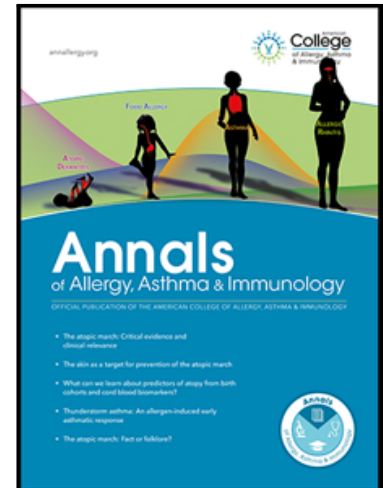


Scoring Tool for Systemic Symptoms During Aspirin Challenge
Detects Mediator Production in Aspirin-Exacerbated Respiratory
Disease

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Title: Scoring Tool for Systemic Symptoms During Aspirin Challenge Detects Mediator Production in Aspirin-Exacerbated Respiratory Disease

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Abbreviations:

AERD Aspirin-exacerbated respiratory disease

COX-1 Cyclooxygenase-1
cysLTs Cysteinyl leukotrienes
FEV₁ Forced expiratory volume in one second
PGD₂ Prostaglandin D₂ metabolites
r_s Spearman Correlation
SD standard deviation
TNSS Total Nasal Symptom Score
TNSS+ Total Nasal Symptom Score plus Systemic Score
uLTE4 urinary Leukotriene E₄
uPGDM urinary Prostaglandin D-metabolite

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Respiratory reactions to cyclooxygenase (COX)-1 inhibitors identify patients with aspirin-exacerbated respiratory disease (AERD), a severe phenotype of asthma and nasal polyposis. Exposure to COX-1 inhibitors classically triggers an acute worsening of upper and lower airway symptoms, however, extra-respiratory symptoms also occur. Gastrointestinal and cutaneous symptoms have been documented in patients with evidence of systemic mast cell degranulation.^{1,2} Aspirin challenge and desensitization in subjects with AERD are routinely performed to confirm the diagnosis and to initiate high-dose aspirin therapy.³

Multiple studies have established prostaglandin (PG)D₂, cysteinyl leukotrienes (cysLTs), and tryptase as key mediators linked to clinical reaction severity following COX-1 inhibitor exposure in patients with AERD. PGD₂ is important in effector cell recruitment and activation, airway hyperresponsiveness, vasodilatation and increased vascular permeability which can be measured in the urine as the PGD₂ metabolite (uPGD-M). During oral aspirin challenge, uPGD-M levels

inversely correlated with the decline in forced expiratory volume in one second (FEV_1) and were associated with cutaneous and gastrointestinal symptoms, and intolerance of aspirin desensitization.¹ CysLTs mediate vascular permeability and airway responsiveness. Urinary LTE_4 , the end metabolite of the cysLT pathway, correlates with severity of respiratory reactions as measured by the decline in FEV_1 .¹ Tryptase is a specific marker of mast cell activation that can be detected in blood and respiratory fluid. Tryptase elevations during oral aspirin challenge have been observed in up to 50% of subjects and identified those with the greatest increase in upper respiratory symptoms and decline in FEV_1 .²

Assessment of mediator production is limited to research settings and is not routinely available to clinicians performing aspirin challenge or desensitization protocols. Scoring tools have been developed to assess predominantly upper airway symptoms during aspirin challenge,⁴⁻⁶ but none ascertain the full spectrum of symptom involvement. Research and clinical management of AERD would benefit from new scoring tools which assesses the full spectrum of symptoms during aspirin-induced reactions.

Thirty subjects with AERD underwent a standardized oral aspirin challenge with montelukast pretreatment as part of an IRB approved protocol.⁴ Total nasal symptom score (TNSS), an 8-question scale ranging from 0-40, was collected every 30 minutes.⁴ Four additional “Systemic Score” questions about the severity of headache, gastrointestinal, cutaneous, and lower respiratory symptoms were included with the TNSS to generate the TNSS+ (Figure 1). Higher scores denoted more severe symptoms. Spirometry, urine, and serum were collected at baseline, at onset of respiratory reaction, and then hourly. Eicosanoids and serum tryptase were assessed

as previously described.⁷ Respiratory reactions were defined by increase in TNSS of ≥ 2 points or decline in FEV₁ of 15% from baseline.⁴ During respiratory reactions, the maximum change for each of the mediators and the individual scoring systems was calculated by subtracting the baseline from the peak level measured during the 3-hour period following reaction onset. Spearman correlation coefficient determined the association between the maximum change in TNSS or TNSS+ and the maximum change in uLTE₄, uPGD-M, and serum tryptase levels.

