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

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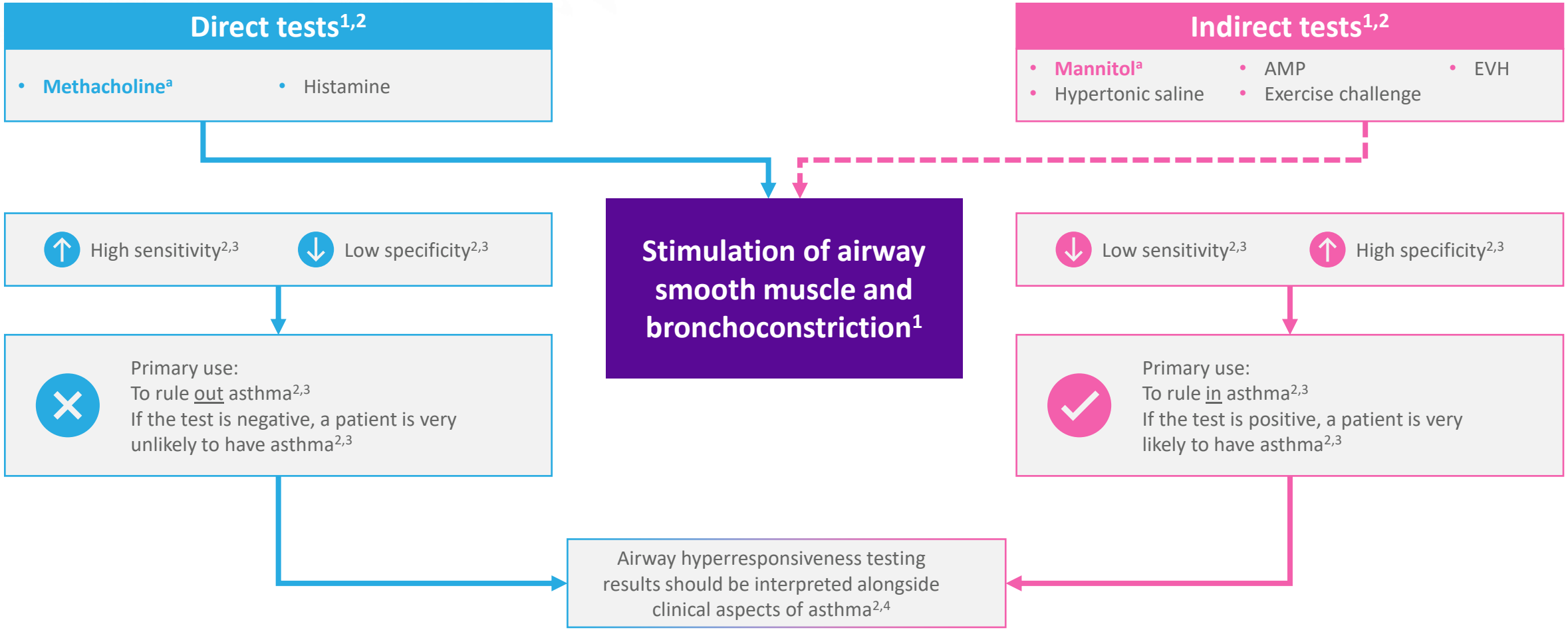

[a]Most commonly used bronchoprovocation challenge tests[1,4,5]

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; 5. Hallstrand TS et al. *Eur Respir J.* 2018;52:1801033

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Airway hyperresponsiveness and airway inflammation

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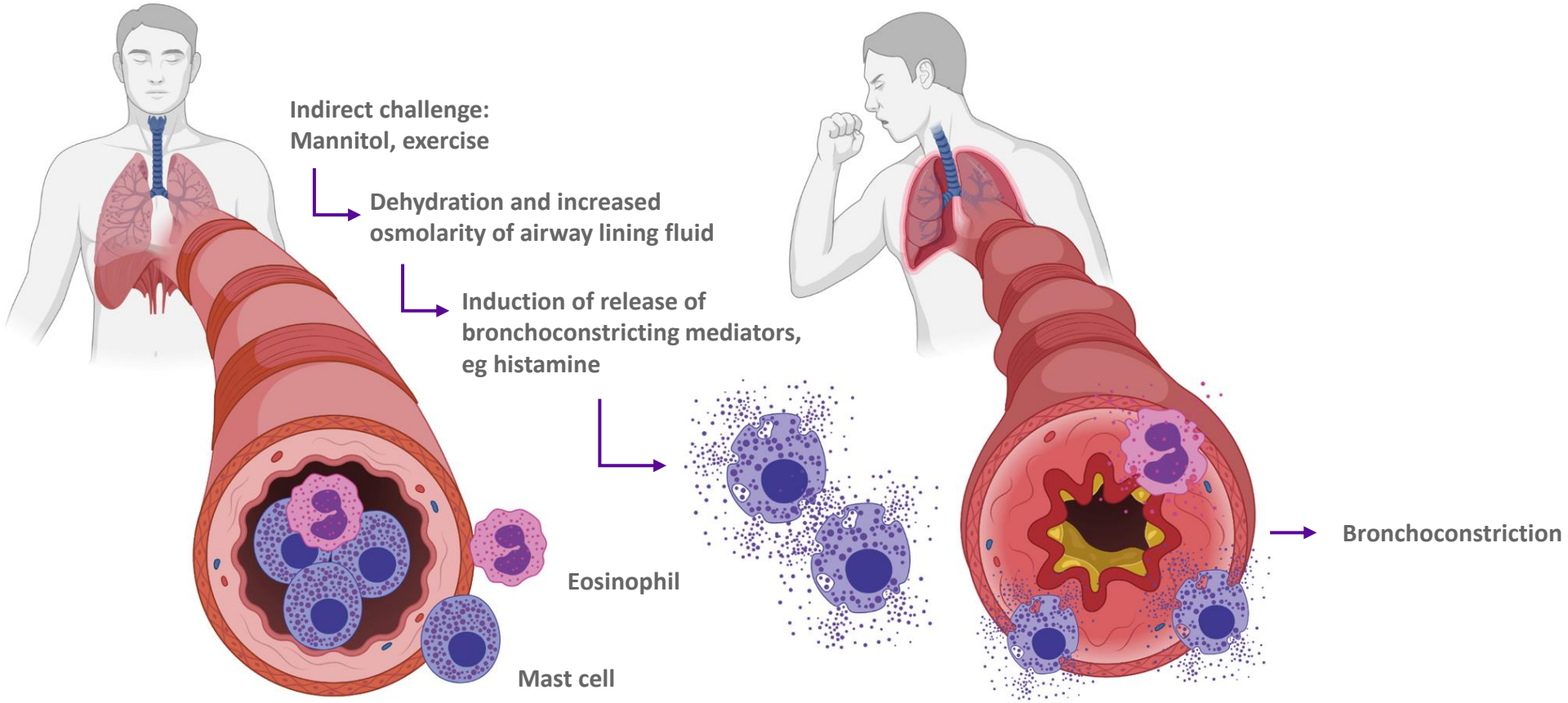
Airway hyperresponsiveness to an indirect bronchial challenge test, such as mannitol, mimics active airway inflammation[1,2]



