

Diagnosing Asthma. Spirometry is Normal, Now What?



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Disclaimer

I recognize that I must follow all guidelines and criteria regarding vested interest. I have the following real or perceived conflicts of interest that relate to this presentation:

I am an employee of Methapharm Respiratory, Inc. manufacturer and distributor of Provocholine® and distributor of Vivatmo pro

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Objectives

Discuss the role of bronchial challenge testing in the diagnosis of asthma

Identify the differences between direct and indirect bronchial challenge tests and when to utilize each

Recognize and discuss the technical standards and guidelines for performing bronchial challenge tests

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I work in Pulmonary Function:

- A. Yes
- B. No
- C. Previously
- D. Hope to in the future

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Is it Asthma?

Patient Presentation, Primary Care

- 25 y/o female
- Full-time Paralegal in a large, busy law office
- Presents with complaints of shortness of breath, chest tightness, occasional daytime cough, nocturnal cough, feels she wheezes at times
- Symptoms appear to be random, no identified triggers

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Question 1

Patient Presentation

First step(s) at the initial visit:

- A. Gather detailed medical history
- B. Physical exam
- C. Spirometry
- D. All of the above



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Question 1

Patient Presentation

First step(s) at the initial visit:

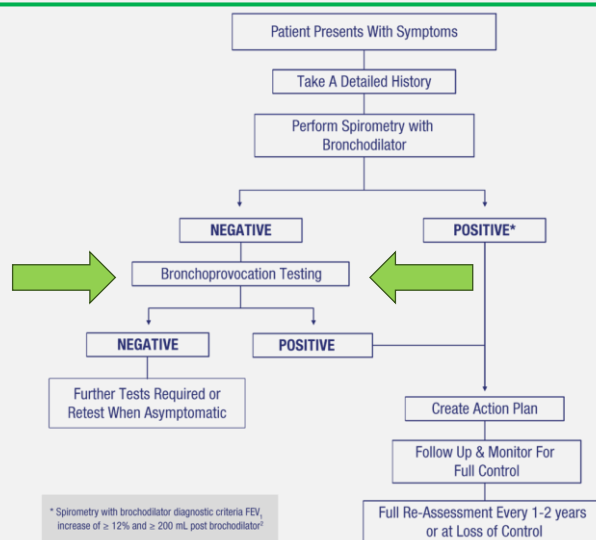
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Diagnosing Asthma



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Question 2

Patient Presentation

Spirometry values are inconclusive.

Next step:

- A. Send patient home with a SABA PRN trial
- B. Send patient to pulmonologist for further evaluation
- C. Refer patient to hospital pulmonary function lab for further testing with bronchodilator challenge
- D. Start patient on ICS and follow up in 4-6 weeks



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Test

Spirometry pre and post bronchodilator

What is it? Measures how an individual inhales or exhales volumes of air as a function of time

Why do it? Valuable as a screening test for:

- ✓ general respiratory health
- ✓ evaluate symptoms, signs or abnormal laboratory tests
- ✓ measure the effect of disease on pulmonary function

Procedure three distinct phases:

- 1) maximal inspiration
- 2) a "blast" of exhalation
- 3) continued complete exhalation to the end of test



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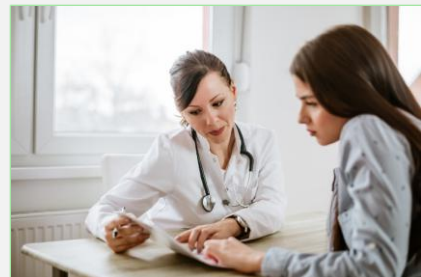
Question 3

Patient Presentation

Spirometry pre and post bronchodilator performed at hospital. Results are inconclusive. Patient reports continued periodic symptoms.

Next step(s):

- A. Refer to asthma allergy or pulmonology
- B. Trial SABA PRN
- C. Trial SABA/ICS
- D. Send for bronchoprovocation testing
- E. A or D



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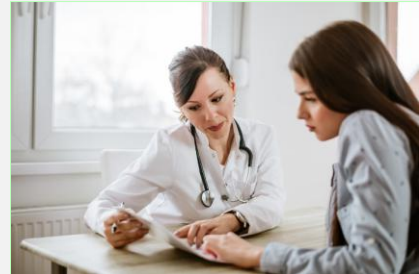
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- C. Trial SABA/ICS
- D. Send for bronchoprovocation testing
- E. **A or D**



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All that Wheezes is Not Asthma!

