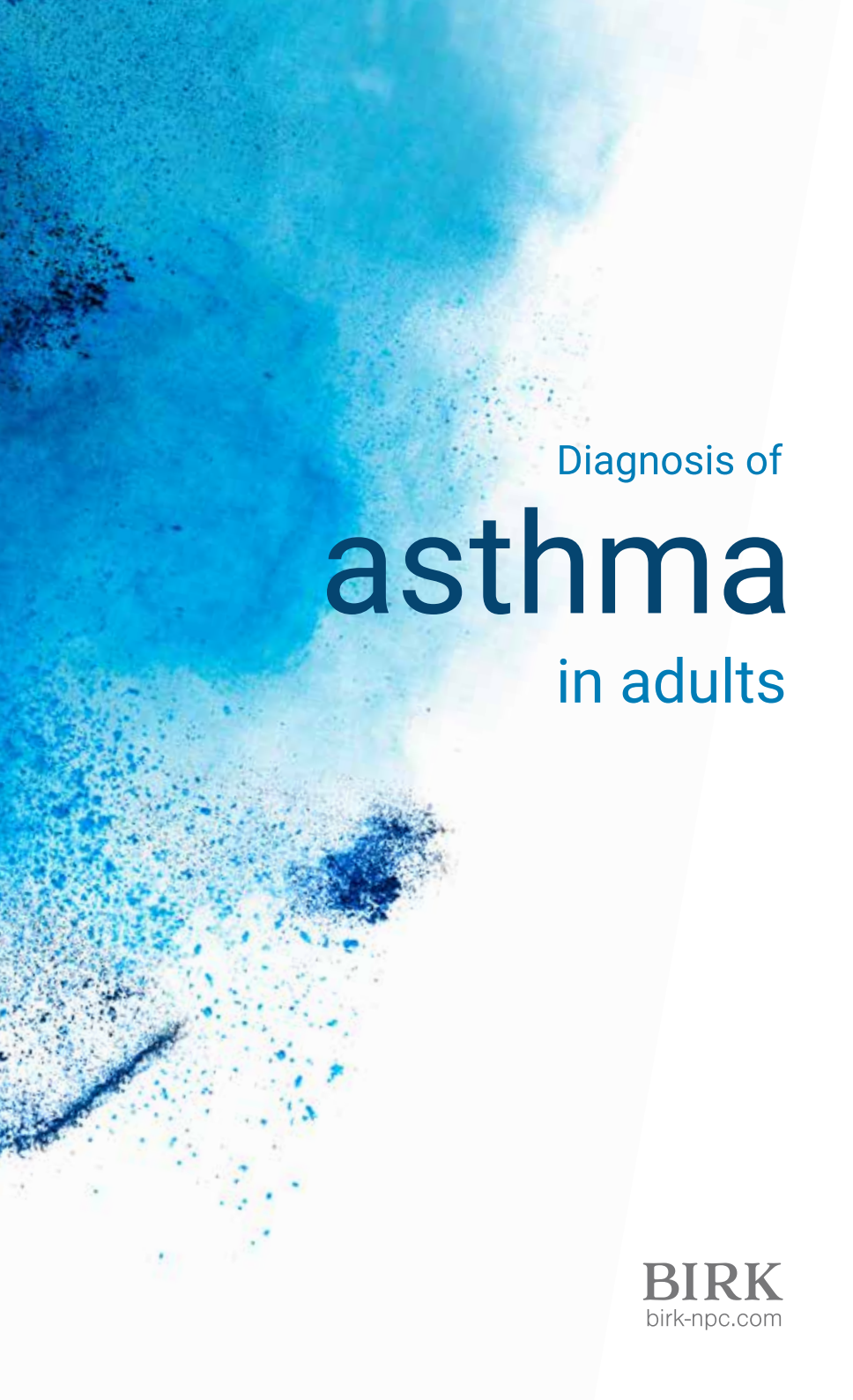

Diagnosis of asthma in adults

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This document is prepared in collaboration with Prof. Sandra Anderson (Sydney, Australia), Prof. Vibecke Backer (Copenhagen,Denmark), Prof. Leif Bjermer (Lund, Sweden) and Prof. emeritus Malcom Sue-Chu (Trondheim, Norway) for use together with the accompanying table “Diagnosis of asthma in adults”.[1]

Diagnosis of asthma in adults

Breathlessness, wheeze, chest tightness or cough in all decades of life can be the presenting complaint of asthma. However, none of these symptoms is specific for asthma; although wheeze is a cardinal symptom of asthma, all that wheezes is not asthma.

