Rational approach to aspirin dosing during oral challenges and desensitization of patients with aspirin-exacerbated respiratory disease

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Background: Aspirin desensitization improves clinical outcomes in most patients with aspirin-exacerbated respiratory disease. Most protocols for desensitization are time-consuming.
Objective: Our objective was to use historical information about the course of aspirin desensitization to enhance the efficiency of the desensitization protocol.
Methods: Four hundred twenty subjects with suspected aspirin-exacerbated respiratory disease underwent oral aspirin challenges. Their clinical characteristics were analyzed in relation to features of reactions during aspirin challenges.
Results: Large (FEV_1 decrease >30%) and moderate (FEV_1 decrease 21% to 30%) bronchial reactions occurred in 9% and 20% of subjects, respectively. Multivariate analysis identified risk factors associated with these larger reactions, including lack of leukotriene modifier use, baseline FEV_1 of less than 80% of predicted value, and previous asthma-related emergency department visits. Seventy-five percent of patients reacted to a provoking dose of either 45 or 60 mg. Only 3% of initial reactions occurred after 150- or 325-mg provoking doses, and none occurred after the 650-mg dose.
Conclusions: Most bronchial and naso-ocular reactions during oral aspirin challenges occurred within a narrow dosing range (45-100 mg). Only 1 of 26 patients without risk factors had a moderate reaction. (J Allergy Clin Immunol 2009;123:406-10.)

Key words: *Aspirin, asthma, aspirin-exacerbated respiratory disease, sinusitis, polyps, oral challenge, drug allergy, drug desensitization*

Abbreviations used
AERD: Aspirin-exacerbated respiratory disease
ASA: Acetylsalicylic acid
ED: Emergency department
LTMD: Leukotriene-modifying drug
NSAID: Nonsteroidal anti-inflammatory drug
OR: Odds ratio

Aspirin-exacerbated respiratory disease (AERD) is a chronic disease characterized by a syndrome of eosinophilic nasal polyposis, sinusitis, and asthma originally described by Stevenson et al[1] and Samter and Beers.[2] Disease onset most commonly occurs in the third to fourth decades of life, frequently after an upper respiratory tract infection.[3] Patients with AERD experience characteristic respiratory reactions to acetylsalicylic acid (ASA) and other nonsteroidal anti-inflammatory drugs (NSAIDs) that inhibit cyclo-oxygenase-1 (COX-1).[4] The reactions include rhinorrhea, nasal congestion, ocular tearing and injection, periorbital swelling, and variable degrees of bronchoconstriction or laryngospasm. Because no *in vitro* test for AERD exists, definitive diagnosis requires a provocative challenge with ASA or another NSAID.[1,5]

During oral ASA challenges, the degree of naso-ocular and lower airway responses varies considerably. Factors associated with a large decrease in FEV_1 in response to ASA include unstable asthma at the time of challenge and high baseline urinary leukotriene E_4 levels.[6] Unfortunately, this laboratory test is not readily available, which excludes it from having a meaningful role in screening patients for the severity of their subsequent reactions. In 3 prior studies use of leukotriene-modifying drugs (LTMDs), usually montelukast daily for at least 1 week before oral ASA challenge, has been shown to reduce or eliminate bronchospastic reactions without blocking naso-ocular reactions.[7-9] Inhaled corticosteroids did not exert a similar protective effect. Currently, it is recommended that patients with AERD continue controller medications before initiation of ASA challenge and desensitization.[10] Although standard protocols are published describing ASA challenge and desensitization,[1] these protocols begin with 30 mg of ASA as the starting dose in all patients. Currently, published studies have not evaluated the typical provoking dose and how it might correlate to an individual's clinical characteristics. This means that a substantial majority of patients have no respiratory reactions during the 3 hours after the 30-mg dose. From a time-management standpoint, it would be helpful to know whether some patients could be started with 40 to 60 mg of ASA as the first challenge dose. In addition, the final recommended ASA dose for desensitization protocols is 650 mg,[10] although the published literature has not assessed what proportion of patients might have initial reactions at this dose.

