Table C.2. Characteristics of the included studies in KQ 1b

| Author, Year (ref) | Study Country, Study Design, Study Settings, Risk of Bias | FeNO and Comparisons | Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, Atopy, etc) | Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test) | Disease Activities and Asthma Outcomes | Test Findings (Mean, SD) | Conclusions |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Agache, 2012 45 | Romania, longitudinal nonrandomized, outpatient setting, low risk of bias. | FeNO, N= 46 | **Non- difficult asthma group (N=22)**Mean age 7.36 years (SD: 0.67),81% male ,86.36% atopy,22.73% tobacco exposure,4.55% Obesity568.18 mcg (SD:49) beclomethasone**Difficult asthma group (N=24)**Mean age 7.71 years (SD: 0.61),66.67% male,91.67% atopy,31.82% tobacco exposure25% Obesity,572.92 mcg (SD: 87.77) beclomethasone  | FeNO measurement was done using (NIOX MINO, Aerocrine AB); exhaled NO values were corrected for height, male sex, atopy, and infection status. The patients were seen regularly at 1- to 4-month intervals for 12 months, depending on the level of asthma control achieved. ≥ 45ppb was used as cutoff for persistently high FeNO | Persistently high FeNO in difficult asthma was a significant risk factor comparing to non-difficult asthma: OR: 0.0297; 95% CI: 0.0010 to 0.8790Asthma exacerbations, which defines as acute attack requiring oral or systemic corticosteroids, atBaseline (at least 3 moderate or severe asthma exacerbations in the previous year) was13.64% in non- difficult asthma group and 79.17% Difficult asthma. | Baseline: Non- difficult asthma:15.85 ppb (SD: 2.70)Difficult asthma: 26.28 ppb (SD: 4.6). | In children with uncontrolled persistent asthma on ICS, persistently high FeNO was an independent risk factor for difficult to control asthma (along with obesity and severe rhinitis) |
| Spirometry, N= 46 | Lung function testing was done using (spirometry; Microlab MK 8, CareFusion) after a washout period of 12 hours for LABAs and of 4 hours for SABAs; postbronchodilator FEV1 and magnitude of the bronchodilator response were considered. The patients were seen regularly at 1- to 4-month intervals for 12 months, depending on the level of asthma control achieved. | Baseline: Non- difficult asthma: 103.53 (SD: 2.53)Difficult asthma: 91.13 (SD: 3.04). |
| Beerthuizen, 2016 46 | Netherlands,RCT, outpatient setting, unclear risk of bias. | **Group 1\_** Standard care; ACT every 4 months (N= 89) | Mean age 10.2 years (SD: 3.2), Male 69 %, atopy 100 %. |  | Cost:Among healthcare cost categories, only the amount of nurse practitioners’ consultations differed significantly between the strategies.  | Group 1\_average €86 annual expenditure (1.20 consultations per patient per year)Group 2\_ €129 annual expenditure (1.79 consultations per year per patient) Group 3\_ €96 (1.33 consultations per patient per year). | RCT of children with atopic asthma compared standard care vs web-based monthly monitoring ACT vs FeNO and ACT every 4 months. Web-based monitoring was preferred from a healthcare perspective, while the FeNO-based strategy was preferred from a societal perspective. QALYs and costs were not statistically significant changes. |
| **Group 2\_** Web-based; Monthly ACT (N= 91) | Mean age 10.6 years (SD: 2.8), Male 66 %, atopy 100%.  |  | Quality of Life (QALY) \_EuroQoL-5 dimensions (EQ-5D): A 5 domains scale; mobility, self-care, usual activities, pain/discomfort and anxiety/depression. All range from 1 to 3, where 1 represents the most favorable score: Group 2 has a statistically non-significant better utility score. | Group 1: 0.928Group 2: 0.939Group 3: 0.932Group 2 vs 1: 0.011 (−0.005 to 0.027)Group 2 vs 3: 0.006 (−0.008 to 0.021)Group 3 vs 1: 0.004 (−0.018 to 0.026) |
| **Group 3\_** FeNO-based; FeNO and ACT every 4 months (N= 92) | Mean age 10.3 years (SD: 2.9), Male 67 %, atopy 100 % | FeNO was measuredonline on the NIOX chemiluminescence analyzer or NIOX MINO (Aerocrine, Stockholm, Sweden) according toguidelines, offline, | Cost effectiveness:Assessed by cost-effectiveness acceptability curves (CEACs). From a healthcare perspective (based on healthcare costs only) at willingness-to-pay threshold of €40000/ QALY, Group 2 was the most cost-effective, followed by Group 3 and 1. From a societal perspective (including both healthcare costs and costs due to loss of productivity) at a willingness-to-pay of about €40000/QALY, Group 3 has the highest chance of being most cost-effective.  | From a healthcare perspective,Group 1: 3%.Group 2: 77% Group 3: 20% From a societal perspective,Group 3: 83%. |