Asthma is both over- and underdiagnosed.[2] Collation of the presenting complaint with symptom history, clinical examination of the thorax, and tests of respiratory physiology and for allergy and marker of T2 airway inflammation minimizes the risk for over-and underdiagnosis of asthma. The likelihood of asthma as the cause of the presenting complaint increases in the presence of the following salient features.

SYMPTOM HISTORY

Symptoms can be episodic or chronic with acute exacerbations. They can be triggered by respiratory virus infection or after exposure to and inhalation of naturally occurring or occupational allergens, and air pollutants, exercise in low humidity environments, and ingestion of NSAIDs in susceptible individuals (NERD - NSAID exacerbated respiratory disease). The onset of symptoms is 10-15 minutes after exercise and 30 minutes - 3 hours after ingestion of an NSAID.

CLINICAL EXAMINATION OF THE THORAX

On auscultation, there may be normal breath sounds or adventitial sounds. The presence of the former does not exclude asthma in patients with episodic symptoms or chronic symptoms without an acute exacerbation. Adventitial sounds are bilateral and may manifest as a prolonged expiratory phase or wheeze on normal or forced expiration or as rhonchi and wheeze heard on expiration and inspiration or on expiration during normal expiration. In an acute exacerbation with respiratory distress, the silent chest, with very diminished breaths sounds, may be present.

Respiratory physiology tests include spirometry, reversibility test and bronchial provocation tests.

SPIROMETRY

Spirometry should be performed in accordance with the ATS and ERS technical statement.[3]

The steps in the assessment of spirometry are:

1. Confirmation of the correctness of patient details of age, height, sex, and ethnicity.
2. Inspection of the volume time curve to confirm that the duration of expiratory time is at least 6 seconds.
3. Inspection of the flow volume curves in expiration and inspiration for artifacts, such as delay in start of forced expiration, cough, and glottis closure, and for normality of shape.
4. In the absence of artifacts, values for FEV_1/FVC, FEV_1 and FVC are evaluated to determine if they are above or below the lower limit of normal (LLN). The LLN was previously defined as 0.7 for FEV_1/FVC and as 80% of predicted value for FEV_1 and FVC. However, the Global Lung Initiative now recommends that LLN is defined by the Z-score, which is computed from the measured and predicted values and the residual standard deviation ((measured – predicted) / standard deviation). A Z-score of -1.64 is at the 5th centile and is defined as the LLN, and a Z- score lower than -1.64 is out with the normal range and is abnormal.

Probability of asthma

The presence of a concave shape in the flow volume curve during expiration, an FEV_1 below the LLN and FEV_1/FVC ratio of < 0.7 or 5th percentile of predicted is compatible with an obstructive ventilatory limitation and an increased probability of asthma. In contrast, the presence of normal values for FEV_1/FVC, FEV_1 and FVC does not exclude asthma in a patient with episodic symptoms.

REVERSIBILITY TEST

This test is indicated when there is evidence of an obstructive ventilatory limitation on spirometry and assesses the effect of 400 µg salbutamol aerosol on the FEV_1.

After an incomplete expiration 100 µg salbutamol aerosol is inhaled from a valved spacer device in one breath to total lung capacity and a breath hold of 5-10 seconds. This is repeated three times, with an interval of 30 seconds between inhalations. Spirometry is performed 10-15 minutes after the last inhalation.

