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Early View

Research letter

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Title

NICE asthma guidelines: time to re-evaluate the diagnostic value of exercise challenge testing?

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To the Editor,

Asthma is a heterogenous chronic inflammatory lower airways disease that affects over 350 million of the global population [1]. It is now recognised that securing a diagnosis is often challenging given clinical examination can be normal at rest and symptoms have a broad differential diagnosis. In support of this concept, a seminal study by Aaron and colleagues observed that almost one third of adults with a physician diagnosis, showed no clinical or laboratory evidence of asthma when re-examined at 12-months [2]. Similarly, underdiagnosis remains a widespread issue, with estimates ranging between 19-73%, depending on the diagnostic methods and population studied [3].

The National Institute for Health and Care Excellence (NICE) (an executive non-departmental public body of the Department of Health and Social Care in England, that publishes clinical practice guidance on the appropriate treatment and care of people with specific diseases and conditions) currently recommend that an asthma diagnosis should be established based on a detailed clinical history, physical examination, and objective physiological testing [4]. Specifically, NICE endorse the measurement of exhaled nitric oxide, as an indirect biomarker of type 2 inflammation, followed by an assessment of airflow parameters via spirometry (+/- bronchodilator reversibility) and peak expiratory flow variability over 2-4 weeks. In cases where diagnostic uncertainty remains, NICE advise that patients are subsequently referred for a direct bronchial provocation test (i.e., methacholine or histamine challenge) to confirm or refute evidence of airway hyper-responsiveness (AHR) [4].

Other diagnostic modalities employed in this setting include indirect bronchial provocation tests (i.e., exercise challenge test (ECT), inhaled mannitol or eucapnic voluntary hyperpnoea). Indirect tests act to increase the osmolarity of the airway surface liquid, promoting the release of pro-inflammatory mediators (i.e., leukotrienes, prostaglandins, and histamines), which leads to airway smooth muscle contraction and bronchoconstriction in susceptible individuals [5]. Specifically,

indirect tests are thought to provide greater specificity (i.e., ability to rule in a diagnosis) in comparison to direct bronchial provocation tests, and thus have application in the assessment of individuals presenting with suspected exercise-induced bronchoconstriction (EIB) - a common condition characterised by transient lower airway narrowing in association with physical exertion [6].

Exercise is also one of the most commonly reported symptom triggers in individuals with underlying clinical asthma; i.e., most people with asthma also experience EIB. On this basis, ECT is considered by many to be an ecologically valid form of bronchial provocation. Despite this, NICE currently oppose the use of ECT to diagnose asthma in adults over 17 years [4]. In contrast, the recent asthma guideline statement published by the European Respiratory Society (ERS), suggest that indirect challenges can be used to confirm the presence of asthma in patients who remain negative to direct constricting agents [7]. Furthermore, the most up-to-date Global Initiative for Asthma (GINA) guidelines endorse the use of indirect bronchial provocation challenges to objectively document variable expiratory airflow limitation, without a prior direct bronchial provocation test, and when presented alongside a history of variable respiratory symptoms [1].

To understand the disparity between NICE [4], ERS [7] and GINA recommendations [1], we sought to evaluate the validity of ECT methodologies underpinning NICE asthma diagnosis guidelines [4]. To achieve this objective, NICE guidelines were examined by two independent reviewers (AS, OP) and evaluated against the recent ERS technical indirect bronchial challenge testing standard [5]. Specifically, compliance to the following six criteria were examined: (i) pre-test medication restrictions (applicable to those with a prior asthma diagnosis), (ii) exercise intensity, (iii) exercise duration, (iv) environmental conditions, (v) post-challenge spirometry and (vi) diagnostic threshold (Table 1). Any conflicts or disparities concerning interpretation were resolved through discussion.