| Berg, 2008 47 | Sweden, cost-effectiveness study, unclear risk of bias | NR | NR | NR | Asthma diagnosis based on FeNO measurement results in a cost of £38 per patient compared with £26 for standard diagnostics ( defined as one or more of the following: spirometry, reversibility testing, bronchial provocation and sputum eosinophil count) . In mild to severe patients, asthma management with FeNO measurement instead of standard guidelines results in cost-savings of £30 per patient and year. In a more severe population, management with FeNO measurement would save costs of £160 per patient |  | Economic evaluation showing that management using FeNO reduced total cost per patient per year compared to standard diagnostic test (spirometry, reversibility testing, bronchial provocation and sputum eosinophil count). |
| Bernstein, 2009 48 | United States & Spain, cross-sectional, medium risk of bias. | FeNO, N=209 | Overall N=100 in Uinted States and 109 in Spain. Age: median (IQR): USA: 50 years (40-60), Spain 37 years (25-49).Male: USA 45%, Spain 38%.Caucasians 79% in United States, and 100% in SpainAtopy: USA 83%, Spain 62%. | using a chemiluminescen e analyzer (Niox model, Aerocrine, Inc. Solna, Sweden) with a range of detection between less than 1 to 500,000 ppb at the US site and the NioxMino analyzer (MiNo, Aerocrine AB; Smidesvagen, Sweden) at the Spain site. | There were no significant differences among FeNO means across ACT categories for patients from the US site (p=0.31). However, for the Spain site, the FeNO mean for ACT <20 (65.8) was significantly higher than the means for ACT 20–24 (41.0, p<0.01) and ACT 25 (35.2, p<0.01). The FeNO mean value for the Spain site, 45.6, was significantly Higher than the USA site, 24.2 (p<0.001). | FeNO: median (IQR): USA 28.8 (14.5 to 51.9), Spain 42.0 (26.0 to 73.0). | In adult asthmatics, FeNO was correlated negatively with ACT only in patients not on ICS. In other subgroups in the study there was no correlation. |
| Spirometry, N=209 | Forced spirometry at the US site was performed using a Koko spirometer, following the guidelines of the American Thoracic Society. Forced spirometry was performed at the Spanish site using a Jaeger APS pro spirometer (Erich Jaeger, Germany). FEV1, FVC, and peak expiratory flow rate (PEFR) were recorded for each subject using Crapo spirometric reference values in US and using Castellsague reference values in Spain. | For each site, FEV1 was positively correlated when patients were dichotomized by ICS usage Correlations was +0.39 (p<0.05) at the USA site, and +0.26 (p> 0.05) at the Spain site. | FEV1 %, median (IQR): USA 72 (58 to 87.5), Spain 103 (89 to 116). |
| Asthma Control Test (ACT), N=209 | Patients from the US completed the English version of the ACT, whereas those from Spain completed the validated Spanish version. | For each site, ACT was positively correlated when patients were dichotomized by ICS usage Correlations was +0.40 (p<0.001) at the USA site, and +0.32 (p< 0.05) at the Spain site. Negative correlations were obtained between ACT and FeNO at the Spain site only. | ACT: median (IQR):USA 18 (13 to 22), Spain 22 (19 to 24). |
| Bora, 2011 49 | Turkey, longitudinal nonrandomized, outpatient setting, high risk of bias. | FeNO, N= 83 | Mean age 42.3 years (SD: 11.4),15.7% male,9% ever smokers,23% current smokers. | Using a nitric oxide analyzer (NIOX MINO Airway Inflammation Monitor; Aerocrine AB; Solna, Sweden) at a flow rate of 0.05 liters per second at baseline and 3 months later. FeNO threshold was accepted as 20 ppb. | The proportions of patients with FeNO levels > 20 ppb were 21%, 45% and 38% in current smokers, non-smokers and ex-smokers, respectively (P =0.189) | Baseline: 15 ppb (11-26).FeNO > 20 ppb (%)Totally controlled asthma (N=8): 38Partially controlled asthma (N=36): 53Uncontrolled asthma (N=39): 25.At 3 months: 14 (11 to 21) FeNO > 20 ppb (%)Totally controlled asthma (N=10): 20Partially controlled asthma (N=39): 26Uncontrolled asthma (N=34): 38. | In adults with asthma on ICS, FeNO did not differentiate those controlled, partially controlled or uncontrolled. |
| ACT score, N= 83 | A 5 items patient-based questionnaire that investigates the disease control. Patients are questioned about their perception of asthma control in the previous 4 weeks. Totally controlled (ACT = 25), partially controlled (ACT = 20-24) and uncontrolled (ACT ≤ 19). | Baseline:18.98 (SD: 4.59)At 3 months:19.65 (SD: 4.11). |