Probability of asthma

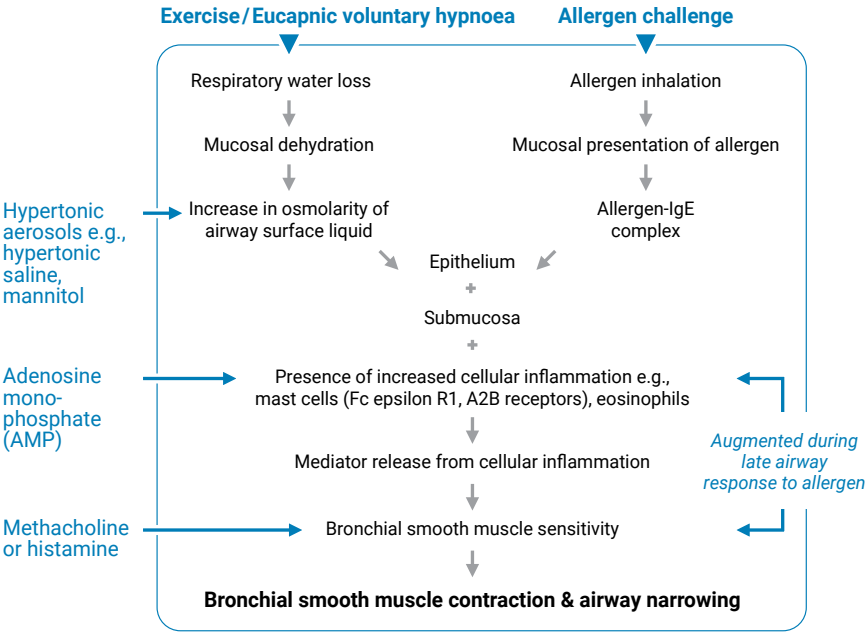
A positive test, defined as an increase in FEV_1 by ≥ 12% and ≥ 200 mL from baseline value, is compatible with an increased probability of asthma as the cause of the presenting complaint. In contrast, the probability of asthma is not excluded by a negative test.

BRONCHIAL PROVOCATION TEST

The responsiveness of the airways to chemical and physical stimuli is greater in patients with asthma than in non-asthmatic subjects. However, there is considerable variability in the airway responsiveness to the different stimuli, both between and within asthma patients.

Airway hyperresponsiveness (AHR) is the increased responsiveness to these stimuli. It is a characteristic finding in patients with asthma, is a manifestation of a dysfunction of the airway smooth muscle and is associated with T2-high and T2-low airway inflammation.

FIGURE 1. Mechanism of action of direct and indirect bronchial provocation stimuli[4]



Adapted from Brannan JD, Lougheed MD and reproduced with permission.[4]

A bronchial provocation test assesses the responsiveness of bronchial smooth muscle to contract on exposure to a stimulus. Based on the mechanism of action, the latter is classified as a direct or indirect stimulus. Inhaled methacholine has a similar action to other muscarine agonists such as acetylcholine and binds directly to the muscarinic M3 receptor and is classified as a direct stimulus. The degree of hyper-responsiveness is independent of presence of inflammatory cells in the airway mucosa.

Indirect stimuli

Indirect bronchial provocation tests include exercise, eucapnic voluntary hyperpnea (EVH) and dry powder mannitol. These tests have a high specificity for identifying currently active asthma and there is a low rate of false positive tests. Importantly a negative result in a subject currently taking anti-inflammatory treatment does not rule out an asthma diagnosis. In a subject with known asthma a positive test result may suggest lack of adherence to treatment or a suboptimal dose of treatment.

In contrast to provocation with methacholine, a positive response to an indirect stimulus only occurs if there is increased cellular inflammation. These indirect stimuli increase the osmolarity of the airway surface liquid directly (mannitol) or via respiratory water loss and mucosal dehydration (exercise and EVH). An increase in osmolarity in the presence of cellular inflammation in the submucosa, results in the release of mediators, such as leukotrienes, histamine and prostaglandins, from mast cells and eosinophils. These mediators cause contraction of the bronchial smooth muscle with subsequent airway narrowing which is manifested by a fall in FEV_1 (figure 1).

It is essential that vigorous exercise is not undertaken within 4 hours of an indirect bronchial provocation test because of possibility of (cross-) refractoriness.

Patient preparation for bronchial provocation tests

Adherence to the withholding times for medication, caffeine, and vigorous exercise (table 1) should be observed to avoid a false negative test.

Airway responsiveness is transiently increased after a viral infection of the upper and lower respiratory tract. Bronchial provocation tests should be delayed for at least 6 weeks after a respiratory tract infection to avoid a false positive test.

