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# NSAID-exacerbated respiratory disease: Clinical review and referral pathway in British Columbia

In BC, greater awareness of NSAID-exacerbated respiratory disease, a complex airway disease, is needed to provide early diagnosis and appropriate management.

**ABSTRACT:** NSAID-exacerbated respiratory disease (NERD) is a triad of asthma, chronic rhinosinusitis with nasal polyposis, and hypersensitivity reactions to NSAIDs. NERD is common, and increased awareness is needed. NERD patients have severe uncontrolled asthma and require multiple sinus surgeries. We have created a referral pathway to provide NERD patients in British Columbia with access to multidisciplinary care in order to promptly address the different aspects of the disease.

**NSAID**-exacerbated respiratory disease (NERD) is a non-IgE hypersensitivity reaction that causes a spectrum of symptoms, including chronic rhinosinusitis with nasal polyposis, asthma, and hypersensitivity reactions to NSAIDs (e.g., aspirin, ibuprofen, naproxen).<sup>1</sup> The triad

of symptoms is also referred to as Samter's triad and aspirin-exacerbated respiratory disease. The pathophysiology is thought to be due to abnormalities in arachidonic acid biosynthesis. Through the COX-1 and 5-lipoxygenase pathways, there is an overproduction of cysteinyl leukotrienes and a decrease in downstream anti-inflammatory prostaglandins such as prostaglandin E2. Without the inhibitory effect of the COX-1 pathway by-products, a pro-inflammatory environment is created.<sup>2</sup> However, multiple mechanisms regarding the underlying pathophysiology and associated clinical consequences are currently being investigated.<sup>1</sup>

## Clinical presentation

NERD patients often present with a triad of symptoms: NSAID hypersensitivity, asthma, and chronic rhinosinusitis with nasal polyposis. NSAID hypersensitivity is due to COX-1 inhibition and presents with upper/lower airway symptoms. NSAID reactions can occur between 1 and 4 hours after exposure and are dose dependent. Patients may be able to tolerate 80 mg of ASA but react at 160 mg. Reactions are not always reliable; in a cohort of 28 patients who were challenged multiple times, 11 had different responses during the challenges.<sup>3</sup> In some cases, NERD patients can react to acetaminophen at doses higher than 1000 mg because acetaminophen is a weak COX-1 inhibitor.<sup>4</sup>

Asthma is difficult to control in NERD patients. A study that compared 2848 NSAID-tolerant patients with asthma and 459 NERD patients showed that the NERD patients had increased use of oral steroids and visits to the emergency department and a higher rate of intubations.<sup>5</sup>

Chronic rhinosinusitis with nasal polyposis presents with chronic nasal obstruction, anosmia, and recurrent facial pain. The symptoms are caused by the overgrowth of nasal polyps in the nasal cavity [Figure 1].

NERD patients have a tenfold higher risk of sinus disease recurrence after surgery compared with other forms of chronic rhinosinusitis with nasal polyposis.<sup>6</sup> These patients also report hypersensitivity to alcohol, hearing loss, and noncardiac chest pain.<sup>7</sup>

NERD is common: 7.2% of patients with asthma and 8.7% to 10.0% of patients with chronic rhinosinusitis with nasal polyposis have the disease.<sup>8</sup> NERD has a prevalence of 0.3% to 2.5%, and it is estimated that there are 1.5 million patients in the United States.<sup>9</sup> Females are primarily affected, and the average age of onset is 30 years.<sup>7</sup> However, 3.5% to 6.0% of NERD patients may present in childhood.<sup>10,11</sup>

## Diagnosis

NERD is a clinical diagnosis. While asthma and chronic rhinosinusitis with nasal polyposis can be easily diagnosed, NSAID hypersensitivity is more challenging. If the

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history of NSAID hypersensitivity is unclear, an ASA challenge must be performed [Table 1].<sup>12</sup> The protocol for challenge and desensitization is the same. The key difference is that patients will continue to take ASA after desensitization. The initial workup includes a complete blood count with differential, rhinoscopy, CT sinus, and pulmonary function tests.<sup>7</sup> Other tests, such as nasal fractional exhaled nitric oxide after ASA ingestion and urine leukotriene E<sub>4</sub>, can be elevated but are not available in British Columbia.<sup>7</sup>

Allergists, respirologists, and otolaryngologists often treat NERD patients in subspecialty silos. Each specialist focuses on their area of expertise and may miss the diagnosis or not address the multisystem nature of NERD.