| Spirometry, N= 83 |  The test was repeated three times using a spirometer (Jaeger Master Screen Pneumo Spirolab II®). Measurements were according to the ATS criteria and the best values were recorded. | FEV1 Baseline: 93.9 ± 13.7At 3 months: 93.0 ± 15.8 (P=0.968)FEV1/FVC Baseline: 78.2 ± 6.9At 3 months: 77.7 ± 7.1 (P=0.387). |
| Methacholine bronchial provocation test positivity, N= 83 | According to the 2-min breathing protocol as described in ATS guideline. The patients inhaled methacholine at the doses of 0.0625, 0.125, 0.250, 0.500, 1, 4, 8 and 16 mg/mL after three repetitive FEV1 measurements. Thereafter, the pulmonary function test was repeated. The dose which caused a 20% or more decrease in baseline FEV1 value was accepted as provocative dose (PD20). A PD20 value of < 8 mg/mL was accepted as an indicator of positive BHR. | Baseline: 59Totally controlled asthma (N=8): 62Partially controlled asthma (N=36): 56Uncontrolled asthma (N=39): 62At 3 months: 45 Totally controlled asthma (N=10): 30Partially controlled asthma (N=39): 54Uncontrolled asthma (N=34): 38 |
| sputum eosinophil > 3%, N= 83 | After medication with a short-acting β2 agonist, sputum was induced by inhalation of 3% hypertonic saline by a nebulizer (Pari Master, Pari Respiratory Equipment Inc. Richmond, VA, USA) with an output of 0.5 ml/min saline for a maximum period of 20 minutes via a mouthpiece. The patients were encouraged to cough and expectorate sputum in a sterile petri dish 10 minutes after the onset of nebulization and every 5 minutes. Three flow-volume curves were obtained before and after each inhalation for patients with a FEV1 value < 80%. The sputum induction was terminated when a > 15% FEV1 decrease was observed in comparison to baseline value or when a symptom occurred. | Baseline: 23Totally controlled asthma (N=5): 0Partially controlled asthma (N=21): 23Uncontrolled asthma (N=21): 29At 3 months: 30 (P=0.791)Totally controlled asthma (N=4): 50Partially controlled asthma (N=15): 27Uncontrolled asthma (N=11): 27 |
| sputum neutrophil, , N= 83 | Baseline: 32 (11 to 50)Totally controlled asthma: 26 (10 to 44)Partially controlled asthma: 22 (9 to 45)Uncontrolled asthma: 33 (15 to 57)At 3 months: 34 (18 to 56) (P=0.241)Totally controlled asthma: 42 (29 to 53)Partially controlled asthma: 28 (18 to 56)Uncontrolled asthma:46 (18 to 64) |
| Cano-Garcinuño, 2010 50 | Spain, longitudinal nonrandomized, outpatient setting, low risk of bias. | FeNO, N=149 | Mean age 10.1 years (SD: 2.1), Males 62.4% Weight 41.2 Kg (SD: 12.7), BMI 19.5 (SD: 3.5) | Using a portable nitric oxide analyzer (NIOX MINO, Aerocrine, Solna, Sweden), which provides FeNO measurements at a flow rate of 50 mL/s.  | Lung function was associated with higher FeNO values only in children treated with ICs. Reduced FEV1/FVC (before or after the bronchodilator test) was the spirometric parameter most strongly related to inflammatory measurements. A low FEV1 (baseline or after salbutamol) was independent of FeNO Level. For the whole sample, FeNO level was not related to asthma control, use of health care resources, limitation of daily activities, or clinical variables. Only cough in the preceding 4 weeks was associated with a higher FeNO.  | cough in the preceding 4 weeks was associated with a higher FeNO level: median 38.5 ppb (IQR, 19.6-64.0) vs 27.5 ppb (IQR, 11.5-51.3); P=.041.FEV1, FEF25-75, and FEV1 values after the challenge with salbutamol were not associated with FeNO level, although patients with reduced FEV1/FVC had higher FENO levels, both before and after inhalation: before, median 64.0 ppb (IQR, 33.1-77.8) vs 32.5 (IQR, 16.9 56.6); P=.023; after, median 61.3 ppb (IQR, 48.0- 106.5) vs 32.8 (IQR, 17.0 57.1); P=.021. | In children with asthma, FeNO correlated with wheezing and cough the previous 4 weeks. No other associations were demonstrated with symptom frequency, bronchodilator use, asthma crises, hospital admissions, limitation of daily activities, or spirometry results. In patients treated with ICs, FeNO was not related to the clinical expression of asthma except for a reduced ratio of forced expiratory volume in 1 second to force vital capacity. |
| Spirometry, N=149 | Patients then underwent a spirometry test and a bronchodilator test by inhaling 400μg of salbutamol through a spacer chamber. We performed pulmonary function testing both before and after the salbutamol challenge and obtained the following: FEV1, the ratio of FEV1 to forced vital capacity (FVC) and the forced expiratory flow, mid-expiratory phase (FEF). |