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
Image copyright: Celeste Porsbjerg

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[1a,b]	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[c]	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

[a]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 done 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] [b]Methacholine challenge is most often used in Europe;[1] [c]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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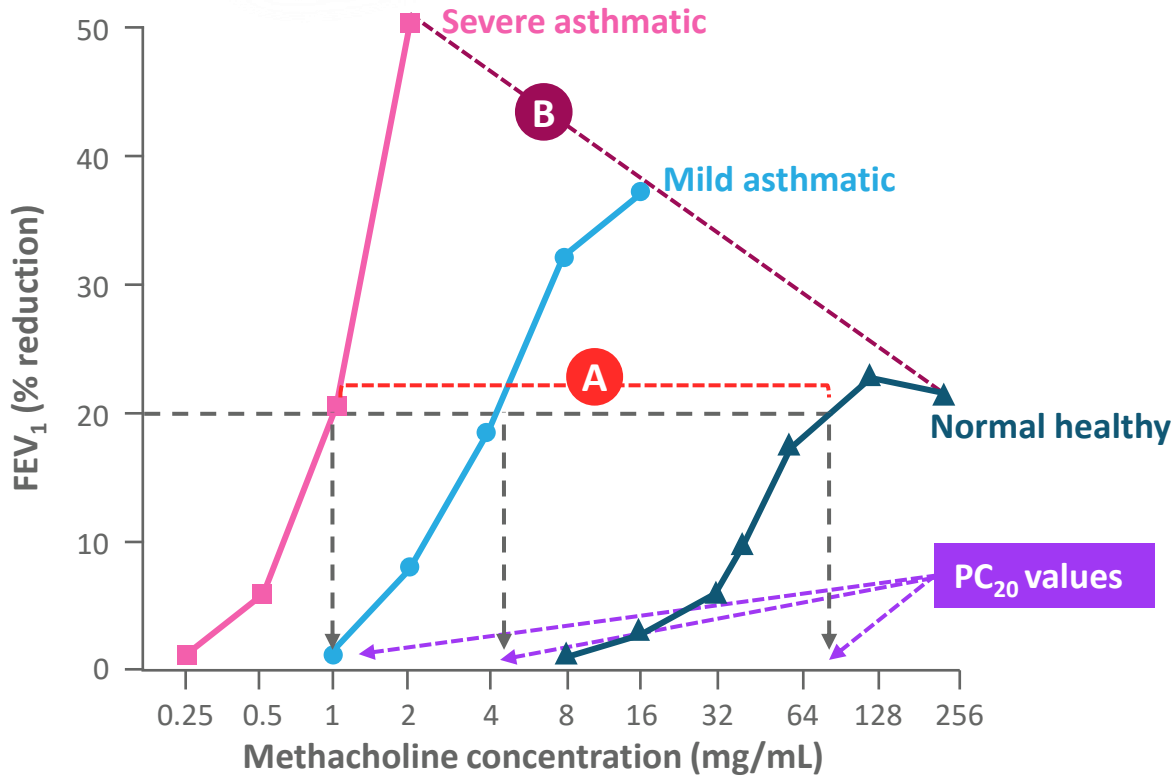
Change in FEV_1 as measured by PC_{20} value by methacholine challenge test in patients with or without asthma[1,2]



- Airway hyperresponsiveness is a valuable tool in the clinical assessment of patients with possible asthma, with asthma-like symptoms, or non-diagnostic, generally normal lung function[3]
- In patients with asthma, bronchoconstriction (PC_{20} as seen by reduction in FEV_1)[a] starts at a lower inhaled concentration of the agonist methacholine[2] A
- Maximal bronchoconstrictor responses are also greater in those with asthma[1,2b] 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]

[a]PC_{20} more than 16 mg/mL is normal airway responsiveness; 4–16 mg/mL is borderline airway hyperresponsiveness; 1–4 mg/mL is mild airway hyperresponsiveness; 0.25–1 mg/mL is moderate airway hyperresponsiveness; and <0.25 mg/mL is marked airway hyperresponsiveness[4]

[b]For safety reasons, methacholine testing is stopped if there has been a >20% fall in FEV_1[4]

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

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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