Asthma Mimics

- Congestive Heart Failure
- Vocal Cord Dysplasia
- Vocal Cord Paralysis
- Allergies
- GERD / Aspiration
- Sinusitis
- Myocardial Ischemia
- Bronchiectasis
- Tumors
- Pulmonary Aspergillosis



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Question 4

Bronchial Challenge Testing

There are 2 categories of bronchial challenge testing.

- A. True
- B. False



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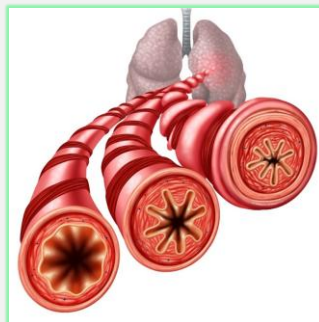
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Question 4

Bronchial Challenge Testing

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- A. True
- B. False

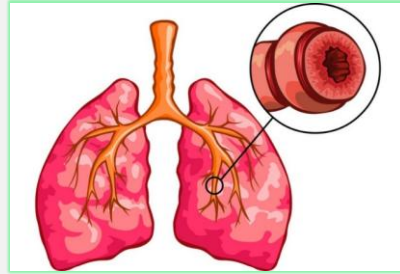


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Direct and Indirect Challenge Testing

Direct stimuli act **directly** on the bronchial smooth muscle to cause bronchoconstriction in susceptible individuals (i.e. methacholine)



Indirect stimuli (via the release act **indirectly** of inflammatory mediators) to cause bronchoconstriction in susceptible individuals (i.e. mannitol)

Bronchoconstriction is measured by performing spirometry to measure lung function (FEV_1)

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Direct and Indirect Challenge Testing Mechanism of Action

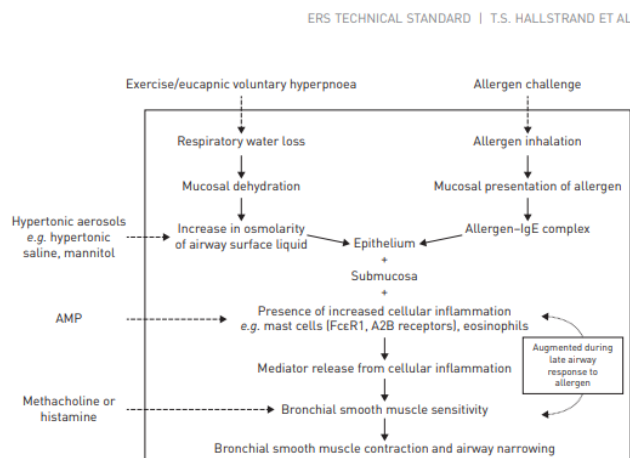


FIGURE 2 Mechanisms of action of indirect challenge tests used in the clinical and research setting. In contrast to the indirect mechanisms of indirect airway hyperresponsiveness, methacholine and histamine are examples of direct challenge tests that cause airway narrowing directly through airway smooth muscle contraction. Reproduced and modified from [4] with permission from the publisher.

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Direct Bronchial Challenge Tests

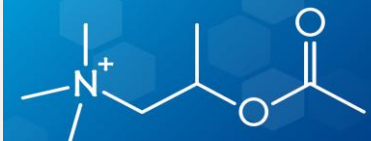
asthma bronchoconstriction
 bronchialchallenge fiveminutes
 direct pediatrics
 histamine sensitive spirometry global
 negativepredictivevalue nebulizer
 coach timing encourage concentrations
 thirtyseconds safe fev adults
 nintyseconds airwayhyperresponse
 dose-response rule-out methacholine

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Direct Bronchial Challenge Tests

METHACHOLINE CHLORIDE



HISTAMINE



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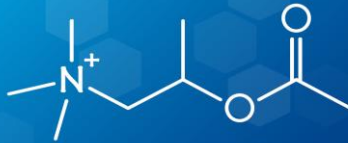
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Direct Bronchial Challenge Tests

Indications -

- Used in the diagnosis of bronchial airway hyperreactivity in subjects who do not have clinically apparent asthma

METHACHOLINE CHLORIDE



HISTAMINE



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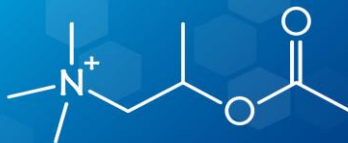
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Direct Bronchial Challenge Tests

Pediatrics

- Methacholine Chloride is approved for patients 5 years of age and older and may be performed in children who can perform good quality spirometry or body plethysmography

METHACHOLINE CHLORIDE



HISTAMINE



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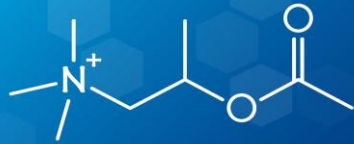
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Methacholine Challenge Test