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Desensitization to ASA and subsequent daily ASA treatment improves the clinical course of respiratory disease in approximately three quarters of patients with AERD.[11,12] However, to diagnose AERD and reach ASA desensitization, oral ASA challenges must be instituted. Currently, patients with AERD are commonly assumed to have severe asthma when in fact a spectrum of disease exists, with some patients having only upper respiratory AERD[13] and others having severe persistent corticosteroid-dependent asthma.[14] Logically, those patients with mild disease and those with severe disease might undergo the same challenges but with different starting doses of ASA. Easy-to-assemble historical markers of disease severity might help us predict which patients are most likely to have larger asthmatic reactions during oral ASA challenges. We recently showed that the severity of the prior full-strength accidental ASA- or NSAID-induced respiratory reactions (average ASA dose of 550 mg) did not predict the severity of bronchospasm during subsequent oral ASA challenges (average provoking dose of ASA, 62 mg).[15] Because the severity of ASA-induced respiratory reactions are dependent on the provoking dose, such information might provide us with a rational basis for selecting the first dose of ASA as either 20 to 30 mg or 40 to 60 mg.

The aim of this study was to identify risk factors in patients with AERD that might predict a more severe bronchial reaction during oral ASA challenges. In addition, we identified and characterized the range of ASA provoking doses for naso-ocular and bronchial reactions in a large group of patients with AERD undergoing ASA oral challenges. From this analysis, we are able to provide a rational basis for a more efficient oral ASA challenge and desensitization protocol.

METHODS

Patient population

Four hundred twenty consecutive patients referred to the Scripps Clinic for ASA challenges and desensitization between 1997 and 2005 were included in the study. The study protocol was approved by the Human Subjects Committee of Scripps Clinic. Because montelukast did not become available until 1999, a substantial number of patients did not receive this drug before challenge. All patients had a history of nasal polyposis, chronic rhinosinusitis, and physician-diagnosed asthma with an FEV_1 of greater than 60% of predicted value or greater than 1.5 L. All patients described a history of at least 1 respiratory reaction to ASA or an NSAID. Approximately one third of the patients had experienced at least 2 ASA- or NSAID-induced respiratory reactions in the past when ingesting a full therapeutic dose of these drugs.[3] All 420 patients had the diagnosis of AERD confirmed during oral ASA challenges and were desensitized to ASA according to published protocols.[10,16] Each patient received 30 mg of ASA as the starting dose and proceeded at 3-hour intervals through 45, 60, 100, 150, and 325 mg up to a final dose of 650 mg over the 2- or 3-day procedure. Doses were repeated if a reaction occurred. Positive reactions included naso-ocular symptoms (rhinorrhea, nasal congestion, ocular tearing and injection, and periorbital swelling), bronchoconstriction (wheezing, dyspnea, and FEV_1 decrease >20% from prechallenge baseline value), or both. Patients who did not experience a respiratory reaction during oral ASA challenges were not included in this study.

Historical information obtained from patients and clinical records

Before oral ASA challenges, patients and their medical records provided information, including age, duration of upper and/or lower respiratory disease, baseline percent predicted FEV_1 before bronchodilator administration, number of prednisone bursts in the preceding 12 months, total number of previous emergency department (ED) visits for asthma (other than those precipitated by ingestion of ASA or an NSAID), atopy, and current asthma and rhinitis controller medications.

Types of responses during oral ASA challenges

ASA challenge responses were classified as follows: naso-ocular reaction only (maximal FEV_1 decrease <10%), naso-ocular reaction with mild bronchial reaction (FEV_1 decrease 10% to 20%), naso-ocular reaction with moderate bronchial reaction (FEV_1 decrease 21% to 30%), or large bronchial reaction (FEV_1 decrease >30%). Patients in the moderate and large reaction categories were grouped together and compared with patients with naso-ocular and no or mild bronchial reactions to calculate odds ratios (ORs) for each assessed variable.

Statistical analysis

The mean and SD were calculated for patient clinical characteristics. For risk factors, univariate ORs were calculated, with a P value of less than .05 used for determining significant associations. Multivariate analysis was performed with SPSS version 16.0 software (SPSS, Inc, Chicago, Ill). Reverse stepwise logistic regression was used to identify significant predictors of moderate or severe reactions.