The study cohort was predominantly female (57%) with the majority Non-Hispanic (93%) and White (97%). Prior sinus surgery was reported by 93% of patients. 29 of 30 subjects met criteria for an aspirin-induced respiratory reaction. Among those subjects, there was no correlation between change in TNSS and change in uLTE₄ ($r_s=0.21$; $p=0.284$), uPGD-M ($r_s=0.12$; $p=0.12$), or serum tryptase ($r_s=0.105$; $p=0.609$). However, the change in TNSS+ significantly correlated with the change uLTE₄ ($r_s=0.411$; $p=0.03$) and the change in uPGD-M ($r_s=0.522$; $p=0.004$). The change in TNSS+ showed a trend towards positive correlation with the change in serum tryptase ($r_s=0.378$; $p=0.057$). The “systemic score” alone did not correlate with mediators (data not shown). In this predominantly postsurgical cohort, we observed no statistically significant correlation between time from last surgery and mediator production or symptom scores.

During aspirin-induced reactions, the assessment of lower respiratory, gastrointestinal, and cutaneous symptoms, in addition to upper respiratory symptoms, using the TNSS+ correlated with classical mediators of AERD. The TNSS+ score most strongly correlated with uPGD-M, and uLTE₄, with serum tryptase, though not significant, showed a similar trend. The lack of correlation between the regular TNSS and systemic mediator production highlights its

limitations. These data support the use of TNSS+ to improve upon the current TNSS for identifying systemic mediator production during aspirin-induced reactions in AERD.

The TNSS was developed to evaluate nasal symptoms and quality of life in allergic rhinitis, not AERD. Given the lack of validated AERD-specific scoring symptoms, the TNSS has been borrowed for clinical trials comparing the severity of aspirin-induced reactions in subjects with AERD. The four additional questions in the TNSS+ were included to assess symptoms frequently reported by subjects, based on clinical observations made during prior studies, but not captured by the TNSS.⁴ Recent work has highlighted the heterogeneity in both clinical manifestations and inflammatory patterns in patients with AERD, yet the exact pathophysiology of AERD remains unknown with no studies confirming the contribution of mediators from each possible tissue source.⁸ The assessment of respiratory and extra-respiratory symptoms is required to standardize the clinical severity of aspirin-induced reactions for mechanistic and multi-site clinical trials in AERD, as well as to aid practitioners performing desensitizations.

This single center study with small sample size and a homogenous patient population limit the generalizability of this work. Alternative COX-1 inhibitor challenge protocols are routinely used, and validation of the TNSS+ in those settings is required. Other published AERD scoring tools lacked a breadth of systemic symptoms and were not linked to mediator production.^{5,6} The lack of impact of time from surgery on symptoms scores or mediator production in our study likely reflects differences in study design, small sample size, and significant interpatient heterogeneity in aspirin-induced reactions in patients with AERD.^{9,10} Future study at multiple clinical sites with diverse patient populations is needed. Lastly, the utility of any scoring system in normal clinical

practice for predicting outcomes of aspirin desensitization and daily aspirin therapy in AERD is not established. Continued development of clinical and research tools for the study of AERD is required to address this severe phenotype.

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Figure Legend:

Figure 1.

Total Nasal Symptom Score (TNSS)		None	A little	Moderate	Quite a bit	Severe	Very Severe
1a	Nasal congestion (LEFT)	0	1	2	3	4	5
1b	Nasal congestion (RIGHT)	0	1	2	3	4	5
1	(1a Score + 1b Score)/2 =						
2	Runny Nose	0	1	2	3	4	5
3	Itchy Nose	0	1	2	3	4	5
4	Sneezing	0	1	2	3	4	5
5	Itchy Eyes	0	1	2	3	4	5
6	Eye Tearing	0	1	2	3	4	5
7	Itchy Ears or Throat	0	1	2	3	4	5
8	Eye Redness	0	1	2	3	4	5
TNSS Total (out of possible 40)							
Systemic Score (TNSS+)							
9	Cough, wheezing, chest tightness, shortness of breath	0	1	2	3	4	5
10	Abdominal cramps, nausea, vomiting, or diarrhea	0	1	2	3	4	5
11	Skin rash, flushing, or itching	0	1	2	3	4	5
12	Headache	0	1	2	3	4	5
TNSS+ Total (out of possible 60)							

Figure 1. Total Nasal Symptom Score plus Systemic Score (TNSS)+. Subjective scoring measure used during aspirin challenges, created by adding 4 “systemic score” questions regarding the severity of headache, gastrointestinal, cutaneous, and lower respiratory symptoms to the Total Nasal Symptom Score (TNSS).