Safety

- 100,000s of MCTs have been performed without serious side-effects.
- Reported symptoms: Transient, generally mild, wheezing, cough, dyspnoea and chest tightness.
- Delayed or prolonged responses to methacholine are rare

METHACHOLINE CHLORIDE



HISTAMINE



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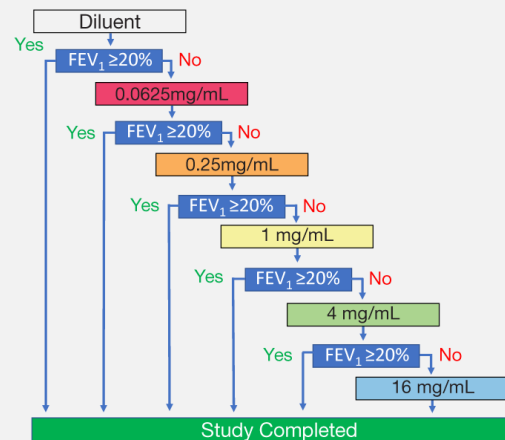
Methacholine Challenge Test

Procedure

- Dose response challenge
- Pre-challenge Spirometry
- Establish baseline FEV₁
- Deliver increasing doses of methacholine followed by spirometry to evaluate FEV₁
- $\geq 20\%$ fall in FEV₁ from baseline is a positive challenge

Methacholine Administration Steps

ATS Short Protocol



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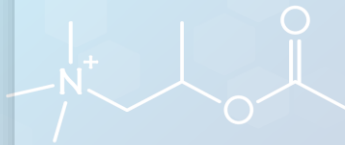
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Histamine Challenge Test

Pediatrics

- Histamine can be used on children

METHACHOLINE CHLORIDE



HISTAMINE



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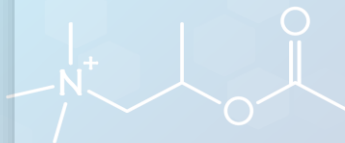
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Histamine Challenge Tests

Procedure

- Dose response challenge
- Pre-challenge Spirometry
- Establish baseline FEV₁
- Deliver increasing doses of histamine followed by spirometry to evaluate FEV₁
- ≥20% fall in FEV₁ from baseline is a positive challenge

METHACHOLINE CHLORIDE



HISTAMINE



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Question 5

Direct Challenge Tests

Direct Challenge Tests

- A. Directly stimulate smooth muscles cells
- B. May cause inflammation
- C. May cause airway hyperresponsiveness
- D. All of the above

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Question 5

Direct Challenge Tests

Direct Challenge Tests

- A. Directly stimulate smooth muscles cells
- B. May cause inflammation
- C. May cause airway hyperresponsiveness
- D. All of the above

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Indirect Bronchial Challenge Tests

confirm pediatrics bronchoconstriction
 mannitol airwayhyperresponse
 exercise timing
 asthma safe adults inflammation
 hypertonicssaline specific rule-in
 evh treadmill
 indirect postivepredictivevalue fev
 bronchialchallenge coach bike
 encourage
 spirometry

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Question 6 Indirect Challenge Tests

Indirect challenge tests

- A. Are easier to perform than direct challenge tests
- B. Do not require spirometry
- C. Stimulate the release of inflammatory mediators
- D. All of the above

Hallstrand TS, Leuppi JD, Joos G, et al. ERS technical standard on bronchial challenge testing: pathophysiology and methodology of indirect airway challenge testing. Eur Respir J 2018