| Ciprandi, 2013 51 | Italy, cross section, inpatient setting, low risk of bias. | FeNO, N= 180 | Median age 13 years, Male 57.2%, | Measured by chemiluminescence analyzer (Model 280 Nitric Oxide Analyzer; Severs Instrument Inc., Boulder, CO, USA) at 50 ml/sec, at one visit, steroid prior to test was 0%.  |  | 34 ppb (range 29 to 38). | In children, FeNO was strongly related with the response to reversibility to bronchodilation testing and could predict bronchial reversibility. |
| Spirometry, N= 180 | Using a computer-assisted spirometer (Pulmolab 435-spiro 235, Morgan, UK), with optoelectronic whirl flow meter. It was performed as stated by the ATS and ERS. |  | FVC, FEV1, and FEF25–75 were 92%, 81%, and 69% of predicted, respectively. |
| Bronchodilator responsiveness, N= 171 | According to international guidelines and using a salbutamol metered dose of 400 mcg. Reversibility (bronchodilator responsiveness, BDR) was considered if an increase of at least 12% of FEV1 was achieved from baseline, according to ERS/ATS guidelines. |  | 95%  |
| de Bot, 2013 52 | Netherlands, longitudinal nonrandomized, outpatient setting, medium risk of bias. | FeNO, N= 93 | Mean age 11.3 years (SD: 3),65% Male,100% allergic rhinitis. | A single measurement of FeNO was performed at baseline and after 2 years using a hand-held portable nitric oxide analyser (NIOX MINO, Aerocrine AB, Solna, Sweden) at a mouth flow rate of 50mL/s over 10 seconds. |   | At baseline (N=91): 36 ppb (18 to 55)At 2 years (N=77): 34 ppb (19 to 59) | In children with allergic rhinitis and asthma, FeNO was elevated and did not correlate with nasal or asthma symptoms |
| House dust mite-specific IgE, N= 93 | Serum IgE antibodies to Dermatophagoides pteronyssinus were determined at baseline and after 2 years using the CAP- Phadiatop, according to the manufacturer’s instructions. Allergen-specific IgE values of >0.7kU/L (class II) were considered positive. | At baseline (N=93): 55.0 kU/L (SD: 37.2).At 2 years (N=77): 58.4 kU/L (SD: 33.8). |
| Symptoms score, N=93 | Symptoms of wheezing/dyspnea and dry cough during the night were subjectively assessed according to a grading scale: 0=no complaints,1=minor complaints, 2=moderate complaints, 3=serious complaints; the maximum score was 6: | At baseline (N=93): 0.9 (SD: 0.9)At 2 years (N=78): 0.4 (SD: 0.8). |
| Delclaux, 2008 53 | France, longitudinal nonrandomized, inpatient setting, medium risk of bias. | FeNO, N=65 | Mean age 34 years (SD: 10),males 40%, weight 68 Kg (SD: 14), atopy (self-reported) 69%, current smokers 30.8%, ever smokers 7.7%.  | Offline Exhaled NO Measurement, The fraction of NO, collected at a constant flow rate of 100 mL/s, was measured using a chemiluminescent analyzer (ENDONO 8000; SERES, Aix en Provence, France). | The severity of an asthma attack did not influence exhaled NO values on emergency department admission (p=0.27). When considering the whole group, no significant modification of FeNO 0.1 was evidenced during emergency department stay (first 6 hours), whereas a highly significant decrease in FeNO 0.1 was observed after 6 to 15 days of treatment (49 [28 to 69] versus 20 [13 to 27], n=38; p<0.0001). | FeNO Baseline: 49 (26 to 78), At 2 Hours: 45 (27 to 69)At 6 hours: 48 (25 to 66). | In adults seen in emergency department, an increase in FeNO is observed in almost all patients with acute asthma. Subsequent increase within 6 hours is associated with a better degree of asthma control in the subsequent week. |
| Spirometry, N=65 |  | PEF rate (L/min%): Baseline: 295 (SD: 111), At 2 hours: 389 (SD: 104), At 6 hours: 424 (SD: 127). |
| Fritsch, 2006 54 | Austria, RCT, outpatient setting, unclear risk of bias. | Rx based on symptoms, beta-agonist use, lung function and FeNO, N=22 | Mean age 11.3 years (SD:3.4),63.6% males | FeNO was measured prior to lung function testing according to ATS recommendations at a flow rate of 50 ml/ sec with the single breath online method using the NIOX1 instrument (Aerocrine AB, Stockholm, Sweden). At each visit repeated exhalations were performed until three NO plateau values agreed at a 10% level. | Significant relationships were found between FeNO and symptoms over the last 4 weeks, as well as with BHR. There was a significant inverse relationship between FeNO and the dose of ICSs (b ¼ 8.67; P < 0.002). | FeNO cutoff of 22.9 ppb, had 80% sensitivity, and 60% specificity, and 53% PPV for predicting exacerbations.FeNO baseline 34.6 ppb (17.5 to 107.5)FEV1 baseline 101 % pred (91.1 to 107.5) | The cut-off point of 22.9 ppb FeNO best predicted exacerbations (sensitivity of 80% and specificity of 60%) in children with mild to moderate asthma. |