## Management

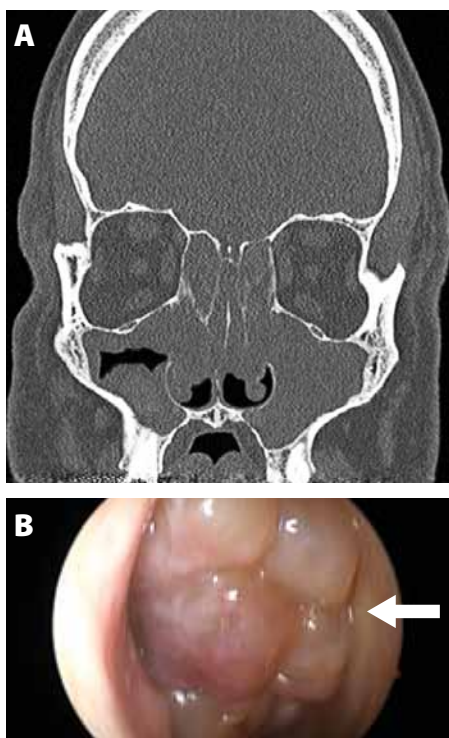
The current treatment of NERD involves a combination of medical and surgical management.<sup>1</sup> Medical management can involve a stepwise or often arbitrary constellation

of intranasal and inhaled corticosteroids, leukotriene modifiers, aspirin desensitization therapy, and monoclonal antibodies.<sup>1</sup> Table 2 provides a summary of treatment modalities. With intranasal corticosteroids, the first line of management in chronic rhinosinusitis with nasal polyposis, large-volume irrigation is preferred because it reaches deeper into the sinus cavities. Combination inhaled corticosteroids and long-acting bronchodilators are the mainstay management of moderate to severe asthma; the Canadian Thoracic Society asthma guidelines provide further details. Leukotriene receptor antagonists can be helpful in managing NERD patients, but clinicians must be aware of the black box warning and counsel patients about neuropsychiatric side effects, including suicidal ideation.<sup>13</sup> Surgical management usually involves a combination of polypectomies and functional endoscopic sinus surgery to open the sinuses and create a greater surface area for administering intranasal steroids.<sup>2</sup> Many patients require revision surgery that targets mainly the frontal sinus through an extended Draf III procedure, which involves drilling out the surrounding bone and creating a common frontal sinus cavity to aid in the delivery of topical medication postoperatively.<sup>14</sup> Only a few subspecialized rhinologists in BC offer Draf III.

Biologics have revolutionized the management of NERD. Currently, there are three approved biologics for NERD: dupilumab (anti-IL4 receptor alpha), mepolizumab (anti-IL5), and omalizumab (anti-IgE). A meta-analysis that compared different biologics among themselves and with ASA desensitization indicated that

dupilumab showed the most significant patient and clinically meaningful outcomes.<sup>15</sup> There are no head-to-head studies between biologics; thus, caution should be used in interpreting the results of the meta-analysis. Yong and colleagues showed that over 10 years, per patient, appropriate medical management after functional endoscopic sinus surgery cost \$54 125.31 and resulted in 2.25 revision functional endoscopic sinus surgeries, ASA desensitization after functional endoscopic sinus surgery cost slightly less and resulted in a 10% decrease in revision functional endoscopic sinus surgery, ASA desensitization with salvage dupilumab cost 2.25 times more and resulted in 17% fewer revisions, and up-front dupilumab cost 3.44 times more and resulted in 33% fewer revisions.<sup>16</sup> Although up-front dupilumab leads to better outcomes, it is not cost-effective. Furthermore, NERD patients will need to stay on biologics for the rest of their lives; those who come off dupilumab will have polyp recurrence.<sup>10</sup> Extended functional endoscopic sinus surgery, steroids, and aspirin desensitization therapy have been shown to reduce polyp recurrence rate in NERD patients, thereby reducing overall health care costs while improving patient outcomes.<sup>17</sup>

Aspirin desensitization therapy is a cumbersome and time-consuming procedure and requires subspecialized care, which is available only in Vancouver. Access to aspirin desensitization therapy has been very limited in BC for years. The COVID-19 pandemic made office spirometry challenging to perform due to complex infection control protocols. Aspirin desensitization therapy has risks, such as gastrointestinal



**FIGURE 1. (A)** Coronal section of CT sinus of a patient with NSAID-exacerbated respiratory disease. Complete opacification of the sinuses. **(B)** Endoscopic view of nasal polyps.

**TABLE 1.** NSAID-exacerbated respiratory disease aspirin desensitization/challenge protocol.

Time	Day 1 Hospital	Days 2–7 Home	Day 7 onward Home
9:00 a.m.	ASA 40 mg*	Continue taking ASA 160 mg by mouth twice a day* AND proton pump inhibitor prophylaxis	Increase dose enteric-coated ASA 325 mg to 650 mg by mouth twice a day AND proton pump inhibitor prophylaxis
10:30 a.m.	ASA 80 mg*		
12:00 p.m.	ASA 160 mg*		
3:00 p.m.	Discharged		

\* Chewable aspirin.