RESULTS

Baseline patient characteristics

The mean patient age was 46 years, with an average duration of respiratory symptoms of 14 years. Mean baseline predicted FEV_1 was 85%, average number of prednisone bursts per year was 3, and 20% of patients required continuous prednisone treatment. Two thirds of patients were taking an LTMD at the time of oral ASA challenge, including montelukast (82% of those taking an LTMD), zafirlukast (15%), zileuton (4%), or zileuton concomitantly with either montelukast or zafirlukast (1%). Most patients (67%) had previously been to the ED because of asthma attacks unrelated to ASA/NSAID ingestion a mean number of 4.36 times. Sixty-eight percent of patients with AERD had prior positive allergy skin test responses.

Information regarding oral ASA challenge/desensitization

The mean ASA provoking dose for bronchial responses was 68 mg, and for naso-ocular reactions it was 61 mg. For all 420 patients, the mean maximal FEV_1 decrease was 13.6%. Thirty-eight (9%) of 420 patients experienced a large decrease in FEV_1 of more than 30%, 83 (20%) of 420 had a moderate bronchial reaction (FEV_1 decreased 21% to 30%), 119 (28%) of 420 had a mild bronchial reaction (FEV_1 decreased by 10% to 20%), and 180 (43%) of 420 had naso-ocular reactions alone (FEV_1 decreased by <10%). Therefore 121 patients, or 28.8% of the 420, experienced an FEV_1 decrease of 21% or greater during the challenge procedure, classifying them as having a moderate or severe bronchial reaction. The remaining 299 (71.2%) patients had naso-ocular reactions with no or minimal associated bronchospasm. The mean elapsed time from ASA ingestion of provoking dose to onset of reaction was 1.7 hours.

ASA provoking doses for bronchial and naso-ocular reactions

Three hundred seventy-six (89.5%) of 420 patients had a bronchial reaction, and 412 (98.1%) of 420 experienced a naso-ocular reaction. Fig 1 shows the distribution of ASA provoking doses for inducing these reactions. Eight patients had bronchial reactions without associated nasal reactions. The lowest provoking dose, 30 mg, produced a response in 9% of patients with positive challenge results. The largest proportion of naso-ocular and bronchial reactions occurred after administration of 45 or 60 mg of

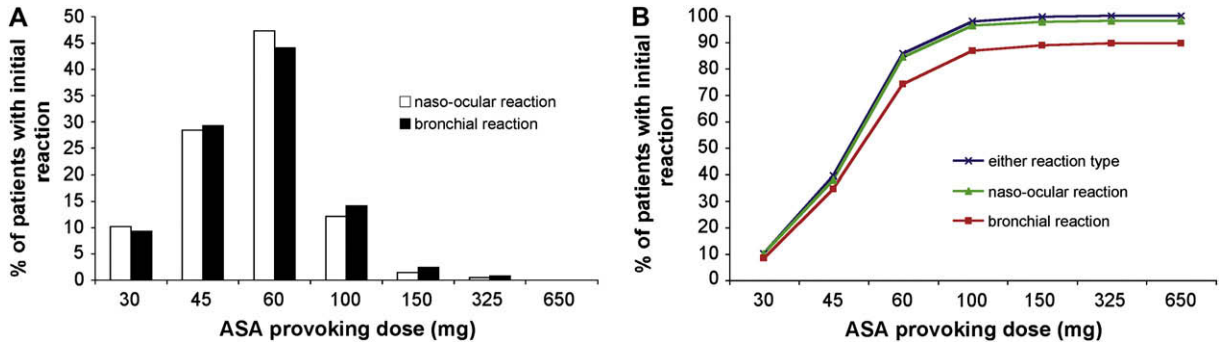

FIG 1. Distribution of provoking doses in patients with AERD undergoing oral ASA challenges. **A**, Frequency of reactions by dose. **B**, Cumulative percentage of positive reactions.