| Rx based on symptoms, beta-agonist use, and lung function only, N=25 | Mean age 12.1 years (SD: 2.8),56% males | Spirometry was performed in a Jaeger Masterlab (Version 4.34, Jaeger, Wuerzburg, Germany) according to ATS recommendations. The best of three maneuvers was recorded and reference values of Zapletal were applied. FEV1 and maximum expiratory flow at 50% of forced vital capacity (MEF50) were used for analyses. | FeNO baseline 31 ppb (20.8 to 54.8)FEV1 baseline 93.7 % pred (83.8 to 99.6) |
| Gelb, 2006 55 | Canada, longitudinal nonrandomized, outpatient setting, low risk of bias. | FeNO, N=44 | Mean age 51 years (SD: 21), males 45.5%, current smoker 0%. | measured using a chemiluminescence analyzer (Sievers NOA 280; Ionics Instruments; Boulder, CO) at an expiratory flow rate of 100 mL/s with varying expiratory airflow resistors (Ionics; Boulder, CO). Exhaled NO was measured at three separate, constant expiratory flow rates: 100, 150, and 200 mL/s in triplicate; and the mean of three values obtained within 10% of each other was used to calculate bronchial NO maximal flow (large airway NO flux [J’awNO]) and small airway/alveolar NO (CANO) using the technique of Tsoukias and George. | If baseline FeNO was ≥28 ppb, exacerbation occurred in 13 of 17 asthmatics (76%); if baseline FeNO was < 28 ppb, exacerbation occurred only in 9 of 27 asthmatics (33%). | When FeNO ≤22 ppb (N= 19), FEV1 2.0 L (SD: 0.6) or 69 % pred (SD: 14), FVC 3.1 L (SD: 1.1) or 89 % pred (SD: 15), FVE1/FVC 63% (SD: 10).When FeNO >22 ppb (N= 25), FEV1 2.2 L (SD: 0.9) or 72 % pred (SD: 25), FVC 3.2 L (SD: 1.1) or 89 % pred (SD: 23), FVE1/FVC 68 % (SD: 11).Baseline FEV1 2.1 L (SD: 0.71) or 70 % pred (SD: 20) of predicted after 180 microgram of albuterol.Healthy subjects (N= 34), FEV1 3.0 L (SD: 0.8) or 91 % pred (SD: 12). FVC 0.07 L (SD: 1) and 96 % pred (SD: 12) FEV1/FVC 81 % (SD: 6). | In controlled asthmatics on ICS, baseline FeNO with cutoff point of 28 ppb can predict first exacerbation over a follow up of 6 months (area under the curve 0.71; sensitivity, 0.59; specificity, 0.82; positive predictive value, 0.77; negative predictive value, 0.87; LR(+), 3.3; LR(-), 0.5; relative risk for exacerbation 3.4 (95% CI, 1.3-9.1). |
| Spirometry, N=44 | When clinically stable for at least 6 weeks, asthmatic patients were instructed to continue all their medications, except to withhold inhaled long-acting 2-agonists for 48 h and inhaled albuterol sulfate and ipratropium bromide for 6 h prior to testing. Lung function, including lung volumes, single-breath diffusing capacity, and static lung elastic recoil pressures were measured using a pressure-compensated flow plethysmograph (Model 6200 Autobox; SensorMedics, Viasys; Yorba Linda, CA). | If the baseline FEV1 in liters was ≤76% of predicted, exacerbation requiring at least one course of tapering oral or parenteral corticosteroids over 18 months occurred in 20 of 31 asthmatics (65%); if FEV1 was >76% of predicted, exacerbation occurred only in 2 of 13 asthmatics (15%) [p 0.003, 2 8.84]. Using ROC plots for first asthma exacerbation, with cutoff point for FEV1 at 76% predicted, the area under the curve was 0.67; sensitivity, 0.91; specificity, 0.50; positive predictive value, 0.65; negative predictive value, 0.85; LR(+), 1.8; and LR(-), 0.18. |
| Gill, 2005 56 | United States, longitudinal nonrandomized, outpatient setting, high risk of bias. | FeNO, N=46 | Mean age 19 years (4–54), 35 % males, 100 % atopics,17% current smoker | Measured by the manufacturer(NIOX; Aerocrine AB, Stockholm, Sweden).Baseline FeNO measurements were recorded either before the first bronchodilator treatment was administered or at the first point in care that did not interfere with the treating physician’s management and patient stabilization. | Changes in FeNO were not associated with NIH class of asthma severity hospitalization, or relapse. |  | FeNO measurements in ED patients with acute asthma exacerbations were poorly reproducible and did not correlate with standard measures of asthma severity. |
| Spirometry, N=46 | Measured using handheld spirometry (KoKo Peak Pro 6; PDS Healthcare Products, Inc., Louisville, CO) in accordance with ATS standards |
