Methacholine Challenge Testing.

Review and 2017 ERS update

Tony Kajnar, RRT/AA, RCPT(P)
Senior Therapist, Sault Area Hospital PFT Lab
kajnart@sah.on.ca

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Affiliations

- Sault Area Hospital: Pulmonary Function Lab
- Canadian Pulmonary Function Symposium: CACPT
- RTSO: Pulmonary Diagnostics workgroup
- Consultant for Methapharm Inc

Objectives

- Review the importance of objective assessment and measurement for asthma
- Review the methacholine challenge test
- Patient preparation, contraindications and special considerations for the MCT
- Review key points from the 2017 ERS Methacholine Challenge Standard update

Impact of asthma: ICES

- Approximately 8.5% of Canadians have asthma. Source: administrative databases
- Objective lung function testing completed in < 50% of Primary Care Practitioner (PCP) diagnosed asthma, more study required to identify barriers
- Symptoms and need for treatment for asthma fluctuate vs other chronic diseases
- Rate of asthma difficult to determine without objective lung measurements

ICES 2012, 2006: Gershon AS, To T, Victor JC, Aaron SD

Re-evaluating Asthma Diagnosis

- 33% of adults diagnosed with asthma Primary Care Practitioners (PCP) did not have active asthma when objective measurements were completed during study
- Objective testing was not completed in 49% of these patients
- Many of these patients continued to use their medications despite their asthma being inactive
- Management of asthma requires confirmation of diagnosis. Objective measurement and reassessment recommended to establish and monitor.

JAMA 2017. Aaron SD, Vandemheen KL, FitzGerald JM.
JAMA 2017. Hollingsworth HM, O'Connor GT

Asthma: exam and history

Symptoms suggestive of asthma:

- Wheezing
- Shortness of breath (dyspnea), chest tightness
- Cough
- Symptoms increase with acute illness (colds), exercise, allergen exposure, weather/seasonal changes, laughter, exposure to irritants (fumes, fragrance, aerosols) or occupation

Related

- Atopy: allergic rhinitis, eczema
- Childhood or family history of asthma or atopy
- GERD
- Vocal cord dysfunction (VCD)
- Obesity