TABLE 1. Withholding times prior to provocation test[5,6]

		Withholding time (hours)	
		Methacholine[5]	Exercise/EVH/ Mannitol[6]
SABA	Salbutamol, Terbutaline	6	8
LABA	Salmeterol, Formoterol	36	36
ULABA	Indacaterol, Olodaterol, Vilanterol	48	48
SAMA	Ipratropium	12	12
LAMA	Tiotropium, Glycopyrronium, Aclidinium, Umeklidinium	≥ 168	72
Theophylline		12-24	24
Budesonide, fluticasone proprionate Beclomethasone		Continue	6
Fluticasone furoate, Ciclesonide, Mometasone		Continue	24
Leukotriene Receptor Antagonists e.g. Montelukast		Continue	96
Antihistamines e.g. Teldane, Loratadine etc.		Continue	72
Cromones e.g. Sodium cromoglycate, Nedocromil		Continue	4
Caffeine		Not applicable	24
Vigorous exercise		1*	4
Cigarette smoking, vaping, water pipe use		1*	1*

SABA: Short-acting beta 2 agonist; LABA: Long-acting beta 2 agonist; ULABA: Ultra long-acting beta 2 agonist; SAMA = short-acting muscarinic antagonist; LAMA: Long-acting muscarinic antagonist

* ATS criteria prior to spirometry[3]

Adapted from Coates AL, Wanger J, Cockcroft DW, et al[4] and Hallstrand TS, Leuppi JD, Joos G, et al.[6]

Measurement of the response to a stimulus in bronchial provocation tests

The response to a provoking stimulus is measured by the change in FEV_1 from the baseline value.

On the day of the test, baseline FEV_1 is determined by the performance of flow volume spirometry in triplicate and in accordance with ATS criteria.[2] The three values for FEV_1 and FVC should agree to within 150 ml, and the highest FEV_1 value is selected as the baseline value. The highest value of FEV_1 from spirometry in duplicate with an exhalation time of more than 2 seconds and with a difference of < 150 ml is selected at each test interval.

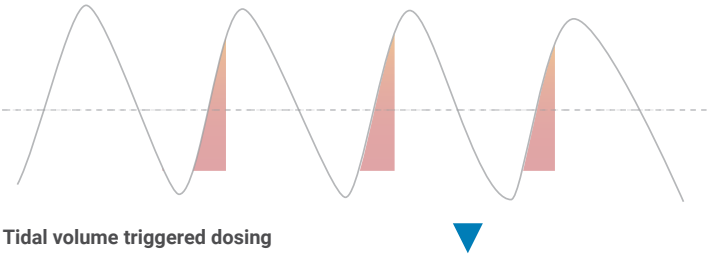
METHACHOLINE TEST

The methacholine inhalation challenge test is widely used both in clinical and in research settings to measure direct airway responsiveness. The degree of hyperresponsiveness is measured as the cumulative dose (PD20) needed for to induce a 20% drop in FEV_1 compared to the baseline value after the inhalation of 0.9% NaCl.

Performance of Methacholine test

The protocol for Methacholine and Provocholine™ is shown in figure 2. At each step, the dosimeter is triggered by inhalation and the delivered dose is determined by the concentration of Methacholine solution (mg/ml), the output of the nebuliser (µL), nebulization time (s) and the number of breaths. Methacholine aerosol is delivered during the inspiratory phase of tidal volume breathing and the response is assessed by the decline in FEV_1 at 60 seconds after dose delivery. The test is stopped when the decline in FEV_1 is greater than 20% from the baseline value after inhalation of 0.9% NaCl.