| Griese, 2000 57 | Germany, RCT, outpatient setting, low risk of bias. | FeNO, N=74 | Mean age 9.7 years (4-16), 76.1 % males, 100 % atoptics. | FeNO was measured online with a chemiluminescence analyzer (Logon LR 2000, Rochester, Kent, UK) sensitive to ENO at concentrations of 1-5000 parts per billion (ppb, by volume). The response time (10-90%) was <0.65 sec. | FeNO in relation to the recommended change in inhaled therapy. | FeNO > 13ppb = Step up (24) vs No change (8) vs step down (5).FeNO < 13ppb= Step up (12) vs No change (11) vs step down (13). | FeNO values did not correlate with current disease severity in children |
| Spirometry, N=74 |  | FEV1 in relation to the recommended change in inhaled therapy. | FEV1< 80% pred = Step up (6) vs No change (1) vs step down (1).FEV1> 80% pred= Step up (26) vs No change (12) vs step down (17). |
| Symptom score, N=74 |  | Symptom score in relation to the recommended change in inhaled therapy. | Symptoms Yes = Step up (34) vs No change (15) vs step down (11).Symptoms no = Step up (2) vs No change (4) vs step down (8). |
| Gruffydd-Jones, 2007 58 | United Kingdom, longitudinal nonrandomized, outpatient setting, low risk of bias. | FeNO, N= 37 | Adults (n=22) median age 56.5 years (37.75-60.5), males 36.4%, ever smokers 36%. Children (n=15), median age 9 years (8-12), males 73%, ever smokers 0%.  | Measurements were performed on the Niox chemiluminescence eNO analyzer (Aerocrine Ltd, Sweden) at an expiratory flow of 50ml/sec as per guideline recommendations. It was aimed to obtain three NO values that agreed within 10% of each other (as per ERS guidelines), and repeated exhalations were performed up to a maximum of 10 or when the subject tired. | There was no statistically significant difference in the coefficient of variation (CV) between children and adults (median (IQR) 35.0 (29.6 to 48.4) and 32.4 (20.9 to 51.7) respectively. A significant correlations were observed in adults between changes in lung function and changes in FeNO (a rise in FeNO was moderately correlated with a fall in %predicted FEV1, (r= -0.33, p<0.001), and between changes inFeNO and changes in Asthma Quality of Life Questionnaire scores (a rise in FeNO was weakly correlated with worsening asthma related health status, r= -0.22, p=0.02). | Adults: 31.2 ppb (11.5 to 61.9).Children:55.3 ppb (11.6 to 102.1). FeNO was reduced significantly between the first and the last study visit in children (median change in FeNO =14.5 ppb (-41.5 to -0.2), p= 0.01) but not significantly in adults (-9.1 ppb (-28.7 to 2.7), p=0.14). FeNO was non-significantly lower at baseline in adults than children (median FeNO: 31.2 ppb (11.5 to 61.9) vs. 55.3 ppb (11.6 to 102.1) ppb, p=0.38), but not at the final visit 30.7 (15.7 to 43.2) vs.24.8 (14.7 to 55.7), p=0.60). | In adults and children seen every 2 weeks for 12 weeks, FeNO values correlated with ACQ, AQLQ and bronchodilator use. |
| Spirometry, N=37 | Spirometry: (Vitalograph) performed as per ERS guidelines. | Adults: FEV1% (median, IQR): 86.5 (57.25 to 101.75), PEF: 435 (400 to 457).Children:FEV1% (median, IQR): 82 (76 to 94), PEF 310 (280 to 410),  |
| Asthma Control Questionnaire (ACQ), N=37 | ACQ: Short-term symptomatic asthma control – the Asthma Control Questionnaire (ACQ) in adults only (this instrument has not been validated in children.) | Adults: 1.1 (0.4-2.3). |
| Asthma Mini Quality of Life Questionnaire (AQLQ), N=37 | Health status: in adults – the Asthma Mini Quality of Life Questionnaire (AQLQ); and in children – the Paediatric Caregivers Quality-of-life Questionnaire (PQLQ). | Adults: 5.6 (4.1 to 6.7).Children:6.1 (5.0 to 6.7). |
| Habib, 2014 59 | Saudi Arabia,cross section study,outpatient setting, high risk of bias. | FeNO, N= 53 | Mean age 36.1 years (SD: 14.3),79.2% male,43.4% ex-smokers,Weight 28.0 Kg (SD: 5.0)60% ICS-treated,64.8% Atopy, | According to the present recommendations of the American Thoracic Society using handheld NIOX MINO Airway Inflammation Monitor (Aerocrine AB, Solna, Sweden). A FeNO level of >47 ppb was used to indicate inflammation and uncontrolled asthma | Mean FeNO values were significantly higher in patients with an ACT score <20 of 65.5 ppb (SD: 35.4) compared with those patients with an ACT score ≥20 of 27.4 ppb (SD: 10.5).Linear regression analysis revealed a significant negative correlation of FeNO with ACT score (r=-0.581, p<0.0001).  There was no significant correlation of FeNO with age, height, weight, asthma duration, and ventilatory function tests. | Baseline: 48.9 ppb (SD: 33.3). | In adult asthmatics, there was an inverse relationship between ACT scores and FeNO. At the international cutoff point of 20, the sensitivity was 95.2, and the specificity was 68.8. Maximum sensitivity and specificity were observed at an ACT score cut off point of 19 (sensitivity: 90.5 and specificity: 81.2). |