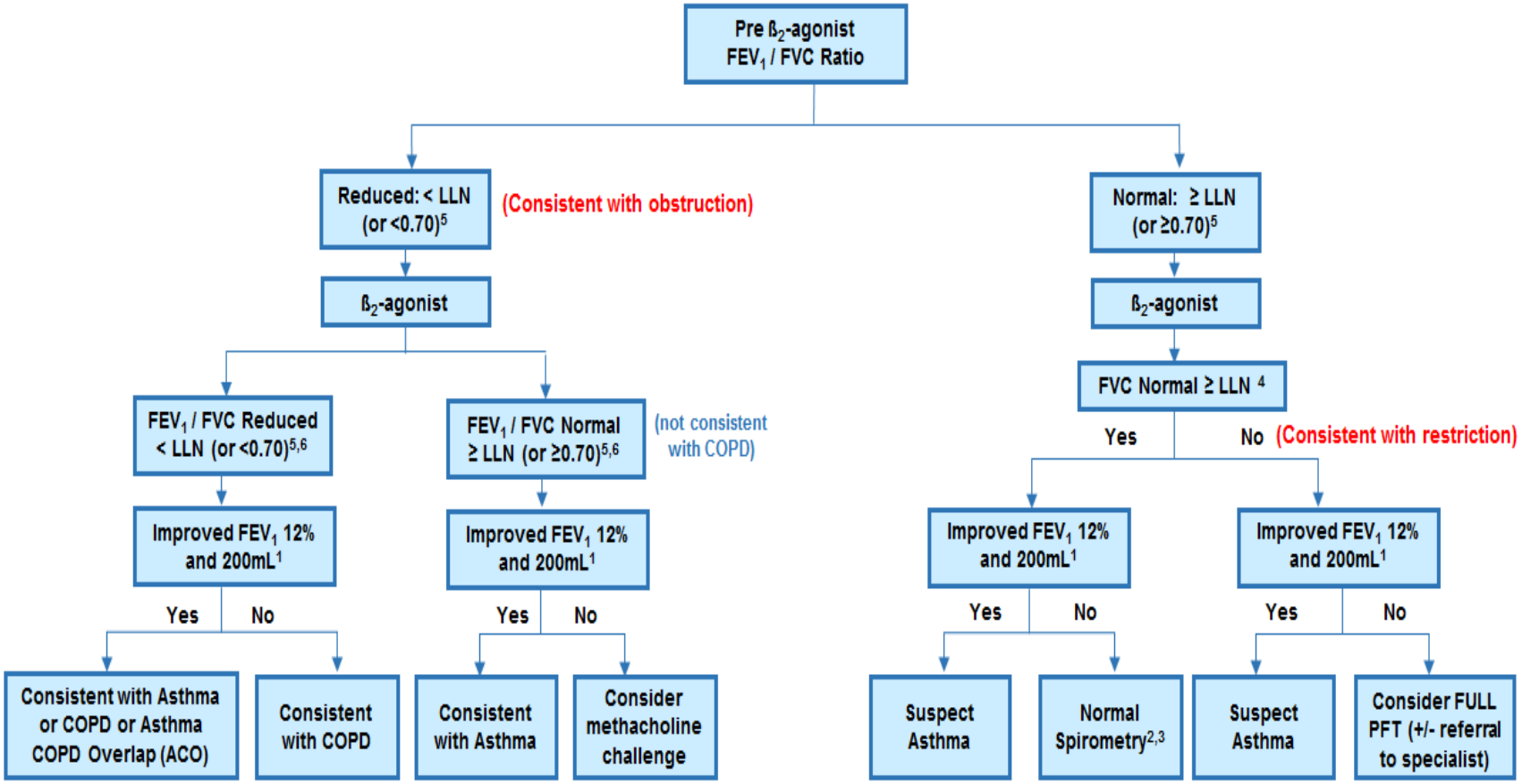
Spirometry testing for asthma

- Reversibility assessment post bronchodilator
  - Adult: 12% and 200 ml increase FEV1 post B/D
  - Pediatric: 12% increase in FEV1 post B/D
  - * Greater confidence if >15% and 350~400 mls
- Airflow limitation
  - Reduced FEV1/FVC
  - FEV1 < LLN
- Serial measurements over time
  - Airflow improves with treatment, decreases without treatment or after step-down in therapy
  - Repeat when symptoms return, seasonal changes
  - Diurnal change: > 10% FEV1, >20% PEFR

BREATHE
the lung association

Spirometry Interpretation Guide

(Consider patient history in all interpretation decision making)



1. 200mL criteria only necessary for adults and children ≥ 12 years
2. Reversibility criteria not met. May occur with chronic asthma - consider methacholine challenge or referral
3. Normal Spirometry: in the context of persistent symptoms consider further clinical testing i.e. methacholine challenge
4. LLN may not be available on outdated systems – use 80% predicted
5. If the LLN is not available use 0.70 in an adult if COPD is suspected and 0.80 in a child
6. If FVC < LLN (or < 80%) predicted, consider hyperinflation/gas trapping. If post-BD FVC remains < LLN (or < 80%) predicted, consider combined obstructive and restrictive defect and full PFT.

LLN=Lower Limit of Normal

Note: Recommended reference equations: GLI, CHMS, and NHANES III

Adapted and revised with permission from Primary Care Respiratory Alliance of Canada (PCRAC)
www.olapep.ca

Limitations of spirometry

- Lack of bronchodilator response with spirometry does not rule out asthma
- Spirometry may be normal in asthma
- Significant reversibility may be present during exacerbations, viral infections or in COPD

Additional testing may be indicated:

- Airways hyperresponsiveness (AHR) is a characteristic feature of asthma: consider bronchoprovocation testing

Airways Hyper-Responsiveness (AHR)

- Increased sensitivity to stimuli: allergic, non-allergic
- AHR is associated with asthma
- Also seen in other lung conditions: such as COPD, bronchitis, cystic fibrosis, sarcoidosis
- AHR increases with acute illness, exacerbations, occupational sensitizers, environmental agents
- AHR may decrease with treatment: antiinflammatory drugs
- AHR varies: may be absent in asymptomatic periods, vary seasonally, time of day
- AHR in athletes: most common in cold air, chlorinated pool sports, only at elite levels