Adapted from Brigham and Women's Hospital.<sup>12</sup>

bleeding, tinnitus, and kidney injury. We use proton pump inhibitors to prevent gastrointestinal bleeds. There are various proposed treatment algorithms, but the most common involves slowly administering


increasing doses of ASA until a reaction is elicited [Table 1].<sup>12</sup> Most protocols administer doses every 90 minutes to 3 hours and can take up to 2 days to complete. Then a maintenance dose of 325 mg to 650 mg

orally twice daily is established for continued treatment.<sup>1</sup> Typically, aspirin desensitization therapy is started 3 to 4 weeks after the patient's first functional endoscopic sinus surgery.<sup>1</sup>

**TABLE 2.** Medical and surgical management of NSAID-exacerbated respiratory disease in adults.

	Advantages	Disadvantages/risks	Example and dosing range (> 12 years of age)
<b>MEDICAL TREATMENTS</b>			
Intranasal steroid spray	<ul style="list-style-type: none"> <li>Reduces polyp size and nasal congestion</li> <li>Improves sense of smell</li> <li>Easy to administer</li> </ul>	<ul style="list-style-type: none"> <li>Nasal crusting</li> <li>Epistaxis</li> <li>Insufficient to control NSAID-exacerbated respiratory disease symptoms in isolation</li> </ul>	<ul style="list-style-type: none"> <li>Mometasone furoate 50 mcg spray: 2 sprays on each nostril every day, twice a day</li> <li>Fluticasone 50 mcg spray: 2 sprays on each nostril every day, twice a day</li> <li>Azelastine/fluticasone 137 mcg/50 mcg: 1 spray on each nostril twice a day</li> </ul>
Intranasal steroid irrigations	<ul style="list-style-type: none"> <li>Deeper penetration into sinuses</li> <li>Reduce polyp size and nasal congestion</li> <li>Improve sense of smell</li> <li>Easy to administer</li> </ul>	<ul style="list-style-type: none"> <li>Nasal crusting</li> <li>Epistaxis</li> <li>Insufficient to control NSAID-exacerbated respiratory disease symptoms in isolation</li> </ul>	<ul style="list-style-type: none"> <li>Budesonide nasal saline irrigation: 0.5 mg/2 mL in 240 cc normal saline rinse bottle; rinse 120 cc in each nasal cavity twice a day</li> <li>Mometasone 2 mg compounded into 240 cc normal saline rinse bottle; rinse 120 cc in each nasal cavity twice a day</li> </ul>
Inhaled steroid for asthma control	<ul style="list-style-type: none"> <li>Can assist with improving bronchodilation and reducing asthma exacerbations</li> </ul>	<ul style="list-style-type: none"> <li>Insufficient control of asthma symptoms even at higher doses for NSAID-exacerbated respiratory disease patients</li> </ul>	<ul style="list-style-type: none"> <li>Budesonide/formoterol 200 mcg: 2 puffs twice a day and as needed</li> <li>Mometasone/indacaterol 160 mcg to 320 mcg/150 mcg: 1 puff every day</li> <li>Fluticasone furoate/vilanterol 100 mcg to 200 mcg: 1 puff every day</li> </ul>
Leukotriene receptor antagonists	<ul style="list-style-type: none"> <li>Improvement in forced expiratory volume in 1 second and asthma scores</li> </ul>	<ul style="list-style-type: none"> <li>Neuropsychiatric side effects</li> </ul>	<ul style="list-style-type: none"> <li>Montelukast 10 mg by mouth every day</li> </ul>
Oral steroids	<ul style="list-style-type: none"> <li>Provide rapid relief of nasal and respiratory symptoms</li> </ul>	<ul style="list-style-type: none"> <li>Hyperglycemia</li> <li>Weight gain</li> <li>Endocrine, musculoskeletal, and neurologic abnormalities</li> </ul>	<ul style="list-style-type: none"> <li>Prednisone 40 mg by mouth once daily for 7 days</li> </ul>
Biologics	<ul style="list-style-type: none"> <li>Reduced steroid use</li> <li>Reduced nasal symptoms and improved patient sinonasal symptom scores (SNOT-22)</li> <li>Improved sense of smell</li> <li>Reduced congestion and nasal polyps</li> <li>Monthly/bimonthly dosing schedules</li> </ul>	<ul style="list-style-type: none"> <li>Expensive</li> <li>Some coverage through BC PharmaCare</li> <li>Specialist medical prescription required</li> </ul>	<ul style="list-style-type: none"> <li>Dosing based on each biologic</li> <li>Options:                             <ul style="list-style-type: none"> <li>Omalizumab</li> <li>Dupilumab</li> <li>Mepolizumab</li> </ul> </li> </ul>
Aspirin desensitization therapy	<ul style="list-style-type: none"> <li>Effective</li> <li>Affordable</li> </ul>	<ul style="list-style-type: none"> <li>Gastrointestinal upset and bleeds</li> <li>Tinnitus</li> <li>Acute kidney injury</li> </ul>	<ul style="list-style-type: none"> <li>ASA 325 mg to 650 mg by mouth twice a day</li> <li>Proton pump inhibitor prophylaxis</li> </ul>
<b>SURGICAL TREATMENTS</b>			
Functional endoscopic sinus surgery +/- extended procedures	<ul style="list-style-type: none"> <li>Improved sinus aeration and access for topical medication</li> <li>Removal of inflammatory tissue and polyps</li> </ul>	<ul style="list-style-type: none"> <li>Orbital hematoma</li> <li>Blindness</li> <li>Cerebrospinal fluid leak</li> <li>Bleeding</li> <li>Infection</li> <li>Recurrence of disease and scarring</li> </ul>	

