Testing methods for airway hyperresponsiveness in asthma[1–3]

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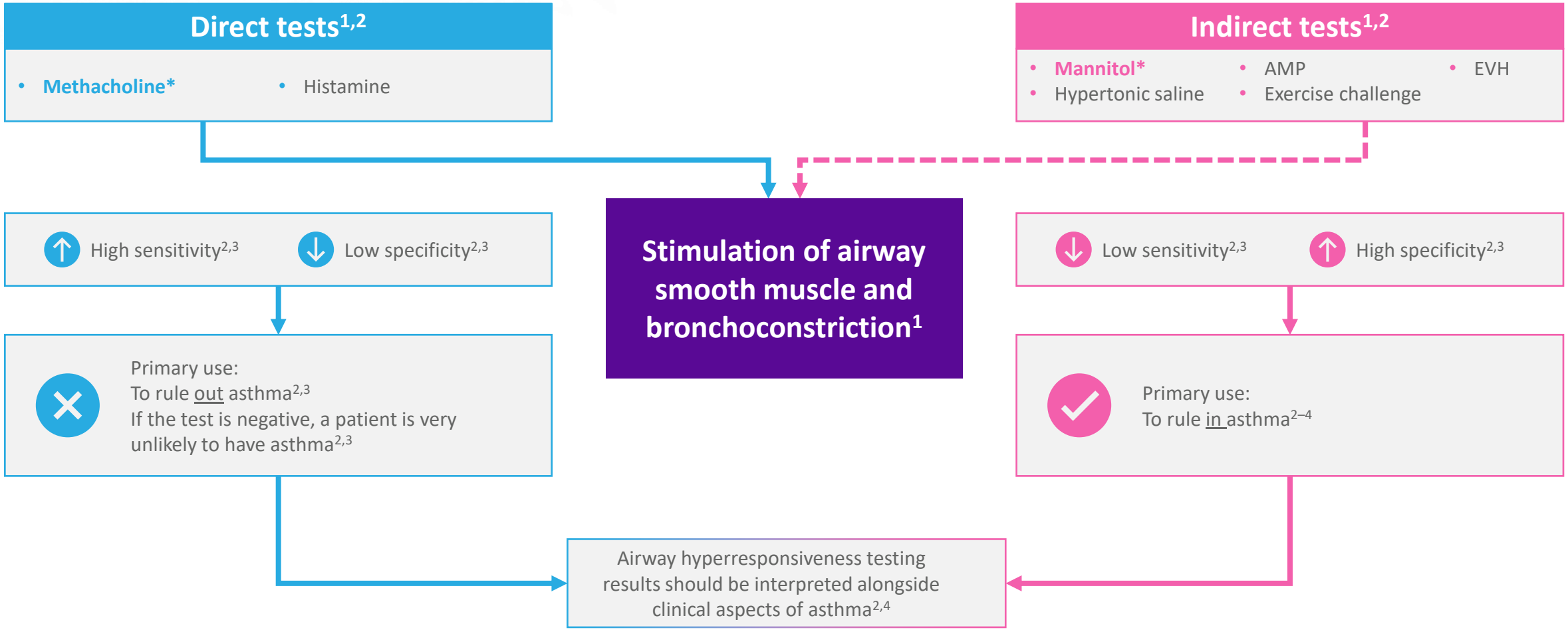

AMP, adenosine monophosphate; EVH, eucapnic voluntary hyperventilation

1. Chapman DG, Irvin CG. Clin Exp Allergy 2015;45:706–719; 2. Comberiati P, et al. Immunol Allergy Clin North Am 2018;38:545–571;
3. Cockcroft DW. Chest 2010;138(Suppl. 2):18S–24S; 4. Coates AL, et al. Eur Respir J 2017;49:1601526

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Airway hyperresponsiveness and airway inflammation

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Airway hyperresponsiveness to an indirect bronchial challenge test, such as mannitol, mimics active airway inflammation[1,2]

