Täiskasvanute astma käsitlus esmatasandil
Tõendusmaterjali kokkuvõte

Kliiniline küsimus nr 2d

*Kas astma kahtlusel tuleks **diagnoosimiseks** kasutada järgmist meetodit vs meetodi mittekasutamisega:*
hingamisteede põletikumarkerite määramine

Kokkuvõte, sh kriitiliste tulemusnäitajate kaupa:

Süstemaatilisi ülevaateid hingamisteede põletikumarkerite kasutamise kohta astma **diagnoosimisel** Pubmed andmebaasist ei leidnud. Süstemaatilised tõendusmaterjali ülevaated FeNO kasutamise kohta on läbi viidud NICE ja Canadian Toracic Society poolt, vastavalt NICE diagnostic assessment report 2013 ja CTS Guideline update 2012 . On avaldatud süstemaatiline ülevaade FeNO kasutamisest kehalisest aktiivsusest tingitud bronhospasmi diagnoosimisel (Feitosa 2012).

2012. a süstemaatiline ülevaade (Petsky 2012) ning 2007 ja 2008 Cochrane'i andmebaasi süstemaatilised ülevaated hõlmasid 2 uuringut FeNO kasutamise kohta täiskasvanutel ja 3 uuringut röga eosinofiilia kasutamise kohta täiskasvanutel **astma ravi tiitrimiseks/astma kontrolli hindamiseks.** Röga eosinofiilia kasutamisel ägenemiste arv mõnevõrra vähenes (52 vs. 77patsienti ≥1 ägenemisega; p=0.0006), FeNO kasutamisel tulemusnäitajad ei paranenud.

Ravijuhendid

Põletikumarkerite kasutamine astma **diagnoosimisel**: üldiselt ravijuhendites soovitused, et võib neid määrata, aga nende kasulikkus diagnoosimisel ei ole teada.

NICE poolt soovitatakse FeNo määramist astma diagnoosimisel ühe võimalusena teatud juhtudel koos teiste diagnoosmistaktikatega (NICE diagnostics guidance [DG12])

Eraldi FeNO-teemaline ATS juhend (vastavalt GRADEle): tugev soovitus (mõõduka kvaliteediga tõendusmaterjal) FeNO kasutamiseks hingamisteede eosinofiilse põletiku *diagnoosimisel (In the setting of chronic inflammatory airway disease including asthma, conventional tests such as FEV(1) reversibility or provocation tests are only indirectly associated with airway inflammation. Fe(NO) offers added advantages for patient care including, but not limited to (1) detecting of eosinophilic airway inflammation, (2) determining the likelihood of corticosteroid responsiveness, (3) monitoring of airway inflammation to determine the potential need for corticosteroid, and (4) unmasking of otherwise unsuspected nonadherence to corticosteroid therapy.)*

Soovitused ravijuhendites põletikumarkerite kasutamise kohta **ravi tiitrimiseks/astma kontrolli hindamiseks** on erinevad:

1) röga eosinofiilia

-määrata vaid spetsialiseeritud keskuses >18a keskmise ja raske astma korral GKS annuse tiitrimiseks (Canada 2012) (soovituse tase 1B- tugev soovitus, mõõdukas tõendusmaterjal)

-ei ole astma diagnoosimiseks piisavalt spetsiifiline, pole vaja (SIGN 2012, VA/DoD)

-jah, võib määrata (GINA 2012)

2) FeNO

-rutiinseks kasutamiseks ei soovitata (Canada 2012, SIGN-2012)(soovituse tase 2B – nõrk soovitus, mõõdukas tõendusmaterjal)-võib kasutada, on soovitatav kasutada (GINA-2012, GEMA-2009, ATS FeNO) - tõendusmaterjal ei ole tugev

Süstemaatilised ülevaated

Kokkuvõte	Viide kirjandusallikale
25 kohortuuringut FeNo diagnostikaks kasutamise kohta. Kokkuvõte palun vt tabel 22	NICE Diagnostic assessment report 2013 http://www.nice.org.uk/guidance/dg12/resources/measuring-