TABLE I. Clinical predictors of moderate or severe bronchial reactions in patients with AERD undergoing oral ASA challenge

Patient characteristic	No. of patients in category (n = 420)	Percentage with moderate-severe bronchial reaction (n = 121)	OR for moderate-severe vs mild bronchial reaction	95% CI
Age at time of challenge (y)				
>60	52	27	0.89	0.47-1.73
51-60	102	25	0.75	0.45-1.25
41-50	135	27	0.86	0.54-1.35
30-40	**93**	**38**	**1.69**	**1.04-2.75**
≤30	38	29	1.01	0.48-2.10
Duration of AERD symptoms (y)				
<10	**185**	**34**	**1.58**	**1.03-2.41**
11-20	152	26	0.78	0.50-1.22
>20	83	23	0.68	0.39-1.20
Baseline FEV_1 (%)				
>80	**264**	**24**	**0.56**	**0.36-0.85**
60-80	**143**	**37**	**1.81**	**1.17-2.80**
<60	13	31	1.10	0.67-1.78
Continuous prednisone use at time of challenge				
Yes	85	26	0.83	0.49-1.43
No	335	30	1.20	0.70-2.06
Current leukotriene modifier use				
Yes	**278**	**25**	**0.57**	**0.37-0.88**
No	**142**	**37**	**1.75**	**1.13-2.71**
Presence of atopy				
Yes	288	30	1.25	0.78-1.98
No	132	26	0.80	0.50-1.28
Ever to ED for asthma other than ASA induced				
Yes	**282**	**33**	**1.93**	**1.19-3.13**
No	**138**	**20**	**0.51**	**0.32-0.84**
No. of prednisone bursts in last 12 mo				
0	88	24	0.68	0.39-1.19
1-3	130	31	1.10	0.68-1.78
>3	202	30	1.24	0.76-2.01

Variables that are statistically significant are in boldface type.

ASA. Only 9 (2%) of 376 patients had an initial bronchial reaction, and 6 (1%) of 412 patients had an initial naso-ocular reaction to 150 mg of ASA. Three (1%) of 376 patients had an initial bronchial reaction, and 2 (0.4%) of 412 patients had an initial naso-ocular reaction to 325 mg of ASA (Fig 1). No patients had an initial ASA reaction of either type at the highest protocol dose of 650 mg.

Risk factors for moderate or severe ASA bronchial reactions

Univariate ORs for a moderate or severe ASA bronchial reaction were calculated for patient variables. The results are shown in Table I. Factors associated with an increased risk of moderate or severe bronchial ASA reactions included age at time of challenge (31-40 years), duration of AERD symptoms of less than 10 years, prebronchodilator FEV_1 of less than 80% of predicted value, lack of use of an LTMD, and previous ED visits for asthma not initiated by ASA or NSAID exposure. Factors associated with a reduced risk of moderate or severe ASA bronchial reaction included baseline FEV_1 of greater than 80% of predicted value, current use of an LTMD, and lack of previous ED visits for asthma not counting ED visits for ASA- or NSAID-induced asthma attacks. Other factors not associated with the risk of a moderate or severe bronchospastic reaction during oral ASA challenges were current or past use of systemic or topical

TABLE II. Moderate or severe reaction frequency increases with number of risk factors

No. of risk factors	0	1	2	3	4	5
No. of patients in category	26	105	155	97	35	2
No. of patients with moderate-severe reaction (%)	1 (3.0)	15 (14.4)	45 (29.0)	41 (42.3)	16 (45.7)	1 (50.0)

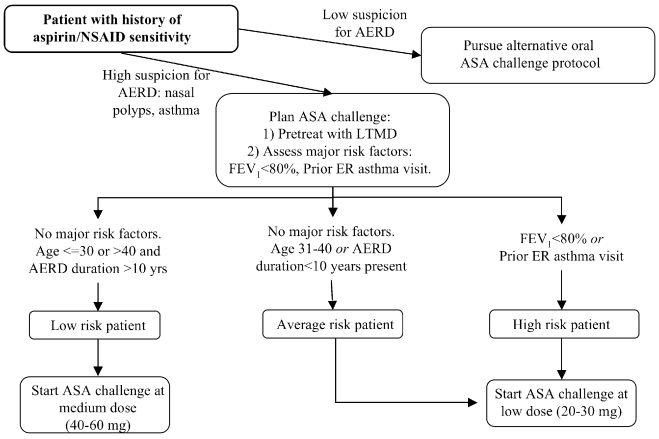

FIG 2. Selection of starting dose for oral ASA challenge in patients with suspected AERD. *ER*, Emergency department.

corticosteroids, atopy, sex, late onset of disease (>40 years), and longer duration of respiratory disease.