| Spirometry, N= 53 | Ventilatory functions were measured using an electronic spirometer (Vitalograph Co, Clare, Ireland), which was calibrated daily |  | FEV1 at baseline: 83.8% pred (SD: 7.7). |
| ACT Score, N= 53 | Arabic version of the ACT score questionnaire was used |  | Baseline: 17.6 (SD: 4.9). |
| Hanson, 2013 60 |  United States, retrospective chart review, outpatient setting, high risk of bias. | FeNO, N=75 | Age mean (range) 6.4 (4.75-7), 52 % males, BMI 16.9 Kg/m2 (12.2-28.4),33% atopic dermatitis,71% allergic rhinitis,33% ever smokers. | Single-breath FeNO testing was performed using the NIOX MINOdevice, using a 10-second exhalation time and measured in partsper billion. For subjects unable to perform this maneuver, a 6- second exhalation time was used. | Regression coefficients forassessment of the overall impact of age, asthma severity, allergicrhinitis, atopic dermatitis, use of ICSs, and use of LTRAs on FeNO | Asthma severity had the greatest impact on FeNO (0.32), followed by ICS (-0.27), atopic dermatitis and age (each 0.23), allergic rhinitis (0.20), and LTRAs (-0.16). | In children age 4-7 FeNO values correlated with asthma severity, atopic dermatitis and steroids use; and marginally with allergic rhinitis (p=0.06) |
| Spirometry. N=36 |  |  | Mean FEV1/FVC 91 % pred (92 to 9.2).Mean FEV1 102 % pred (SD: 20.1). |
| Childhood Asthma Control Test (C-ACT) score, N=43 | Validated Childhood Asthma Control Test (C-ACT) score (ACT score>19 indicating inadequate control). |  |  Mean C-ACT 17.9 (SD: 5.9) range 4 to 27. |
| Harkins, 2004 61 | United States, longitudinal nonrandomized, outpatient setting, medium risk of bias. | FeNO, N=22 | Age range 28-48.years, current smokers 0%. | Using off-line in 10-L Mylar bags after subjects inhaled through an NO-free filter. Content of the bags was measured for NO via chemiluminescnence. | Those with exacerbation within 2 weeks of routine appointment had a higher mean FeNO 29.67 ppb (SD: 14.48) compared with those who did not 12.92 ppb (SD: 5.17). | Patients without exacerbation:FeNO 12.92 ppb (SD: 5.17)FEV1 1.82 L (SD: 0.99)FEV1 53.6 % pred (SD: 23.2).Patients with exacerbation:FeNO 29.67 ppb (SD: 14.48).FEV1 1.81 L (SD: 0.61)FEV1 62.5 % pred (SD: 15.6). | Adult asthmatics who had an exacerbation in the previous 2 weeks had a higher mean FeNO (29.67 vs 12.92). |
| Spirometry, N=22 | Spirometry was obtained following ATS guidelines. |
| Hayata, 2013 62 | Japan,longitudinal nonrandomized,outpatient setting, medium risk of bias. | FeNO, N= 297 | **Group 1: Low PEF variability (Min% Max ≥80%) (N=245):** Mean age 47.7 years (SD: 15.1),41.6% male,75.5% atopy,BMI 22.4 (SD: 3.7),31.4% Ex-Smokers,356 ug/day (SD: 133) dose of inhaled steroid.**Group 2; High PEF variability (Min% Max < 80%) (N=52):**Mean age 51.7 years (SD: 13.5),51.9% male,82.7% atopy, BMI 23.4 (SD: 4.1),48.1% Ex-Smokers,433 ug/day (SD: 225) dose of inhaled steroid. | Online electrochemical nitric oxide analyzer (NIOX MINO; Aerocrine AB, Solna, Sweden) over a week. |  | At baseline:Group 1: 25.3 ppb (SD: 12.8).Group 2: 51.8 ppb (SD: 22.1.FeNO for predicting Min%Max < 80%: 1.08; (95% CI: 1.05 to 1.11). | In adults asthmatics on ICS, FeNO 40 ppb yielded 75% sensitivity and 90% specificity for identifying the subjects with high variability in PEF. |
| Spirometry, N= 297 | It was measured at baseline and after a week. | FEV1 at baseline:Group 1: 100.4% pred (SD: 12.8)Group 2: 82.8 % pred (SD: 12.3.FEV1 for predicting Min%Max < 80%: 1.14; (95% CI: 1.05 to 1.24)FEV1/FVC at baseline:Group 1: 78.1 % pred (SD: 9.1).Group 2: 70.3 % pred (SD: 10.6)FEV1/FVC for predicting Min%Max < 80%: 1.03; (95% CI: 0.95 to 1.12) |
| Asthma Control Questionnaire (ACQ), N= 297 | The ACQ-5 is a questionnaire that assesses asthma condition according to five items, each of which can be rated on a seven point scale.0 represents excellent asthma control and 6 represents extremely poor control. The overall score was the mean of the five responses. It was measured at baseline and after a week. | At baseline:Group 1: 0.4 ± 0.4Group 2: 0.9 ± 0.5 (P <0.001)OR for predicting Min%Max < 80%: 11.86; 95% CI: 3.55 to 39.61 |