lk 128-131 (tabel on liiga suur siia kopeerimiseks)	fractional-exhaled-nitric-oxide-concentration-in-asthma-niox-mino-niox-vero-and-nobreath-diagnostic-assessment-report2 Lk 104-150
INTRODUCTION: The gold-standard method for the diagnosis of exercise-induced bronchospasm (EIB) is an exercise test combined with spirometry. However, this test is expensive, time consuming and requires specialized equipment and trained personnel. Exhaled nitric oxide (eNO) is a fast, easy, noninvasive method for the diagnosis of EIB. The aim of the present study was to assess the accuracy of the measurement of eNO for the diagnosis of EIB through a systematic review of the literature. **METHODS:** A search was carried out in the PubMed, Lilacs, SciELO and SCOPUS databases by two independent researchers. **RESULTS:** Fifty-six papers were found. Following the application of the eligibility criteria to the title, abstract and text, six papers remained for analysis. There was a significant heterogeneity in sex (X(2)=56.44, p=0.000) and clinical spectrum (X(2)=504.00, p=0.000) between studies. In children between 3.8 and 7.8 years old a cutoff point >28ppb EIB can be ruled in and in children between 5 and 16 years old at a cutoff point <20EIB can be ruled out. For adults a cutoff point <7EIB can be ruled out and it can be ruled in with a cutoff point >12. Four papers reported negative predictive values above 88%. **CONCLUSION:** The measurement of eNO seems to be effective for ruling in and ruling out EIB in some specific groups. Therefore, the measurement of eNO levels could be an important tool to safely avoid the need for an exercise test when the result is negative, reducing the individual and economic impact of this disease.	Rev Port Pneumol. 2012 Jul-Aug;18(4):198-204. doi: 10.1016/j.rppneu.2012.01.008. Epub 2012 May 4. Diagnostic accuracy of exhaled nitric oxide in exercise-induced bronchospasm: Systematic review. Feitosa LA[1], Dornelas de Andrade A, Reinaux CM, Britto MC.
Asthma severity and control can be measured both subjectively and objectively. Traditionally asthma treatments have been individualised using symptoms and spirometry/peak flow. Increasingly treatment tailored in accordance with inflammatory markers (sputum eosinophil counts or fractional exhaled nitric oxide (FeNO) data) is advocated as an alternative strategy. The objective of this review was to evaluate the efficacy of tailoring asthma interventions based on inflammatory markers (sputum analysis and FeNO) in comparison with clinical symptoms (with or without spirometry/peak flow) for asthma-related outcomes in children and adults. Cochrane Airways Group Specialised Register of Trials, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE and reference lists of articles were searched. The last searches were in February 2009. All randomised controlled comparisons of adjustment of asthma treatment based on sputum analysis or FeNO compared with traditional methods (primarily clinical symptoms and spirometry/peak flow) were selected. Results of searches were reviewed against predetermined criteria for inclusion. Relevant studies were selected, assessed and data extracted independently by at least two people. The trial authors were contacted for further information. Data were analysed as 'intervention received' and sensitivity analyses performed. Six (2 adults and 4 children/adolescent) studies utilising FeNO and three adult studies utilising sputum eosinophils were included. These studies had a degree of clinical heterogeneity including definition of asthma exacerbations, duration of study and variations in cut-off levels for percentage of sputum eosinophils and FeNO to alter management in each study. Adults who had treatment adjusted according to sputum eosinophils had a reduced number of exacerbations compared with the control group (52 vs. 77 patients with ≥1 exacerbation in the study period; p=0.0006). There was no significant difference in exacerbations between groups for FeNO compared with controls. The daily dose of inhaled corticosteroids at the end of the study was decreased in adults whose treatment was based on FeNO in comparison with the control group (mean difference -450.03 µg, 95% CI -676.73 to -223.34; p<0.0001). However, children who had treatment adjusted according to FeNO had an increase in their mean daily dose	Thorax. 2012 Mar;67(3):199-208. A systematic review and meta-analysis: tailoring asthma treatment on eosinophilic markers (exhaled nitric oxide or sputum eosinophils). Petsky HL, Cates CJ, Lasserson TJ, Li AM, Turner C, Kynaston JA, Chang AB. http://www.ncbi.nlm.nih.gov/pubmed/20937641