Multivariate analysis

Reverse stepwise logistic regression confirmed the importance of several of these associations. Evaluating baseline FEV_1 as a continuous variable identified a significant association for baseline FEV_1 (OR, 0.975; 95% CI, 0.959-0.991), with each 1% increase in FEV_1 predicting reduced risk of a moderate or severe reaction. More practically, a baseline FEV_1 of less than 80% of predicted value was a significant predictor of increased risk (OR, 1.87; 95% CI, 1.19-2.94). Multivariate analysis confirmed that LTMD use (OR, 0.544; 95% CI, 0.347-0.854) predicted a reduced risk of a moderate or severe reaction, and a history of any ED visit for asthma was associated with an increased risk of a more severe reaction (OR, 1.99; 95% CI, 1.21-3.29). Each yearly increase in the duration of AERD symptoms also significantly predicted a reduced risk of a moderate or severe reaction (OR, 0.965; 95% CI, 0.941-0.989); analyzed as a grouped variable, patients with AERD symptoms for a duration of less than 10 years had a higher risk (OR, 1.80; 95% CI, 1.15-2.82). However, age at the time of desensitization, identified as a potential predictor in univariate analysis, was not significant in multivariate analysis either as a continuous function of yearly age increase (OR, 0.991; 95% CI, 0.971-1.01) or grouped into the age 31 to 40 years category (OR, 1.53; 95% CI, 0.912-2.56).

Subset analysis of patients taking an LTMD at the time of desensitization

On the basis of the results found in this analysis and prior published studies,[8,9] we have recommended LTMD use, most commonly a leukotriene receptor antagonist, at the time of ASA challenge and desensitization procedures. It was therefore of interest to analyze patients already taking LTMDs to determine whether predictors might be useful in assessing their risk for moderate or severe bronchial reactions. Multivariate analysis of the 278 patients using LTMDs confirmed that higher baseline FEV_1 (OR, 0.972; 95% CI, 0.951-0.994) was significantly associated with reduced risk, and the group of patients with a baseline FEV_1 of less than 80% of predicted value had an increased risk (OR, 2.05; 95% CI, 1.16-3.62). A history of any ED visit for asthma (OR, 2.31; 95% CI, 1.19-4.49) predicted a significantly higher risk of a moderate or severe reaction. However, in this subset analysis duration of AERD symptoms did not significantly predict risk of a moderate or severe reaction as a continuous variable (OR, 0.992; 95% CI, 0.958-1.03) or for duration of less than 10 years (OR, 1.64; 95% CI, 0.927-2.89; $P = .89$).

Increasing number of risk factors correlates with moderate or severe reactions

Of the 121 patients with moderate or severe bronchial reactions, most had risk factors identified in our analysis, except for 1 patient without risk factors whose FEV_1 decreased by 21%. The population was analyzed by number of risk factors present and reaction severity. As shown in Table II, additional risk factors correlated with an increased chance of moderate or severe bronchial reactions, suggesting a dose-response relationship.

FEV_1 and previous ED visits for asthma correlate with risk of severe reaction

An analysis was performed to assess risk factors associating with severe bronchial reactions. Only baseline FEV_1 (OR, 2.26; 95% CI, 1.15-4.43) and a history of a previous ED visit for asthma (OR, 2.38; 95% CI, 1.02-5.55) had a significant positive association with an FEV_1 decrease of more than 30% during ASA challenge. Of the 38 patients experiencing a severe bronchial reaction, all had at least one of the 5 identified risk factors, with 3 having only 1 risk factor and 17 having 2 risk factors. Only 2 of these 20 patients had neither a low FEV_1 nor a previous ED visit as risk factors.

DISCUSSION

In this study we identified the risk factors associated with larger bronchial reactions during oral ASA challenges. LTMD nonuse at the time of challenge, baseline FEV_1 of less than 80% of predicted value, and a history of any previous ED visit for asthma correlated most robustly with higher risk, remaining statistically significant by using multivariate analysis and, for the latter 2 factors, subset analysis of patients already taking LTMDs at the time of their oral challenges. Age at the time of challenge (31-40 years) and duration of disease symptoms of less than 10 years were significant risk factors in univariate analysis but not in multivariate and subset analyses, respectively. In addition, we have detailed the natural course of 420 ASA challenge procedures, finding that 74% of reactions occur after the 45- or 60-mg doses. None of 420 patients with AERD had an initial reaction after the 650-mg dose.