Direct and indirect bronchial challenge tests

Direct Challenges	Indirect Challenges
Direct effect on bronchial tone • Effector cells • Muscarinic receptors	Indirect effect on bronchial tone • Intermediary cells • Inflammatory cells • Neuronal cells
Airflow Limitation	
• Methacholine • Histamine • Prostaglandins • Leukotrienes	• Exercise • Mannitol • Eucapnic hyperventilation (cold or room temperature) • Hyper/hypotonic aerosols • Adenosine monophosphate (AMP) • Allergen

Methacholine challenge test (MCT)

- Assess airway response to increasing doses of methacholine chloride
- Provocative dose of methacholine which results in a 20% fall in FEV1 from baseline (PD20, PC20)
- Other markers can be considered to document AHR:
  - Airways resistance: 40% decrease in sGAW (PD40)
  - Oscillometry: increase in R5 or resonant frequency

Methacholine challenge

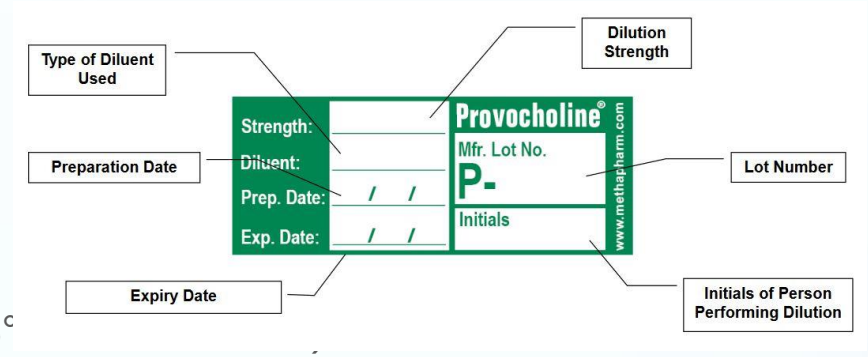
- Most commonly administered direct challenge to assess AHR
- Sensitive but not specific for asthma
- Negative predictive value is greater than positive predictive value: **More useful to exclude asthma than confirm it**
- Negative MCT excludes current asthma, when symptoms are recent and patient off controller therapy
- Negative MCT cannot exclude past asthma

Methacholine chloride USP

- Manufactured by Methapharm (Provocholine®), Brantford, Ontario. www.methapharm.com
- Available as powder for reconstitution: 100 mg, 160 mg, 320 mg, 1280 mg, 1600 mg
- Inhalation only, for diagnosis of asthma
- Cholinergic agent (parasympathomimetic): synthetic derivative of neurotransmitter, acetylcholine
- Direct stimulation to muscarinic receptors to cause brief bronchial smooth muscle contraction
- Short half-life with small cumulative effect at 5 minute intervals
- Proper preparation, labeling and storage essential

Methacholine solution preparation

- Powder form: storage at room temperature up to 3 years (15 - 30° C or 59 – 86°)
- Reconstitution by pharmacist or other well trained person using sterile technique
- Precise mixing is essential
- Diluents:
  - 0.9% normal saline
  - 0.9% saline with 0.9% benzyl
  - 0.9% saline with 0.4% phenol
- Reconstituted solutions (stored at 2 - 8°
  - Use within 2 weeks
- Solutions must be at room temperature during testing (remove from fridge 30 mins prior)
- Bacterial filter recommended



Methacholine solution preparation

NAPRA Guidance Document for Pharmacy Compounding of Non-sterile Preparations

“Reconstituting or manipulating commercial products that may require the addition of one or more ingredients as directed by the manufacturer is not considered compounding by Health Canada”

“Although mixing and reconstituting are not considered to constitute compounding in Canada, personnel are encouraged to use the compounding area and follow Level A requirements for these activities”

- (clean, orderly, good state of repair, appropriate storage, space reserved for compounding)

Guidance Document for Pharmacy Compounding of Non-sterile Preparations – Companion to the Model Standards for Pharmacy Compounding of Non-sterile Preparations. The National Association of Pharmacy Regulatory Authorities (NAPRA)