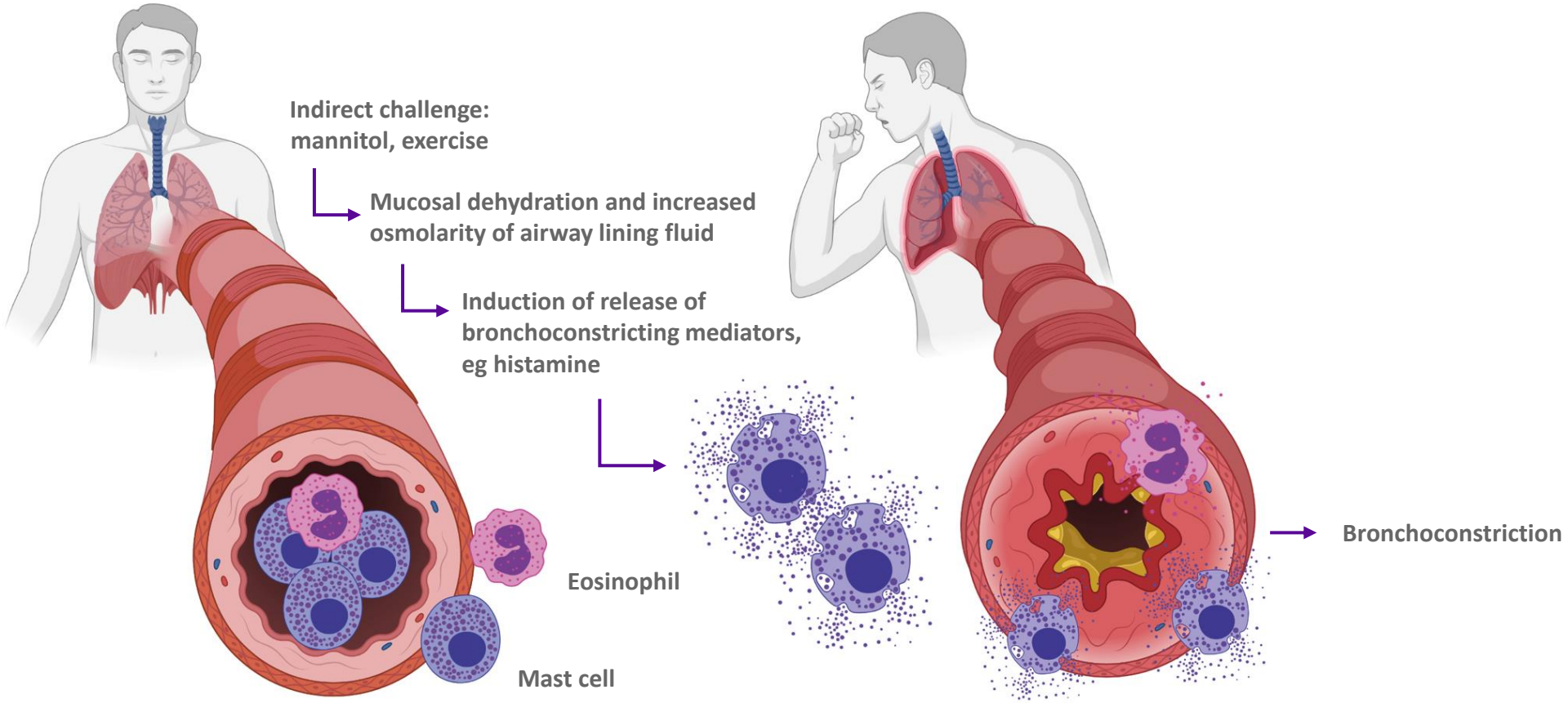

Image copyright: Celeste Porsbjerg

This is an illustrative representation of the airway and the effect of an indirect airway hyperresponsiveness challenge; the airway and inflammatory cells are not to scale

1. Brannan JD, Lougheed MD. Front Physiol 2012;3:460; 2. Sverrild A, et al. Clin Exp Allergy 2016;46:288–297

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Methacholine and mannitol challenge tests