We propose that patients at low or moderate risk of significant bronchial reactions can start at a modestly higher first dose of ASA (40 or 60 mg) during the challenge procedure, with the caveat that they all be pretreated with an LTMD (Fig 2).[7-9] Patients with a history of ED visits for asthma, a low baseline FEV_1, or both should start at the lowest available ASA dose (20 or 30 mg). In addition, we would recommend stopping the

challenge at 325 mg of ASA and foregoing the 650-mg provoking dose in patients with a negative challenge result to that point. As per our recent study,[17] we recommend that the starting ASA treatment dose be 650 mg twice a day for the first 6 months if tolerated and then decreased to 325 mg of ASA twice daily. Assuming a 3-hour dosing interval, which was used for all of the challenges described here, these 2 changes to the protocol would save 3 hours for all negative challenge results and would save 3 hours for the almost half of patients (42% in this study) who would qualify as low risk. Although a rapid desensitization protocol has been published for treating patients with ASA/NSAID-relate-durticaria/angioedema,[18] we believe that the recommendations presented here will result in substantial time savings for patients with AERD undergoing ASA desensitization.

Each of the identified risk factors suggests a correlation with the pathophysiology of AERD. The risk factors of age of 31 to 40 years and duration of symptoms of less than 10 years might represent patients in a similar early phase of the AERD disease process, given that the average age of onset of disease in our AERD population is 34 years.[3] These factors were not significant after further analysis, suggesting they interact with other variables analyzed. Given the findings here, it appears that patients with markers for more severe asthma (eg, lower FEV_1 and previous ED visits) are at a higher risk for larger bronchial reactions during ASA challenge. For safety concerns, only patients with well-controlled asthma, as assessed based on current symptoms and medication use, are allowed to begin an oral ASA challenge.[19] Patients with a baseline FEV_1 of less than 60% are usually excluded from even starting oral ASA challenges, and therefore this patient characteristic could not be analyzed meaningfully because of the small number of patients.

Interestingly, previous use of corticosteroids, whether in bursts or used continuously, did not predict an increased risk of a severe bronchial reaction during oral ASA challenges. In our database patients were asked to report corticosteroid use without identifying the reason for use. Given that a large number of patients are referred for ASA desensitization for treatment of overwhelming sinus and nasal polyp disease, it is likely that a significant proportion of corticosteroid use was for treatment of upper airway disease rather than for asthma. As such, corticosteroid use appears to be a less important indicator of asthma severity during oral ASA challenges.

Weaknesses of this type of study include the retrospective nature of the data collection. Since data collection began, newer measures of assessing asthma severity and control, such as exhaled nitric oxide and sputum eosinophil count measurements, have received increased attention and more widespread use in research studies. However, to our knowledge, a large prospective cohort of patients with AERD followed at only 1 institution from the onset of disease to oral ASA challenge does not exist.

In conclusion, desensitization to ASA with subsequent maintenance therapy improves the clinical course of most patients with AERD, and this study will assist allergists in performing efficient challenge and desensitization procedures that minimize the risk of a severe bronchospastic reaction. The effort involved in performing ASA challenges and desensitization procedures has hindered allergists' ability to confirm the diagnosis of AERD in patients with a suggestive clinical history. Many patients who undergo ASA desensitization have relatively mild responses during their clinical challenges. However, in patients with multiple risk factors, addition of an LTMD before challenge, starting with 30 mg of ASA and a more gradual increase in ASA doses, is appropriate. For patients without risk factors, starting ASA challenges with 40 to 60 mg seems reasonable and is likely to apply to almost half of the patients undergoing oral ASA challenges. As with all ASA challenges and other procedures performed in the course of practicing allergy and immunology, it is important to have in place safeguards to assist in preparing for a reaction with a larger decrease in FEV_1. These measures include intravenous access, adequate training of support staff in recognizing ASA-induced respiratory reactions, and the availability of medications to treat the symptoms as they occur. In future studies, we hope to validate this approach if instituted in a prospective manner.

Clinical implications: Identification of patient risk factors for more severe bronchial reactions, combined with efficient selection of ASA dosing, offers the potential for significant time savings during oral challenges for AERD.

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