ATS 1999 dosing schemes

Stage	Doubling Dose mg/ml	Quadrupling Dose mg/ml
Diluent	Diluent	Diluent
1	0.03 mg/ml	
2	0.06 mg/ml	0.0625 mg/ml
3	0.125 mg/ml	
4	0.25 mg/ml	0.25 mg/ml
5	0.5 mg/ml	
6	1.0 mg/ml	1.0 mg/ml
7	2.0 mg/ml	
8	4.0 mg/ml	4.0 mg/ml
9	8.0 mg/ml	
10	16.0 mg/ml	16.0 mg/ml
Post	B/D	

Indications for MCT

- Help rule out asthma: active symptoms at time of testing, where spirometry (pre/post bronchodilator or between test intervals) have not helped establish diagnosis of asthma
- Evaluate asthma severity
  - Response to therapy, medication trials
- Pre-employment clearance:
  - Military, Firefighter, Police, Commercial Diving
- Elite athletes: validate inhaler use in competition
- Occupational asthma symptoms, WSIB claims
- Research
- Evaluate risk of developing asthma

Factors which can affect MCT

- Patient factors: active illness, exposures, occupational environment, medications
- Ability to perform acceptable and repeatable spirometry
- Methacholine protocol used: delivery of methacholine aerosol, dosing scheme, breathing interval, environmental controls, QC, preparation and storage of methacholine concentrations
- Reported FEV1: largest FEV1 should be reported from valid efforts
- Keep cumulative effect of methacholine constant: maintain 5 minute interval between nebulizer starts

Contraindications to MCT

Airflow limitation on baseline spirometry:

- FEV1 <60% predicted or 1.5 L

Unacceptable spirometry quality:

- Inability to perform acceptable and repeatable spirometry manoeuvers during testing

Cardiovascular problems:

- MI, CVA within last 3 months
- Uncontrolled HTN (SPB> 200 mmHg, DBP >100 mmHg)
- Known arterial aneurysm

Recent surgery

- Any condition where increased ocular, cranial, thoracic or abdominal pressure is harmful

Relative Contraindications to MCT

- Pregnancy, nursing mothers
- Current use of cholinesterase inhibitor medications for myasthenia gravis
- Active upper or lower respiratory infection (2 – 6 weeks)
- Significant fall in FEV1 from baseline after diluent step:
  - >20% fall in FEV1 - stop challenge
- Patient on beta-adrenergic blocking agents
  - Synergistic effect
  - May be more difficult to reverse effects with $ß_2$-agonist

Medication withhold times:
Drugs affecting MCT held for duration of their action

Medication	Minimum hold time
Short acting bronchodilator (salbutamol, albuterol)	6 hrs
Ipratropium (atrovent)	12 hrs
Long acting B-agonsits (LABA's like salmeterol)	36 hrs
Ultra-Long acting B-agonists (LABA's like indecaterol, vilanterol, olodaterol)	48 hrs
Long-acting anti-muscarinic agents (tiotropium)	168 hrs (7 days)
Oral theophylline	12-24 hrs

Modified from 2017 ERS technical standard

Other pre-test considerations

- Cromones, inhaled corticosteroids and leukotriene modifiers have little effect at single doses but their antiinflammatory effects may last **weeks**
- Oral or inhaled corticosteroid do not need to be routinely held but their anti-inflammatory effects may decrease response to methacholine
- Normal dietary servings of caffeine (food or drink) have little or no clinical significance on MCT
- Antihistamines do not affect methacholine response
- Tiotropium (Spriva) – 1 week hold may be required
- Vilanterol (LABA in Anoro, Breo): mechanism of action 72 hours
- No concerns with: flu shot, menstrual cycle, contraceptives

Patient safety

- Staff performing testing should be well trained
- Staff will remain with patient the entire test
- Rescue medications available in the testing room
  - Short acting bronchodilator
  - Epinephrine
- Equipment
  - Stethoscope, pulse oximeter, oxygen/delivery device, Blood Pressure monitor
- Complete appropriate pre-test questionnaire