of inhaled corticosteroids (mean difference 140.18 µg, 95% CI 28.94 to 251.42; p=0.014). It was concluded that tailoring of asthma treatment based on sputum eosinophils is effective in decreasing asthma exacerbations. However, tailoring of asthma treatment based on FeNO levels has not been shown to be effective in improving asthma outcomes in children and adults. At present, there is insufficient justification to advocate the routine use of either sputum analysis (due to technical expertise required) or FeNO in everyday clinical practice.	
BACKGROUND: Asthma severity and control can be measured both subjectively and objectively. Sputum analysis for evaluation of percentage of sputum eosinophilia directly measures airway inflammation, and is one method of objectively monitoring asthma. Interventions for asthma therapies have been traditionally based on symptoms and spirometry. **OBJECTIVES:** To evaluate the efficacy of tailoring asthma interventions based on sputum analysis in comparison to clinical symptoms (with or without spirometry/peak flow) for asthma related outcomes in children and adults. **SEARCH STRATEGY:** The last search was on 31 October 2006. **SELECTION CRITERIA:** All randomised controlled comparisons of adjustment of asthma therapy based on sputum eosinophils compared to traditional methods (primarily clinical symptoms and spirometry/peak flow). **MAIN RESULTS:** Three adult studies were included; these studies were clinically and methodologically heterogenous (use of medications, cut off for percentage of sputum eosinophils and definition of asthma exacerbation). There were no eligible paediatric studies. Of 246 participants randomised, 221 completed the trials. In the meta-analysis, a significant reduction in number of participants who had one or more asthma exacerbations occurred when treatment was based on sputum eosinophils in comparison to clinical symptoms; pooled odds ratio (OR) was 0.49 (95% CI 0.28 to 0.87); number needed to treat to benefit (NNTB) was 6 (95% CI 4 to 32). There were also differences between groups in the rate of exacerbation (any exacerbation per year) and severity of exacerbations defined by requirement for use of oral corticosteroids but the reduction in hospitalisations was not statistically significant. Data for clinical symptoms, quality of life and spirometry were not significantly different between groups. The mean dose of inhaled corticosteroids per day was similar in both groups and no adverse events were reported. However sputum induction was not always possible. **AUTHORS' CONCLUSIONS:** Tailored asthma interventions based on sputum eosinophils is beneficial in reducing the frequency of asthma exacerbations in adults with asthma. This review supports the use of sputum eosinophils to tailor asthma therapy for adults with frequent exacerbations and severe asthma. Further studies need to be undertaken to	Cochrane Database Syst Rev. 2007 Apr 18;(2):CD005603. Tailored interventions based on sputum eosinophils versus clinical symptoms for asthma in children and adults. Petsky HL, Kynaston JA, Turner C, Li AM, Cates CJ, Lasserson TJ, Chang AB. http://www.ncbi.nlm.nih.gov/pubmed/17443604

strengthen these results and no conclusion can be drawn for children with asthma.	
OBJECTIVES: To evaluate the efficacy of tailoring asthma interventions based on exhaled nitric oxide in comparison to clinical symptoms (with or without spirometry/peak flow) for asthma related outcomes in children and adults. **SEARCH STRATEGY:** We searched the Cochrane Airways Group Specialised Register of Trials, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE and reference lists of articles. The last search was completed in December 2006. **SELECTION CRITERIA:** All randomised controlled comparisons of adjustment of asthma therapy based on exhaled nitric oxide compared to traditional methods (primarily clinical symptoms and spirometry/peak flow). **DATA COLLECTION AND ANALYSIS:** Results of searches were reviewed against pre-determined criteria for inclusion. Relevant studies were independently selected in duplicate. Two authors independently assessed trial quality and extracted data. Authors were contacted for further information but none were received. Data was analysed as "intervention received" and sensitivity analyses performed. **MAIN RESULTS:** Four (2 adult and 2 paediatric) studies were included; these studies differed in a variety of ways including definition of asthma exacerbations, FeNO cut off levels and duration of study. Of 356 participants randomised, 324 completed the trials. In the meta-analysis, there was no difference between groups for the primary outcome of asthma exacerbations or for other outcomes (clinical symptoms, FeNO level and spirometry). In post-hoc analysis, a significant reduction in mean final daily dose inhaled corticosteroid per adult was found in the group where treatment was based on FeNO in comparison to clinical symptoms; WMD -282.46 (95% CI -422.08 to -142.84). There was no difference in ICS dose between the groups in the overall daily dose in the adult studies or in the paediatric studies. **AUTHORS' CONCLUSIONS:** Tailoring the dose of inhaled corticosteroids based on exhaled nitric oxide in comparison to clinical symptoms was carried out in different ways in the four studies that were found, and the results show only modest differences. The role of utilising exhaled nitric oxide to tailor the dose of inhaled corticosteroids is currently uncertain.	Cochrane Database Syst Rev. 2008 Apr 16;(2):CD006340. Tailored interventions based on exhaled nitric oxide versus clinical symptoms for asthma in children and adults. Petsky HL, Cates CJ, Li AM, Kynaston JA, Turner C, Chang AB. http://www.ncbi.nlm.nih.gov/pubmed/18425949

"Asthma/diagnosis"[Mesh] AND ("Eosinophils"[Mesh] OR "Inflammation Mediators"[Mesh] OR "Nitric Oxide"[Mesh] OR "Sputum"[Mesh]) AND (Meta-Analysis[ptyp] OR systematic[sb] OR Randomized Controlled Trial[ptyp])