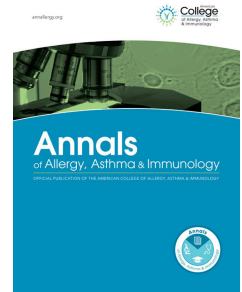


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*Invited Perspective:*

**Aspirin desensitization vs biologics for patients with aspirin-exacerbated respiratory disease**

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1           As the director of one of the largest evaluation and treatment centers for patients with  
2 aspirin-exacerbated respiratory disease (AERD) in the world, I am often asked how we should  
3 approach the use of aspirin desensitization followed by high-dose aspirin therapy for our AERD  
4 patients in the current age of newly available biologics. I feel strongly that, at least for now, there  
5 is a place for both treatment modalities, sometimes even both in the same patient at the same  
6 time. In the end it is always a set of decisions that needs to be made on an individual patient  
7 basis and there are four general domains that I consider when approaching the decision and my  
8 recommendation: efficacy, safety, cost, and patient preference.

9           The efficacy of biologics, for either the treatment of uncontrolled asthma or for the  
10 treatment of nasal polyposis, is relatively well established, in part because in order to be  
11 awarded FDA approval, rigorous prospective studies with clear endpoints were required. The  
12 mean expected improvement in FEV1 or likely decrease in need for chronic oral steroids for  
13 asthma control has been published for the use of omalizumab, mepolizumab, benralizumab,  
14 reslizumab and dupilumab. Similarly, the mean reduction in nasal polyp burden or increase in  
15 sense of smell is known for dupilumab, with detailed results expected soon from Phase 3 nasal  
16 polyp trials with omalizumab and mepolizumab, as earlier Phase 2 studies with these agents  
17 showed promise. In contrast, there have been no international multi-site industry-sponsored  
18 randomized controlled trials of aspirin desensitization, followed by initiation of high-dose aspirin  
19 treatment. Several groups have published careful clinical studies of the efficacy of high-dose  
20 aspirin in AERD, but the total daily aspirin dose has differed, as has the length of treatment, and  
21 the prespecified endpoints of each study. There have only ever been four randomized, placebo-  
22 controlled trials of high-dose daily aspirin in AERD [1] (totaling only 163 patients studied) and  
23 even with the addition of several other studies that included low-dose daily aspirin in lieu of a  
24 true placebo, the data are difficult to summarize in aggregate. Those of us who have offered  
25 aspirin desensitizations to our AERD patients for many years will confirm with dozens of

26 anecdotes to say that “when it works, it works magically”. We each have long lists of contented  
27 patients who had suffered through the regrowth of polyps despite multiple repeat surgeries and  
28 appropriate standard post-operative care, and after initiating high-dose aspirin their polyps have  
29 not returned, their asthma control has been more consistent, and their steroid requirements are  
30 at an all-time low. However, if we are to be honest, we each can also dig up anecdotes of  
31 patients whose desensitizations were particularly difficult, or whose gastrointestinal tracts simply  
32 could not put up with the higher doses of aspirin, or whose sinuses and asthma refused to  
33 respond and polyp regrowth sprang back unabated. Without careful, prospective, well-designed,  
34 multi-center trials of high-dose aspirin therapy, our data on efficacy for the treatment of  
35 respiratory disease in AERD will remain lacking. However, in addition to the utility of high-dose  
36 aspirin for the prevention of nasal polyp regrowth, aspirin desensitization also provides the  
37 opportunity for patients to use aspirin or NSAIDs for other indications, including for non-opioid  
38 pain control, cardioprotection, and as anti-inflammatory agents for a myriad of inflammatory  
39 disorders. As far as we know, none of the available biologics will completely prevent all NSAID-  
40 induced reactions in patients with AERD, and therefore this endpoint is one that is unique to  
41 aspirin desensitization.