Five cross-sectional studies published between 1978-2009 informed NICE recommendations [8-12]. Of these, none of the studies adhered to the current criteria for indirect bronchial challenge testing, with at least one violation identified for each study (breakdown summarised in Table 1). Specifically, four studies failed to adhere to medication restrictions [8,10-12], whereas one study provided insufficient information [9]. The most common violation concerning medication was in relation to the requirement to withhold inhaled corticosteroid (ICS) (n = 3 studies) and/or long-acting beta-2-agonist therapy (n = 2 studies) for an appropriate duration. One study failed to adhere to exercise testing intensity by not utilising heart rate or ventilation as a personalised target [10]. All studies adhered to the appropriate exercise duration ≥4 min [8-12], with most (n = 4 studies) adhering to the 'preferable' 6-min duration [9-12]. Only one study adhered to the appropriate environmental conditions [12]. Two studies conducted testing in an inappropriate laboratory environment (i.e., exceeded the required minimum temperature and/or humidity) [10-11] and two studies failed to provide sufficient information [8-9]. Three studies failed to conduct spirometry at the appropriate post-challenge timepoints [8,10,12] and only one study employed the recommended diagnostic threshold (i.e., pre-to-post ≥10% fall in FEV_1) [11].

Our analysis indicates that current NICE asthma guidelines [4] are based on studies that do not adhere with established ECT criteria [5] which raises concern regarding the quality of evidence underpinning current recommendations. The consequence of failing to standardise or control key factors recognised to impact the airway response to exercise (e.g., exercise intensity, environmental conditions and medication restrictions) can be significant and includes a potential for misdiagnosis (i.e., under-detection), disparity in test outcome when comparing different forms of bronchial provocation, and/or inability to evaluate the efficacy of therapeutic intervention.

On this basis, we propose that further research is conducted to determine the role of ECT for the diagnosis of asthma, with strict adherence to current bronchial provocation guidelines. Our findings confirm that the most common breach of ECT criteria was in relation to environmental conditions. Indeed, an appropriate environment was only reported in a single study, whereby participants were tested on an indoor ice-rink. More practical methods to provide a cold/dry air inspirate include conducting exercise in an environmental chamber with the capacity to control temperature and humidity, or the inhalation of dry medical grade gas (<10mg H_2O/L) [6]. It is essential that these aspects are considered moving forward when conducting ECTs for both clinical and research purposes.

It is also important to acknowledge that due to the effect of ICS on airway inflammation and AHR, establishing an asthma diagnosis becomes more difficult following a course of inhaler therapy. This is reflected in the latest GINA guidelines which propose a separate diagnostic pathway for individuals receiving controller medication [1]. Future research in this setting should therefore focus on assessing steroid naive patients, or at least ensure that a detailed history is obtained and/or ensure an appropriate medication washout period. In addition, there remains longstanding debate regarding the most appropriate diagnostic threshold when conducting an ECT. Population based studies in asymptomatic individuals, without a prior asthma diagnosis or use of asthma medication, are therefore required in order for the (ab)normal airway response to exercise to be established (i.e., identify the upper and lower limits of normal).

In conclusion, our findings highlight that NICE asthma guidelines, that currently oppose ECT, are based on a limited number of studies that violate current ECT criteria. Further research is required to re-evaluate the diagnostic value of ECT (i.e., determine sensitivity and specificity) to detect and monitor asthma when conducted in accordance with up-to-date international guidance.

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Table 1. Study compliance with guideline specification (Hallstrand et al., *Eur Respir J*, 2018) [5]