Patient safety

- Methacholine causes bronchoconstriction. This is the outcome of the test.
- Low risk when appropriate pre-test screening and test protocols are followed
- Ensure proper preparation, labeling, administration and storage of methacholine
- Measure spirometry 30 seconds, 90 seconds after inhalation of methacholine. Additional spirometry may be advised if FEV1 continues to fall prior to administering higher doses of methacholine
- Monitor for symptoms: tachypnea, cough, wheeze, chest tightness

Staff safety

- Minimize exposure to methacholine aerosol
  - At least 2 air exchanges/hour
  - Fume hood
  - Scavenging system
- Use quality filter on patient exhalation port
- Use mouthpiece with nose clips vs face mask
- Start aerosol after patient is connected, stop aerosol before patient disconnection
- Use of breath actuated aerosol devices
- Evaluate if testing appropriate for staff with AHR/asthma

2017 Standard **update**

ERS technical standard on bronchial challenge testing: general considerations and performance of methacholine challenge tests

- Coates AL, Wanger J, Cockcroft DW, et al.
- Eur Respir J 2017; 49: 1601526

2017 ERS Technical Standard Qualifications for Staff/Technologist

1. Have background knowledge of respiratory diseases, be familiar with practice guidelines and knowledge of specific test procedures
2. Be capable of managing the equipment including set-up, calibration, verification of function, maintenance, hygiene and
3. Ability to achieve acceptable and repeatable spriometry
4. Understand contraindications and factors which can affect MCT
5. Be familiar with safety and emergency procedures
6. Know when to stop the test
7. Be proficient with the administration of inhaled bronchodilators and evaluation of the response to them

Modified from ERS technical standard

Staff Qualifications

Intended to ensure quality data, patient and staff safety

- Adequate background knowledge
- 4 days hands on training
- 20 supervised tests for new/junior staff
- Documentation of training, evaluation and qualification by pulmonary lab director

2017 inhalation protocol

- Tidal breathing recommended with suitable nebulizer or dosimeter (quiet, relaxed breathing)
- Avoid TLC breathing pattern (bronchodilatory effects)
- Tidal breathing interval of 1 minute (or longer)
- Diluent step recommended
- Initial dose of methacholine: 1-3 µg with doubling or quadrupling concentrations up to 400 µg
- Maintain consistent time between methacholine starts (constant cumulative effect). Not recommended to decrease interval due to shorter nebulization time of modern nebulizers

New recommendations

- Provocative dose (PD20) of methacholine causing 20% drop in FEV1 is to be reported rather than the provocative concentration (PC20)
- Intended to provide comparable results between different devices and protocols
- Manufacturer to provide characterization of nebulizer: quantified emitted drug mass of methacholine at respirable fraction
- Methacholine dosing scheme will depend on nebulizer system used
- Gravimetric calibration of nebulizer output no longer recommended

Older aerosol delivery devices

English Wright

Wright-type with hans rudolph valve, mouthpiece and filter

Bennett twin Jet

Modern delivery devices

Aeroeclipse

Aerogen

APS pro

Challenges adopting modern nebulizers

- Nebulizer characteristics will impact methacholine dosing scheme and/or tidal breathing interval
- Gravimetric calibration alone over-estimates output
- Nebulizers not manufactured specifically for methacholine challenge (low output)
- No regulation or standard for manufacturers use when testing operational characteristics for nebulizers
- Non-standardized data and testing conditions from manufacturers and vendors
- Indiscriminate use of alternate nebulizers, prevents comparison of AHR between devices and protocols

Aerosol delivery of methacholine

- Nebulizers are drug delivery devices
- Output of nebulizer must be known, reproducible and provide particles < 5 µm. Determined from assay and factored for evapourative loss (pre and post diluent analysis)
- Respirable Fraction must be known: fraction of the mass of aerosol (≤ 5 µm) that deposits below the vocal cords
- Delivery of aerosol also affected by other factors: driving flow rate, inspiratory flow, I:E (duty cycle time Ti/Ttot), environmental conditions, fill volume