This not an exhaustive list of medications; it is strictly for learning purposes. We do not endorse the medications listed over other medications in the same drug class.

 <b>Providence Health Care</b>  <b>ASPIRIN EXACERBATED DISEASE (AERD) CLINIC REFERRAL</b>	Place Patient Form Label Here																																																										
<b>Aspirin Exacerbated Disease Clinic (AERD)</b>	<b>Location: ENT Clinic, Providence 2, St. Paul's Hospital 1081 Burrard Street</b> <b>Phone: 1-604-806-8353 Fax: 1-866-308-2123</b>																																																										
<p><i>We serve patients with ASA/NSAID exacerbated disease across the province of British Columbia. The AERD multidisciplinary clinic is served by Allergy and Otolaryngology Physicians. Our hope is to provide patient centered care for those diagnosed with AERD or suspected of having AERD. The clinic runs once per month at St. Paul's Hospital.</i></p>																																																											
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**FIGURE 2.** Aspirin Exacerbated Respiratory Disease Clinic referral form.

The form can be found on Pathways and Plexia.

## Aspirin Exacerbated Respiratory Disease Clinic

The Aspirin Exacerbated Respiratory Disease (AERD) Clinic was started in November 2021 at St. Paul's Hospital in Vancouver to help facilitate interdisciplinary care and optimize outcomes. The clinic pays homage to the dated name of AERD over NERD because most clinicians are unfamiliar with the new term. Dr Ruiz (allergist) and Dr Thamboo (rhinologist) created the AERD clinic, which offers ASA challenge/desensitization, surgical consultation, biologics start, follow-up with endoscopy, and optimization of medical and lifestyle management. Baseline biological markers through allergy testing and serology are collected as preoperative endoscopy scores. Patients who are eligible for surgical intervention proceed with functional endoscopic sinus surgery and postoperative aspirin desensitization therapy if deemed appropriate. These patients can also participate in multiple landmark research studies that investigate AERD, aspirin desensitization therapy, and functional endoscopic sinus surgery.

Although biologics have demonstrated clinical- and patient-reported benefits, they are expensive and difficult to obtain for patients. The process is quite cumbersome and often requires facilitation by a subspecialist. The AERD Clinic acts as a referral centre for patients to be thoroughly assessed by the relevant specialists and provides the necessary treatment (aspirin desensitization therapy, surgery, and/or biologics) to manage their disease. NERD patients can be referred through Pathways or can fax the referral form [Figure 2]. We have adapted previously published protocols [Table 1]<sup>12</sup> to work within the constraints of the BC health care system.

Since November 2021, 10 patients have been desensitized at the AERD/NERD clinic. One of those patients has very severe sinus disease and had multiple sinus surgeries. The patient's "asthma was so bad [they were] waking up during the night to take [their] inhalers. The polyps kept growing, even after surgery. By 2021, [the polyps] got so bad, they were pressing against [their]

eye, and [they] almost lost [their] vision." "[They] had surgery again and aspirin desensitization therapy in March, and it's changed everything."<sup>11</sup>

### When to refer

Any patient with the full triad of NERD symptoms or asthma and chronic rhinosinusitis with nasal polyposis should be assessed. NSAID hypersensitivity can be difficult to elicit in history, and many patients will require an ASA challenge.

### Summary

NERD is a complex airway disease that requires subspecialized care from multiple health care providers to optimize outcomes. In BC, greater awareness of NERD is needed to provide early diagnosis and appropriate management. French researchers described NERD in 1922, but it was largely unnoticed until Samter and Beers published their landmark case series 46 years later.<sup>7</sup> We hope to bring NERD to the forefront in BC in a timelier manner. ■

### Competing interests

None declared.

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