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Question 6

Indirect Challenge Tests

Indirect challenge tests

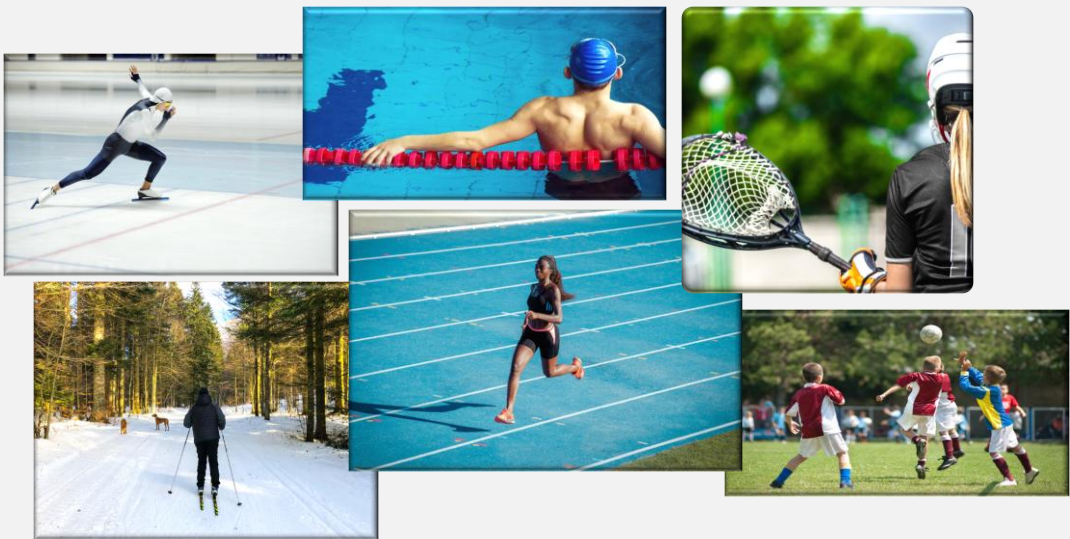
- A. Are easier to perform than direct challenge tests
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Indirect Bronchial Challenge Tests

Exercise Induced Bronchoconstriction



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Indirect Bronchial Challenge Tests

Exercise Induced Bronchoconstriction

ATS Guideline Recommendations

- The diagnosis of EIB is established by changes in lung function provided by exercise, not on the basis of symptoms alone.
- Spirometry after a specific challenge to determine if EIB is present and to quantify the severity of the disorder.

Exercise Induced Bronchoconstriction

- Formerly Exercise-Induced Asthma
- Narrowing of the airways causing asthma-like symptoms after exercise
- Symptoms typically present 15 minutes after exercise and self resolves within 60 min

EIB Prevalence

- Common in all level of athletes
- Varies by sport
- More common in female athletes
- 10-20% of children
 - higher in girls
 - higher in urban settings
- 19.4% of adults without hx of asthma

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Indirect Bronchial Challenge Test

Exercise Challenge



Eucapnic Voluntary Hyperpnea



Mannitol



Hypertonic Saline



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Indirect Bronchial Challenge Test

Exercise Challenge



- High intensity exercise to replicate the physiological response specific to individual sport
- Gives a real-life look at cause of symptoms
- Guidelines are well defined and current
- Used in pediatric and adult patients

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Indirect Bronchial Challenge Test

Exercise Challenge



Procedure

- Patient exercises until a specific heart rate or respiratory rate has been maintained for 4-6 minutes

Measurement

- Measure FEV_1 immediately and at 3, 6, 10, 15, & 30 min
- Continue to measure FEV_1 all the way to 30 min to capture severity of bronchoconstriction
- A 10% drop of FEV_1 from baseline = positive test

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Indirect Bronchial Challenge Test

Exercise
Challenge

Eucapnic Voluntary
Hyperpnea



Mannitol

Hypertonic
Saline

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Indirect Bronchial Challenge Test

Eucapnic Voluntary
Hyperpnea



- Creates response similar to exercise without stress of exercise
- Yields faster results than an exercise challenge through the patient's voluntary maximum ventilation efforts
- Does not require space for exercise equipment

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Indirect Bronchial Challenge Test

Eucapnic Voluntary Hyperpnea



Procedure

- Patient breaths dry air containing 5% CO₂ at 85% MVV for 6 minutes

Measurement

- FEV₁ is measured immediately post-test and at 3,6,10,15 and 30 minutes
- Positive EVH if FEV₁ falls $\geq 10\%$ from baseline

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Indirect Bronchial Challenge Test

Exercise Challenge

Eucapnic Voluntary Hyperpnea

Mannitol



Hypertonic Saline

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Indirect Bronchial Challenge Test

Mannitol



- Incremental dose response challenge
- Patient is not required to exercise
- No capital equipment, treadmill, bike needed
- Useful to establish treatment and step up/down of ICS

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Indirect Bronchial Challenge Test

Mannitol



Procedure

- Deliver dose via dry powder inhaler
- Increasing concentration (0mg, 5, 10, 20, 40, 80, 160, 160, 160mg)

Measurement

- FEV₁ 60 seconds post each dose
- Two maneuvers, the highest FEV₁ is reported
- A drop of 15% from baseline FEV₁
- Or 10% between consecutive doses = positive test

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Indirect Bronchial Challenge Test

Exercise
Challenge

Eucapnic
Voluntary
Hyperpnea

Man

Hypertonic
Saline



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Indirect Bronchial Challenge Test

Hypertonic
Saline



- Incremental dose response challenge
- Quick and simple
- Does not require capital equipment
e.g. treadmill or stationary bike
- Used in pediatrics and adults