FIGURE 2. Schematic of PD_{20} Methacholine test



Tidal volume triggered dosing

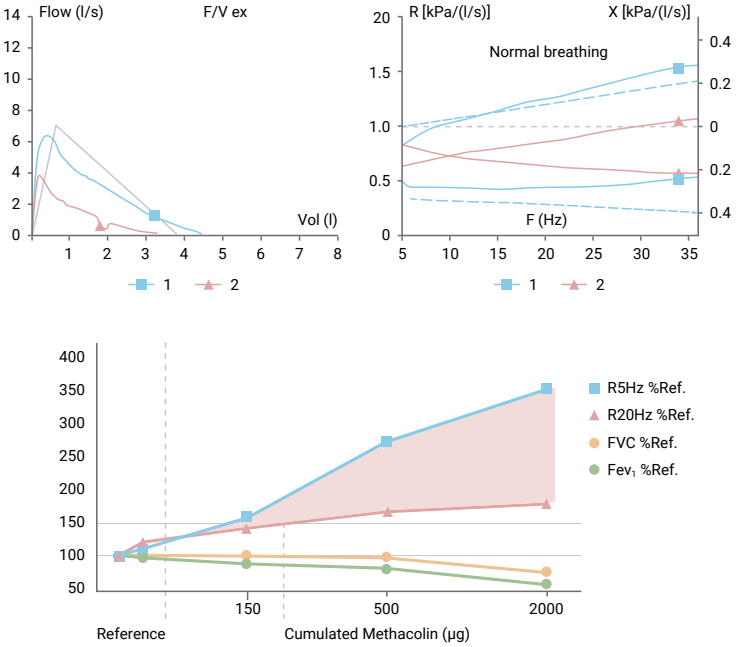
Methacholine/Provocholine™

Substance	Conc	No actuations	Dose µg	Cumulated dose µg
NaCl	0.9%	3	-	-
Metacholine	2 mg/ml	2	15	15
	2 mg/ml	4	30	45
	2 mg/ml	8	60	105
	2 mg/ml	16	120	225
	16 mg/ml	3	180	405
	16 mg/ml	6	360	765
	16 mg/ml	12	720	1485

Combining flow volume spirometry with forced oscillometric technique (FOT) / impulse oscillometry (IOS) to assess the response

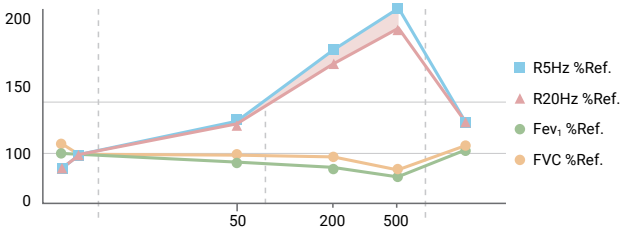
The concomitant use of IOS with flow-volume spirometry provides valuable information that helps to distinguish asthma from other conditions where a fall in FEV_1 may be a false positive. A typical asthma reaction includes obstruction in the small airways measured as increase in R5-R20 [frequency dependent resistance (FDR)] while other conditions, such as rhinitis with positive FEV_1 response without symptoms, induces increased resistance in the proximal airways (R20Hz) and no increase in FDR.

FIGURE 3. A typical example of a patient with asthma



A typical example of a patient with asthma. A fall in FEV_1 and volume response measured as fall in FVC together with an increase of peripheral resistance (R5Hz). Note that the peripheral resistance increases before there is a significant fall in FEV_1.

FIGURE 4. A patient with proximal obstruction



A patient with proximal obstruction. No asthma symptoms but occasional cough when exposed to irritants. Note that there is no increase in FDR.

EUCAPNIC VOLUNTARY HYPERPNEA TEST (EVH)

EVH with dry air containing 5% CO_2 is a surrogate test for exercise to identify exercise-induced bronchoconstriction (EIB) in individuals without asthmatic symptoms and exercise-induced asthma in individuals with asthmatic symptoms.

Equipment

The minimal equipment requirements are a source of the gas mixture, a system for delivery of the mixture and for measurement of minute ventilation during the test, and a mouthpiece with a two-way valve with low resistance and low dead space volume. A detailed description of the set-up of these component parts is given by Anderson et al[7] and Hull et al.[8] A compact pre-assembled system (Eucapsys™, SMTEC, Switzerland) is also commercially available.[9]

Performance of EVH test (table 2)

Flow volume spirometry is performed at baseline. The EVH test should only be performed in those with an FEV_1 within the normal predicted range , as severe responses can occur. Then with a nose clip in place, the subject is asked to hyperventilate a dry gas mixture of nitrogen (74%), oxygen (21%) and carbon dioxide (5%) over 6 minutes to achieve a target ventilation of 30 x FEV_1 l/min. Minute ventilation is recorded at 30 seconds intervals during the test. The test is considered satisfactory if the achieved average minute ventilation (VE) is ≥ 60% of maximum voluntary ventilation (MVV). The latter is defined as 35 x FEV_1.

After EVH, spirometry is performed at intervals of 3, 5, 7, 10, 15, 20 and 30 minutes. Then Salbutamol 0.4 mg from spacer is administered, with repeat spirometry after 10 minutes. At each interval, the best value of at least two acceptable FEV_1 tests with a difference of < 0.15 L is recorded.

Note on Safety

While thousands of EVH tests have been performed without serious unwanted side effects, EVH has the potential to provoke severe broncho-constriction, and for this reason a bronchodilator and supplemental oxygen should be available at the site of testing. It is recommended that, as with the performance of any other bronchial provocation tests, medical personnel and resuscitative equipment are readily available.