42         As for efficacy, our understanding of the safety of daily high-dose aspirin in AERD is  
43 hampered by small trial size and few longer-term studies. The aspirin-induced increased risk of  
44 gastritis is something we counsel our patients on carefully, and see in around 10% of our  
45 patients, and though frank gastrointestinal bleeding is rare, it does occasionally occur. An  
46 idiosyncratic worsening in asthma control or worsening pruritic rash while on high-dose aspirin  
47 is also reported by about 10% of patients with AERD, leading to total of about a 15% patient  
48 drop-out rate due to aspirin-induced side effects.[1, 2] The use of aspirin does come with  
49 decades of historical data from the cardiovascular literature that can be extrapolated to our  
50 patients. Recent clinical research suggests that daily aspirin does cause a very small but

51 significantly higher risk of major bleeding and hemorrhage[3, 4] and possibly a higher all-cause  
52 mortality in older adults,[5] suggesting that perhaps high-dose aspirin should be contraindicated  
53 in elderly patients with AERD. In contrast, the use of biologics in allergy and rhinology is a  
54 comparatively new practice, with safety data going out for only 1 year for several of the available  
55 drugs. However, in the short term, there does seem to be a relatively safe profile for the existing  
56 biologics, with less than a 5% drop-out rate for most of the published studies.

57 A discussion of the therapeutic utility of biologics must be contextualized with a  
58 consideration of cost. The annual cost of any of the FDA-approved biologics for asthma or nasal  
59 polyposis ranges from about \$33,000 to \$49,000 (as per Medi-Span<sup>®</sup> Price Rx<sup>®</sup>, 2019).  
60 Although in many states the health insurance coverage of these agents is quite good, allowing  
61 for low out-of-pocket costs for some patients, the cost to our health care system at large is still  
62 very high. The cost of an aspirin desensitization procedure is generally billed at \$1,000-\$4,000,  
63 with an annual cost of over-the-counter enteric-coated aspirin of less than \$100.

64 Please, let's not ever make an elective clinical decision without including the patient in a  
65 shared decisionmaking process. We as specialists must be sufficiently knowledgeable and  
66 informed to provide patients with current evidence-based information, and then work with our  
67 patients and their families to take into account their values and preferences, and come together  
68 to an optimal treatment decision. There are patients who are terrified of undergoing an aspirin  
69 desensitization procedure, and perhaps justifiably so, considering how severe some of their  
70 previous NSAID-induced reactions may have been. There are also patients for whom the notion  
71 of an injectable biologic or new antibody conjures up fears of medical experimentation,  
72 exploitation, or mistrust. Thoughtful education and a patient-centered approach are often  
73 enough to provide reassurance, but it takes time and care to get there.

74 In conclusion, there are some patients for whom a sinus surgery followed by aspirin  
75 desensitization and high-dose aspirin therapy is clearly the best choice – particularly younger

76 patients whose asthma seems to temporarily disappear after sinus surgery and for whom  
77 prevention of nasal polyp regrowth is the main goal. There are also some patients for whom a  
78 biologic is the best choice – especially those with multiple comorbidities including severe  
79 asthma, recalcitrant nasal polyps, or uncontrolled allergies or atopic dermatitis. For everyone  
80 else, the answer is “it depends”, and it is our job to provide guidance where we can.

- 81 1. Chu, D.K., et al., *Benefits and harms of aspirin desensitization for aspirin-exacerbated*  
82 *respiratory disease: a systematic review and meta-analysis*. *Int Forum Allergy Rhinol*,  
83 2019. **9**(12): p. 1409-1419.
- 84 2. Berges-Gimeno, M.P., R.A. Simon, and D.D. Stevenson, *Long-term treatment with*  
85 *aspirin desensitization in asthmatic patients with aspirin-exacerbated respiratory*  
86 *disease*. *J Allergy Clin Immunol*, 2003. **111**(1): p. 180-6.
- 87 3. McNeil, J.J., et al., *Effect of Aspirin on Cardiovascular Events and Bleeding in the*  
88 *Healthy Elderly*. *N Engl J Med*, 2018. **379**(16): p. 1509-1518.
- 89 4. Group, A.S.C., et al., *Effects of Aspirin for Primary Prevention in Persons with Diabetes*  
90 *Mellitus*. *N Engl J Med*, 2018. **379**(16): p. 1529-1539.
- 91 5. McNeil, J.J., et al., *Effect of Aspirin on All-Cause Mortality in the Healthy Elderly*. *N Engl*  
92 *J Med*, 2018. **379**(16): p. 1519-1528.