MCT procedure

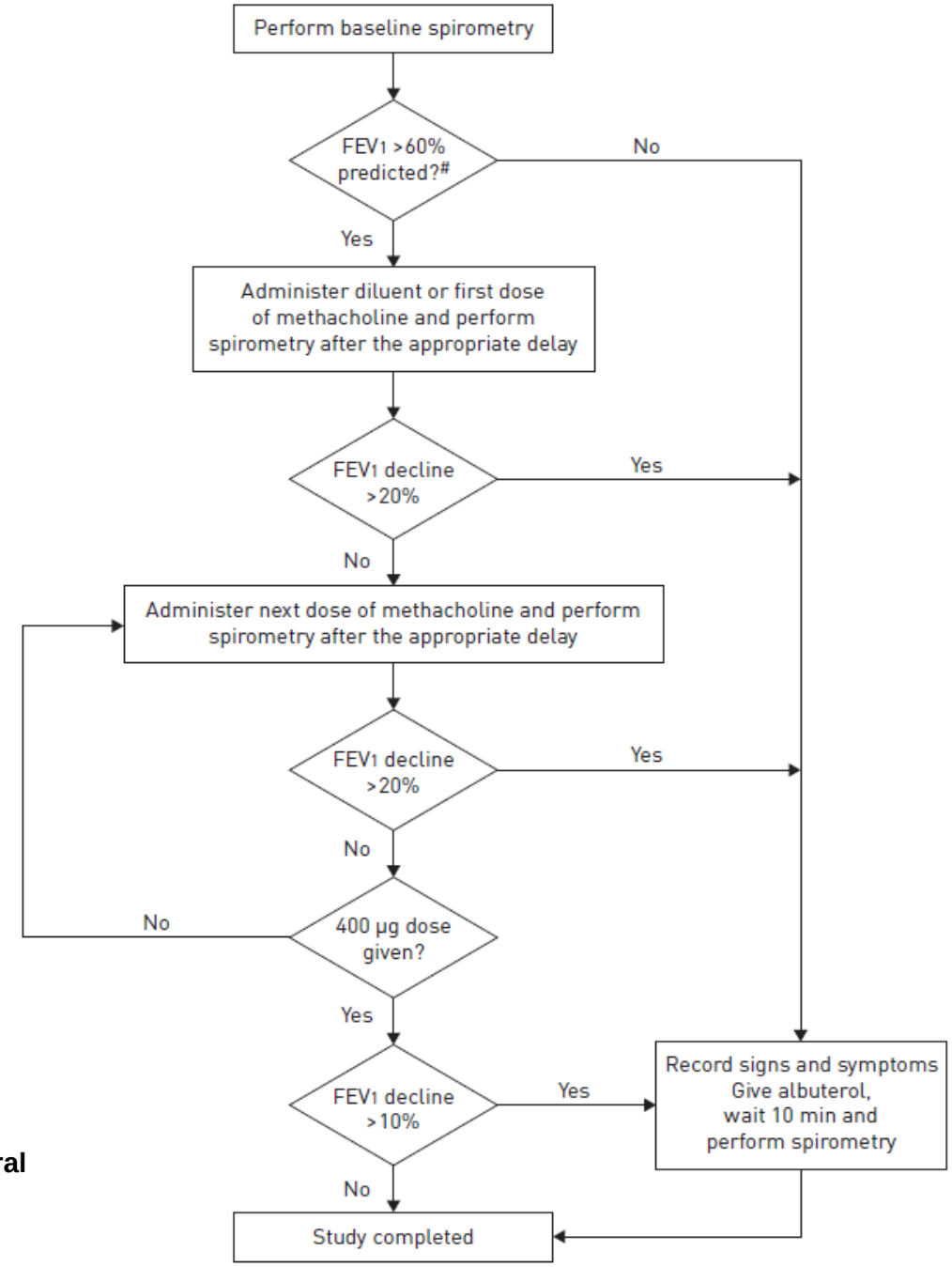


FIGURE 1 Testing sequence flow chart. FEV1: forced expiratory volume in 1 s. #: FEV1 <1.5 L in adults is an additional contraindication. Reproduced and modified from [3] with permission.

Coates AL, Wanger J, Cockcroft DW, et al.
ERS technical standard on bronchial challenge testing: general considerations and performance of methacholine challenge.
Eur Respir J 2017; 49: 1601526.