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Test	Mechanism	Measurements	Cutoff level	Interpretation of airway hyperresponsiveness
Methacholine challenge[1]*†	Inhaled methacholine mimics the neurotransmitter acetylcholine to directly interact with muscarinic receptors on airway smooth muscle, resulting in bronchoconstriction	PC_{20} or PD_{20} to methacholine: the provoking concentration or delivered dose of methacholine required to induce 20% reduction in FEV_1 from baseline†	25–100 µg / 0.13–0.50 µmol / 1–4 mg/mL	Mild
			6–25 µg / 0.03–0.13 µmol / 0.25–1 mg/mL	Moderate
			<6 µg / <0.03 µmol / <0.25 mg/mL	Marked
Mannitol challenge[2–5]	Inhalation of mannitol rapidly increases the osmolarity of the airway surface liquid, causing stimulation of inflammatory cells (ie mast cells and eosinophils) and release of mediators, mimicking airway inflammation	PD_{15} to mannitol: the provoking cumulative total dose of mannitol required to induce ≥15% reduction in FEV_1 from baseline or a 10% decrease in FEV_1 between two consecutive mannitol doses	>155 mg	Mild indirect
			>35 mg to ≤155 mg	Moderate indirect
			≤35 mg	Severe indirect

*Challenge test results expressed as provocative dose (PD) or provocative concentration (PC) are dependent on the output rate of the administration device, time of aerosol inhalation and particle size distribution. Evidence shows that the methacholine dose, expressed as PD_{20}, allows more consistent correlation of results than PC_{20} when comparing responses captured by different protocols. Consistency of timing between steps and from dosing to spirometry remains important to properly compare results. The PD_{20} is the dose of methacholine that causes a 20% fall in FEV_1 and is calculated in the same way as the PC_{20}.[1] †To determine changes in airway reactivity following therapy in patients known to have asthma, using doubling doses will give more precise PD_{20} values to compare[1]

FEV_1, forced expiratory volume in 1 second

1. Coates AL, et al. Eur Respir J 2017;49:1601526; 2. Hallstrand TS, et al. Eur Respir J 2018;52:1801033; 3. Comberiati P, et al. Immunol Allergy Clin North Am 2018;38:545–571; 4. Brannan JD, Lougheed MD. Front Physiol 2012;3:460; 5. Sverrild A, et al. Clin Exp Allergy 2016;46:288–297

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Interpreting results of airway hyperresponsiveness bronchoprovocation tests

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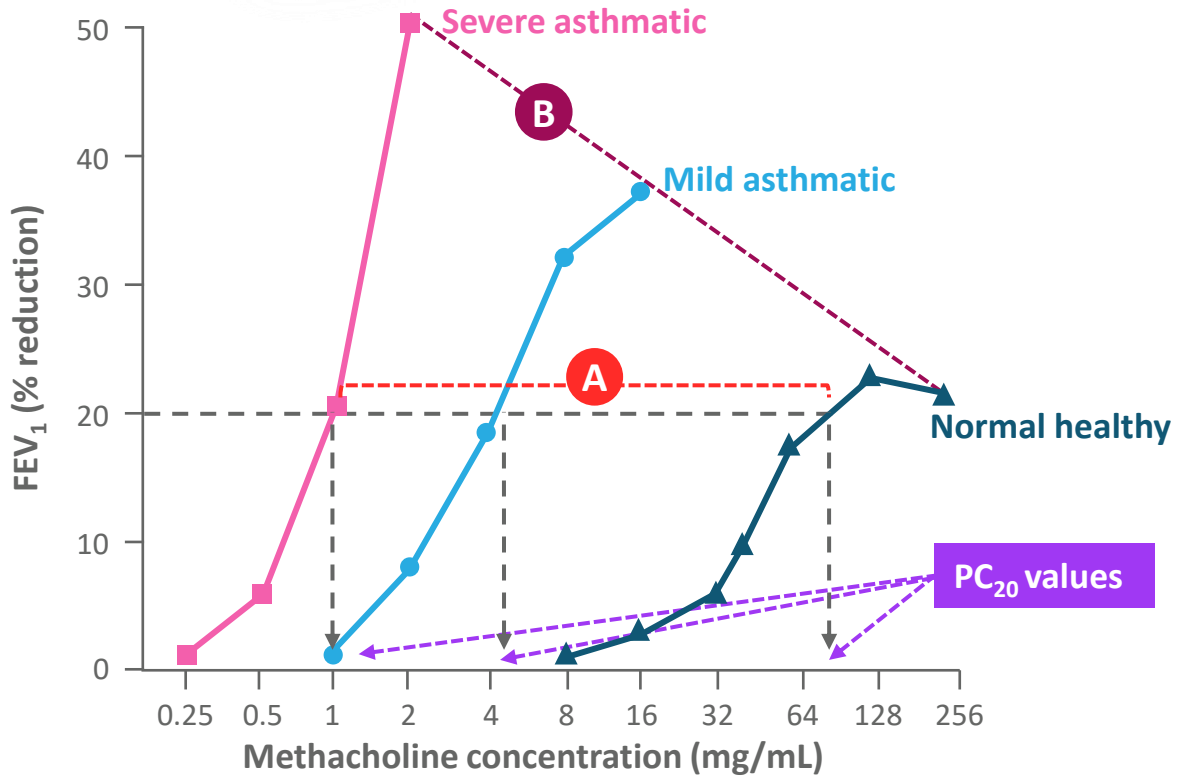
Change in FEV_1 as measured by PC_{20} value by methacholine challenge test in patients with or without asthma[1,2]