Assessment of response to EVH test[10]

A satisfactory provocation by eucapnic voluntary hyperpnea (EVH) is defined as one that achieves an average VE of 60 % of maximum voluntary ventilation (MVV) over 6 minutes. MVV is approximately 35 times FEV_1 in litres.

The maximum response of FEV_1 to EVH usually occurs 3 to 10 minutes after the end of the challenge. However, a fall in FEV_1 may occur as late as 20 minutes after the test.

A fall in FEV_1 of < 10% is defined as normal airway responsiveness to EVH. Presence of airway hyperresponsiveness (AHR) is defined as a fall in FEV_1 of ≥ 10% that is sustained over ≥ 2 consecutive intervals.[6] Grading of AHR as mild, moderate, and severe is determined by the average V_E, expressed as % MMV, and the maximal fall in FEV_1 (ΔFEV_1) after the challenge.[4]

TABLE 2. Worksheet for EVH test

Spirometry	FEV_1 (L)	ΔFEV_1 (%)*	FVC (L)	FEF_{25-75} (L/sec)
Baseline				
	Perform test only if FEV_1 is above LLN (Z-score is above -1.64)			
- 3 min post EVH				
- 5 min post EVH				
- 7 min post EVH				
- 10 min post EVH				
- 15 min post EVH				
- 20 min post EVH				
- post Salbutamol**				

EVH test	Target VE = greater than or equal to (Baseline FEV_1 (BTPS) x 21		=		L/min
	Predicted MVV = Baseline FEV_1 (BTPS) x 35		=		L/min
time (min)	VE (L/min)	Average VE		≥ 60% MVV	
		L/min	%MVV	No ☐	Yes ☐
0.5		Assessment of EVH test			
1.0		%MVV	Δ FEV1 (%)* (≥ 2 consecutive intervals)	Conclusion	
1.5		≥ 60	< 10%	Normal	
2.0			≥ 10% - < 20%	Mild AHR	
2.5			≥ 20% - < 30%	Moderate AHR	
3.0			≥ 30%	Severe AHR	
3.5		< 60	< 10%	Inconclusive	
4.0			≥ 30%	Severe AHR	
4.5		≥ 30 - < 60	≥ 10% - < 30%	Moderate AHR	
5.0			≥ 10% - < 30%	Severe AHR	
5.5		< 30	≥ 10% - < 30%	Severe AHR	
6.0		≥ 12% after Salbutamol ** from lowest FEV_1 or lability index ≥ 20% *** supports an EIA/EIB diagnosis			

* $\Delta FEV_1 (\%) = \frac{(FEV_1 \text{ at Baseline} - FEV_1 \text{ at interval after EVH}) \times 100}{FEV_1 \text{ at Baseline}}$

** at 10 minutes after 0.4 mg Salbutamol from spacer

*** ΔFEV_1 (%) after Salbutamol + ΔFEV_1 (%) post EVH

DRY POWDER MANNITOL PROVOCATION TEST

Performance of test

The test protocol is shown in table 3 and each step of the test is illustrated in figure 6. FEV_1 after inhalation of 0 mg Mannitol is defined as the baseline value. The test is stopped when Δ FEV_1 exceeds 15%. Salbutamol 0.2 mg is administered from spacer after the test if Δ FEV_1 is ≥ 10%.

TABLE 3. Performance test – protocol

Inhalation	Capsule (mg)	Cumulative dose (mg)	FEV_1*	Δ FEV_1**
1	0	0		
2	5	5		
3	10	15		
4	20	35		
5	40	75		
6	2 x 40	155		
7	4 x 40	315		
8	4 x 40	475		
9	4 x 40	635		

* FEV_1 x 2 at 60 s post inhalation, use highest value of FEV_1

** Δ FEV_1 = % decrease in FEV_1 relative to baseline FEV_1

$$= \frac{(FEV_1 \text{ at Baseline} - FEV_1 \text{ after dose})}{FEV_1 \text{ at Baseline}} \times 100$$

FIGURE 6. Illustration of steps in inhaled Mannitol test[11]

1. Remove cover

2. Open

3. Insert capsule

4. Close

5. Perforate capsule

6. Tilt inhaler, apply nose clip, perform full exhalation away from inhaler

7. Rapid deep inhalation followed by breath hold for 5 seconds, then normal breathing

8. Check that capsule is empty. If not empty, repeat steps 6 & 7, using same capsule

Adapted from Test Instructions » Aridol[11]

Assessment of response to Mannitol provocation test

A negative test is defined as a Δ FEV_1 of < 15% after a cumulative dose of 635 mg.