Key points during MCT procedure

- Acceptable and repeatable spirometry
  - Essential: fill to TLC, start of test and FEV1
  - Report best FEV1
  - Verify that FEV1 isn't continuing to drop prior to next stage of methacholine, may need to repeat spirometry prior to next dose
  - If VCD suspected, document max Inspiratory curves
  - Post B/D FEV1 should return to within 10% of baseline
- Ensure relaxed, quiet breathing through nebulizer during tidal breathing interval
- Use timer to maintain 5 minute starts between methacholine
- Remind patient they can remove nebulizer at any time if symptoms of concern develop
- Monitor for symptoms, know when to stop the test

Reporting MCT results

- Reason for test
- History, symptoms and current medications
- Statement on spirometry quality
- Statement on any symptoms observed during testing
- Highest FEV1 recorded from each stage
- PD20: graphic plot of PD20, change in FEV1
- PD20 value displayed on report (mcg)
- Do not extrapolate response curve

Interpreting MCT results

- Increased diagnostic value when pre-test probability of asthma is 30-70% and symptoms consistent with asthma are present
- Consider any factors which may affect results
- PD20 in micrograms (µg) of delivered dose of methacholine

PD20 µg	PC20 mg/ml	Interpretation
> 400	> 16	Normal
100-400	4-16	Borderline AHR
25-100	1-4	Mild AHR
6-25	0.25 -1	Moderate AHR
< 6	< 0.25	Marked AHR

Modified from ERS technical standard

MCT: final thoughts

- MCT testing and results must be standardized and recorded in order to ensure accurate results for interpretation
- Assessing AHR characterizes degree of reactivity at time of testing
- Ensure nebulizers are appropriate for use with MCT
- More supportive data needed to validate impact of devices and protocols on assessing reactivity

MCT : bonus round

Coates, A, Culver, B, Cockcroft, D, Hallstrand, T, Haynes, J, Kaminsky, D, MacIntyre, N, Wanger, J. **Characterizing Nebulizer Performance for Methacholine Challenge Tests**. AJRCCM Article in Press. Published on 30-Augus-2018 as 10.1164/rccm.201805-094ED

Institute for Clinical Management in Healthcare

https://iqmh.org

Delivered Dose (DD): wright nebulizer

Example of simplified delivered dose calculation:

Output (mass of drug) x RF x breathing interval = DD (µg)

- Wright output 0.19±0.07 mg/min (from assay) delivered from 16 mg/ml concentration over 2 minutes.
- Since all particles ≤ 5 µm Respirable Fraction (RF) was 100% or “1”

0.19 mg/ml x 1 x 2 = 0.38 mg **(380 µg)**

Dose = [conc(mg/ml)/16mg/ml] x 380 µg

Modified from ERS technical standard

Wright nebulizer delivered dose

Wright nebulizer ***doubling concentrations example ****2 minutes tidal breathing**	
Concentration (mg/ml)	Delivered Dose (µg)
0.03	**0.7**
0.06	1.425
0.125	2.969
0.25	5.938
0.5	11.875
1.0	23.75
2.0	47.5
4.0	95
8.0	190
16	**380**

Table modified from ERS technical standard

Delivered Dose: Aeroeclipse example

- Output = 2.7±0.22 mg/min, RF = 76%, **20 second** breathing interval (breath actuated)

2.7 mg/min x 0.76 x 20/60 min = 0.68 mg **(680 µg)**

ERS technical standard recommended tidal breathing interval 1 minute (or longer), therefore over **1 minute tidal** breathing:

2.7 mg/min x 0.76 x 60/60 min = 2.052 mg **(2052 µg)**

- 1 minute tidal breathing interval requires recalculation of methacholine dosing scheme to offset higher delivered dose

- Initial delivered dose 1-3 µg requires methacholine concentration of 0.015 mg/ml

Aeroeclipse with 1 minute breathing?

AeroEclipse example recalculated 1 minute tidal breathing interval. *initial dilution	
Methacholine concentration (mg/ml)	Delivered Dose (µg)
***0.015625**	1.9
0.03	3.8
0.0625	7.65
0.125	16
0.25	32.1
0.5	64.1
1.0	127
2.0	256.5
4.0	510

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GINA 2018: Quality Assurance

"Lung function testing should be carried out by well-trained operators with well-maintained and regularly calibrated equipment"

Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2018.