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Indirect Bronchial Challenge Test

Hypertonic Saline



Procedure

- 4.5% hypertonic saline is delivered via ultrasonic nebulizer for increasing periods of time
- Breathing time is 30 seconds, 1, 2, 4 and 8 minutes

Measurement

- FEV₁ is monitored after each delivery step at 30 and 90 seconds
- Decrease > 15% from baseline = positive test
- Decrease 10-15% from baseline, repeat dose

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Additional Tests



Cold Air

FeNO

Oscillometry

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Additional Tests



Cold Air

Cold Air

- Cold air is added to the exercise challenge or EVH
- Cold air requires less time than EC or EVH alone
- A cold air generator is used to create temperatures of 14 - 4F/ -10 to -20 C

FeNO

- Nitric oxide (NO) is in exhaled breath
- Is a marker of inflammation
- Point of care test for asthma assessment

Oscillometry

- Measures the mechanical properties of the airways during passive breathing
- Uses oscillating pressure signal at the mouth

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Additional Tests



FENO

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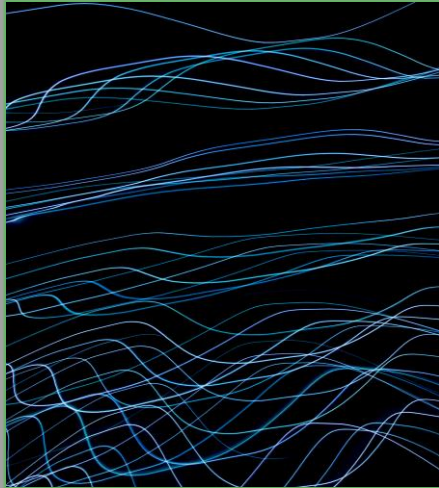
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Question 7 Patient Presentation

Patient returns to Pulmonologist. Test reviewed and results of MCT are negative, patient's FEV_1 did not decrease $\geq 20\%$. What else might the patient be diagnosed with?

- A. GERD
- B. Vocal Cord Dysfunction
- C. Anxiety
- D. All of the above



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Question 7

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- C. Anxiety
- D. All of the above



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Summary



Diagnosing Asthma

Should not be done based on symptoms alone

Bronchial Challenge Tests

Should be utilized when initial Spirometry with bronchodilator does not confirm or rule out asthma

Direct vs. Indirect

Depends on the patient, symptoms and question being asked

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Thank You

Contact Us:
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 800-287-7686 x 7338

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Resources

- Aaron, S.D., Vandemheen, K.L., FitzGerald, J.M., Ainsle, M, Gupta, S, Lemiere, C,...Boulet, L. (2017). Reevaluation of Diagnosis in Adults with Physician-Diagnosed Asthma. *Jama*, 317(3):269-279. DOI 10.1001/jama.2016.19627
- Aridol US Package Insert (available for download at aridolchallenge.com)
- Coates AL, Wanger J, Cockcroft DW, et al. ERS technical standard on bronchial challenge testing: general considerations and performance of Methacholine challenge tests. *Eur Respir J* 2017;49:1601526
- Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention 2023. Updated July 2023. Available from : www.ginasthma.org
- Hallstrand TS, Leuppi JD, Joos G, et al. ERS technical standard on bronchial challenge testing: pathophysiology and methodology of indirect airway challenge testing. *Eur Respir J* 2018
- King GG, Bates J, Berger KI, et al. Technical standards for respiratory oscillometry. *Eur Respir J* 2020; 55: 1900753 [<https://doi.org/10.1183/13993003.00753-2019>]. ABSTRACT Oscillometry
- Use of Fractional Exhaled Nitric Oxide to Guide the Treatment of Asthma An Official American Thoracic Society Clinical Practice Guideline Sumita B. Khatri, Jonathan M. Iaccarino, Amisha Barochia, Israa Soghier, Praveen Akuthota, Anna Brady, Ronina A. Covar, Jason S. Debley, Zuzana Diamant, Anne M. Fitzpatrick, David A. Kaminsky, Nicholas J. Kenyon, Sandhya Khurana, Brian J. Lipworth, Kevin McCarthy, Michael Peters, Loretta G. Que, Kristie R. Ross, Elena K. Schneider-Futschik, Christine A. Sorkness, and Teal S. Hallstrand; on behalf of the American Thoracic Society Assembly on Allergy, Immunology, and Inflammation THIS OFFICIAL CLINICAL PRACTICE GUIDELINE OF THE AMERICAN THORACIC SOCIETY WAS APPROVED SEPTEMBER 2021

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