Author (year)	Study population	Medication restriction		Exercise intensity		Exercise duration		Environmental conditions		Post-challenge spirometry		Diagnostic threshold	
		SABA, 8h; LABA, 36 h; LABA in combination with an ICS, 36 h; Ultra-LABAs, 48 h; ICS, 6 h; Long-acting ICS, 24 h; Leukotriene receptor antagonists, 4 days; Leukotriene synthesis inhibitors, 12h / 16 h; Antihistamines, 72 h; Short-acting muscarinic acetylcholine antagonist 12 h; Long-acting muscarinic acetylcholine antagonist, 72 h; Cromones, 4 h; Xanthines, 24 h; Caffeine, 24 h; Vigorous exercise, 4 h.		Target ventilation is 60% of maximum (MVV or FEV_1 × 40) or Heart rate of >85% of maximum can serve as a surrogate for ventilation target		Maintain target ventilation for ≥4 min, preferably 6 min		Inspired air should be dry, and ambient temperature <25°C. This can be accomplished by conducting the study in an air-conditioned room (with ambient temperature at 20–25°C) with low relative humidity (⩽50%). An ideal system delivers dry air through a mouthpiece and a two-way valve from a talc-free reservoir filled with medical-grade compressed air.		Serial assessments of spirometry for 30 min after exercise.		≥10% fall in FEV_1	
Eggleston et al., 1979 [8]	n=45; Range 16-30 years; Young adults with asthma	SABA, 8 h; LABA, 12 h; Corticosteroids therapy was continued; Cromones, 14 days.	×	Treadmill speed and slope adjusted to maintain 90% predicted HR.	✓	5 min of treadmill running	✓	No information provided	?	1, 5, 10, 15 and 20 min after exercise	×	No information provided	?
Lin et al., 1991 [9]	n=22; Range 20-40 years; stable unmedicated asthma	Bronchodilators, 7 days; Corticosteroids, 28 days; Cromones, 28 days; methylxanthine, 7 days; antihistamine, 7 days.	?	Treadmill rate and slope adjusted to achieve 90% predicted HR.	✓	6 min of treadmill running	✓	No information provided	?	5, 10, 15, 20, 25 and 30 min after exercise	✓	>20% fall in FEV_1	×
Avital et al., 2000 [10]	n=135; Mean (SD) 12.4 (3.9) years; Children and young adults with asthma	Bronchodilators, 12 h; ICS therapy was continued. Cromones (sodium cromoglycate), 20 h; Xanthines, NA.	×	Treadmill at 10° slope and 5 km/hr speed	×	6 min of treadmill running	✓	Temperature ranged from 22–26°C and 48–56% RH.	×	1, 3, 5, 10, and 15 min after exercise	×	≥8.2% fall in FEV_1	×
Klepac et al., 2004 [11]	n=35; Range 15-48 years; Asthma or allergic rhinitis	SABA, 12-48h; ICS, therapy was continued; Short-acting muscarinic acetylcholine antagonist (Ipatropium), 24h; Xanthines (Theophyllines) 72 h; Antihistmaines, 4 days; Caffeine, on day of study; Cromones; NA.	×	Treadmill speed and slope adjusted to maintain 85% predicted HR.	✓	6 minutes of treadmill running	✓	Temperature ranged from 18-28°C mean 24.1 (3)°C and humidity 40-85% RH mean 62.35 (14.3)% RH.	×	Immediately and 3, 5, 7, 10, 15, 20 and 30 min after exercise	✓	≥10% fall in FEV_1	✓
Kersten et al., 2009 [12]	n=25; Mean (SD) 12.4 (2) years; children with allergic	SABA, 8 h; LABA, 24 h; Corticosteroids, 28 days; Antihistamines, 14 days; Cromones, 14 days; anticholinergics, 14 days; ICS, 24 h; Vigorous exercise,	×	Treadmill speed adjusted to maintain 90% predicted HR.	✓	Max 6 min of treadmill running	✓	Cold, dry air was obtained by testing in an ice rink with a constant temperature of 18°C	✓	1, 3, 6, 9, 12, 15 and 20 min after exercise	×	>15% fall in FEV_1	×

	asthma and EIB.	4 h											

***Definitions of abbreviations**: SABA, short-acting β2-agonist; LABA, long-acting β2-agonist; ICS, inhaled corticosteroid; MVV, maximum voluntary ventilation; FEV_1, forced expiratory volume in 1 s. ✓, criteria met; ×, criteria not met; ?, insufficient information provided; EIB, exercise-induced bronchoconstriction.*