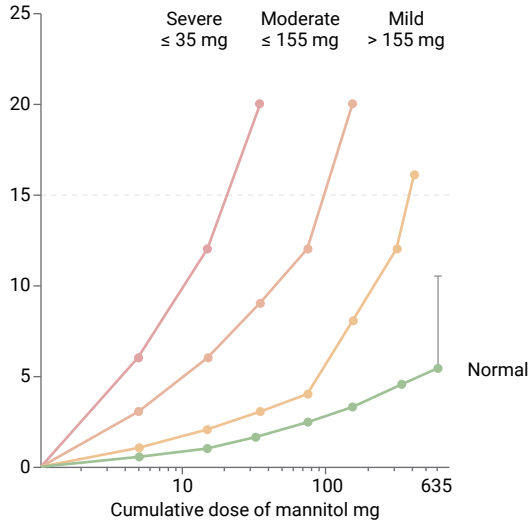
A positive test is defined as Δ FEV_1 of ≥ 15% or a 10% decrease in FEV_1 between two consecutive mannitol doses.

A positive test "rules in" a diagnosis of asthma. However, a negative test does not "rule out" a diagnosis of asthma.

The severity of AHR to mannitol is classified by the provocative cumulative dose that causes a 15% fall in FEV_1 from baseline (PD_{15}) which is derived from the dose-response curve.

AHR to mannitol is mild with a PD_{15} > 155 mg, moderate with a PD_{15} > 35 and ≤ 155 mg or severe with a PD15 ≤ 35 mg.

FIGURE 7. Severity of AHR to Mannitol[11]



Reproduced with permission and adapted from Test Instructions » Aridol[11]

EXERCISE TEST

Performance of test

The exercise test consists of a run on a 10% slope on a treadmill for 6 minutes in children, 7 minutes in adolescents and 8 minutes in adults. The speed should be adjusted to maintain the heart rate at 80% of the maximum heart rate. A constant ambient air temperature and relative humidity of 21 °C and 40-50%, respectively, are preferable.

Note on safety

It is recommended that the patient wears a belt which is connected to a line that is attached to the ceiling.

Assessment of response to exercise test

FEV_1 should be measured before the test, immediately after (time 0) and after 3, 5, 10, 15, 20 and 30 minutes. The highest value of three FEV_1 measurements at each point is used for analysis.

Decrease in FEV_1 at each point is calculated as follows:

(FEV_1 before exercise – FEV_1 after exercise / FEV_1 before exercise) x 100%.

A decrease of at least 10% over 2 consecutive time points is often defined as exercise-induced broncho-constriction (EIB), whereas a decrease of 15% or more often is defined as exercise-induced asthma (EIA), not least when the patient suffers of asthma symptoms.

A positive EIB test supports the asthma diagnosis but does not exclude EIA. When the direct EIB test is negative, increased variability, i.e., a β2 reversibility of ≥12% or a lability index ≥ 20% (defined as (Δ FEV_1 (%) after Salbutamol + Δ FEV_1 (%) post EVH) supports a diagnosis of EIA/EIB.

BIOMARKER

$FeNO_{50}$ is a biomarker of T2-driven airway inflammation, which can be measured noninvasively and safely. Measurement of $FeNO_{50}$ is always performed prior to spirometry and in accordance with 2005 ATS/ERS recommendations for standardized procedures.[12]

In the proper clinical context of auscultatory findings and respiratory physiology tests, an FeNO50 level of > 50 ppb increases the probability that the clinical history is compatible with asthma which is responsive to inhaled corticosteroid therapy.[13]

ALLERGY INVESTIGATION

Symptoms of rhinoconjunctivitis on exposure to seasonal and/or perennial allergens should be investigated with skin prick tests or serological tests for specific IgE to inhalational allergen panels that are specific for that region. Positive tests with symptoms of rhinoconjunctivitis and respiratory symptoms in the allergen season increases the probability of an asthma diagnosis.

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