM	60-100 mg	325 mg

- Intranasal treatment with lysine–aspirin after desensitization may be effective to relieve symptoms of CRS with an effective dose of 75 mg/day (Grade 3 C)

6.5 | Novel treatments and endotype-driven approaches

The asthma endotype of N-ERD can be heterogeneous, but in most cases is characterized by dysregulation of AA metabolism and prominent blood and respiratory tissue eosinophilia, which is accompanied by overproduction of cysteinyl leukotrienes (CysLTs), prostaglandin D_2 (PGD_2), and Th2 cytokines. Underproduction of the protective prostaglandin E2 and lipoxins may also be part of the pathogenesis, and increasing levels of these protective mediators could also be a therapeutic target in the future.

Innovative approaches targeting the type 2 inflammation with monoclonal antibodies have been recently suggested for the treatment of N-ERD. There are several case reports regarding the successful use of omalizumab, and a recent study showed clear omalizumab-induced reduction in urinary levels of LTE_4 and a PGD_2 metabolite that accompanied patient-reported improvement in respiratory symptoms.[59] Mepolizumab, an anti-IL-5 monoclonal antibody that has been approved for severe eosinophilic asthma, has been shown in two studies to decrease nasal polyposis,[60,71] and dupilumab, the IL-4Rα antagonist that blocks both IL-4 and IL-13 signaling, has also been shown to decrease nasal polyps burden.[61] New biologicals may provide substantial benefit to patients with N-ERD and eosinophilic nasal polyposis.

Recent work suggests that the innate immune response pathways (cytokines IL-33 and TSLP) may be involved in N-ERD pathogenesis and research efforts targeting these novel innate pathways should be explored.[30,72] Inhibition of other recently described putative leukotriene receptors, like GPR99,[73] or the PGD2 receptor CRTH2, is also potential future targets for N-ERD-directed therapeutics.

7 | CONCLUSIONS AND UNMET NEEDS

The expert panel believes that the current document, by summarizing up-to-date knowledge, and proposing practical recommendations for the diagnosis and treatment of N-ERD will help physicians to offer comprehensive and effective management for a patient with this complex disorder. However, the panelists realize that despite significant progress recently made in the understanding of the pathomechanism of N-ERD, there are not sufficient data available to fully

address all issues important for diagnosis and management of patients in clinical practice. According to the panel, the following are the major gaps in our knowledge on N-ERD and unmet needs, which should be addressed in the future:

- Assessment of N-ERD prevalence among various patient populations, including children and elderly
- Understanding of genetic, cellular, and molecular mechanisms underlying the development of severe eosinophilic inflammation in patients with N-ERD
- Characterization of emerging sub-phenotypes, and sub-endotypes of N-ERD, and investigation of potential sub-phenotype/sub-endotype-specific management
- Development and evaluation of new in vitro tests to confirm hypersensitivity to NSAIDs
- Identification and characterization of new biomarkers specific for N-ERD and its sub-endotypes
- Development and evaluation of protocols for more effective ATAD with improved safety
- Evaluation of the effectiveness of new biologicals for the treatment of CRS and asthma in N-ERD patients
- Development and testing of novel treatment modalities, based on endotype/sub-endotype-driven approaches

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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