- Airway hyperresponsiveness is a valuable tool in the clinical assessment of patients with possible asthma, asthma-like symptoms, or, generally normal/ non-diagnostic lung function[3]
- In patients with asthma, bronchoconstriction (PC_{20} as seen by reduction in FEV_1)* starts at a lower inhaled concentration of the agonist methacholine[2] A
- Maximal bronchoconstrictor responses are also greater in those with asthma[1,2†] B
- Patients with **normal healthy** airways achieve a plateau response to the bronchoconstrictor stimulus, whereas patients with **mild** to **severe** asthma may not[1,2]

Figure adapted from O'Byrne PM, Inman MD. Chest 2003;123(Suppl. 3):411S–416S and Nair P. J Allergy Clin Immunol Pract 2017;5:649–659

*PC_{20} greater than 16 mg/mL represents normal airway responsiveness;[4] 4–16 mg/mL is borderline airway hyperresponsiveness;[4] 1–4 mg/mL represents mild airway hyperresponsiveness;[4] 0.25–1 mg/mL represents moderate airway hyperresponsiveness;[4] and <0.25 mg/mL represents marked airway hyperresponsiveness.[4] †For safety reasons, methacholine testing is stopped if there has been a >20% fall in FEV_1[4]

FEV_1, forced expiratory volume in 1 second; PC_{20}, provocation concentration of methacholine causing a 20% fall in FEV_1

1. O'Byrne PM, Inman MD. Chest 2003;123(Suppl. 3):411S–416S; 2. Nair P. J Allergy Clin Immunol Pract 2017;5:649–659; 3. Cockcroft DW, et al. Allergy Asthma Clin Immunol 2020;16:14;
4. Coates AL, et al. Eur Respir J 2017;49:1601526

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Contraindications for airway hyperresponsiveness testing

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There are several **general contraindications** for performing tests for airway hyperresponsiveness[1]

- Moderate/severe airflow limitation
- Cardiovascular problems
- Eye surgery
- Pregnancy or nursing mothers
- Inability to reproduce quality spirometry results consistently

There are also several **specific contraindications** for performing direct and indirect tests[1,2]

Direct tests[1]

- Current use of cholinesterase inhibitor medication

Indirect tests[2]

- Hypersensitivity to mannitol
- Presence of comorbidities that could be exacerbated by frequent coughing

1. Coates AL, et al. Eur Respir J 2017;49:1601526; 2. Hallstrand TS, et al. Eur Respir J 2018;52:1801033

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