| Hsu, 2013 63 | Taiwan,cross sectional,outpatient setting, high risk of bias. | FeNO, N=56 | Mean age 62.3 years (SD: 16.3),62.5% male. | Flow of 50mL/sec, using an offline and online chemiluminescence (NOA 280i; Sievers Boulder, CO) in one visit. |  | Online FeNO groups:Age >65 (N=29): 37.2 ppb (SD: 19.9)Age 20-65 (N=27): 39.8 ppb (SD: 33.8).Online FeNO groups:Controlled/partially: 35.1 ppb (SD: 20.4)Uncontrolled: 45.5 ppb (SD: 38.8).Offline FeNO groups:Age >65 (N=29): 19.2 ppb (SD: 9).Age 20-65 (N=27): 20.5 ppb (SD: 13.5).Offline FeNO Group Controlled/partially: 18.1 ppb (SD: 9)Uncontrolled: 23.2 ppb (SD: 14.4). | In elderly asthmatics, FeNO measurement was feasible and correlated with ACT |
| Spirometry, N=56 |  | FEV1% pred Age >65 (N=29): 76.3% pred (SD: 21.9).Age 20-65 (N=27): 85.6 % pred (SD: 17.8).FEV1/FVC Age >65 (N=29): 62.8 % pred (SD: 9.9)Age 20-65 (N=27): 71.4 % pred (SD: 8.6). |
| Asthma Control Test (ACT), N=56 | ACT score of ≤19 was defined as poorly controlled asthma | Overall: 20.7 (SD: 4.1).Age >65 (N=29): 19.8 (SD: 4.8).Age 20-65 (N=27):21.8 (SD: 2.8). |
| Kavitha, 201764 | India, prospective study, outpatient setting, medium risk of bias | FeNO, N = 100 | Mean age 34.2 years (SD: 11.6), 52.3% males, steroid naïve nonsmokers, 34.4% were atopics (allergic rhinitis).92% received ICS with long acting beta agonists, 82% LeukotrieneAntagonists and 6% systemic steroids. | FeNO was measuredbefore any other respiratory tests using a handheld NioxMino point of care device that measure nitric oxide molecules at very low concentrations. | There is significant correlation between change in FeNO from baseline to 6-week follow up with the change in FEV1, BDR, ACT score, and PEFR variability, with the strength of association strongest with change in PEFR variability(-0.85), followed by ACT score(-0.73) and FEV1 (-0.72). | FeNO cutoff ≥48 ppb at baseline and FeNO ≥36 ppbAt 6 week follow up provide optimal sensitivity (66.6%) and specificity (65.6%) to differentiate patients with controlled and uncontrolled symptoms. | FeNO may be useful to assess asthma control in both steroid naïve asthmatics and asthmatics on treatment. However, the suboptimal sensitivity and specificity may limit its utility as a point of care single monitoring tool. |
| Spirometry, N = 100 |  | FeNO showed significant increased between patients according to both airflow obstruction severity and asthma control according to GINA guidelines. | FEV% predicted: FeNO>70%: 21 ppb60-69%: 39 ppb50-59%: 48 ppb35-49%: 82 ppb<35%: 138 ppb |
| Asthma control test (ACT), N = 100 |  |  | Controlled:25.5 ppbPartially controlled:35 ppbUncontrolled:40 ppb. |
| Ko, 2011 65 | China,longitudinal nonrandomized,outpatient setting, low risk of bias. | FeNO, N= 379 | Mean age 46.1 years (SD: 13.2),31.7% male,0% current smokers. | using chemiluminescence analyser (NOA280i, Sievers Instruments, Boulder, CO, USA) at a flow rate of 50 mL/sec. |  | Baseline: 66.9 ppb (SD: 51.9).Asthma exacerbation at 6 months prediction: AUC 0.45, (P: 0.16).Urgent health-care utilization at 6 months prediction: AUC 0.44, (P: 0.15). | In men with asthma, FeNO level at baseline did not predict healthcare utilization over 6 months |
| Spirometry, N= 379 | Spirometry pre- and postbronchodilatorwas performed using theVitalograph (Buckingham, UK) spirometer in the sitting position, according to the ATS/ERS standards.The updated predicted spirometry values for the Hong Kong Chinese were adopted. | Baseline:Pre-bronchodilator FEV1 (N = 339): 85.2% pred (SD: 20.5).Post-bronchodilator (N = 374) FEV1: 90.4% pred (SD: 20.8).Asthma exacerbation at 6 months prediction: Pre-bronchodilator: AUC 0.54, (P: 0.33)Post-bronchodilator: AUC 0.55, (P: 0.19).Urgent health-care utilization at 6 months prediction: Pre-bronchodilator: AUC 0.53, (P: 0.50).Post-bronchodilator: AUC 0.53, (P: 0.48). |
| ACT score, N= 379 | The ACT is a five-item questionnaire to assess asthma control in the previous 4 weeks. The sum of the scores of the five questions gave the total ACT score (range 5–25). The higher the score, the better the asthma control. The ACT questionnaire was translated into Chinese by a qualified translator and thenback-translated into English by another qualifiedtranslator, and any inconsistencies found were appropriately corrected | Baseline: 20.0 (SD: 4.1).Asthma exacerbation at 6 months prediction:AUC 0.69, (P: <0.0001).Urgent health-care utilization at 6 months prediction: AUC 0.66, (P: <0.0001). |
| Kostikas, 201166 | Greece,cross section study,outpatient setting, medium risk of bias. | FeNO, N= 274 | Well controlled (N = 99)Mea age 51 years (SD: 18),35% male,31.3% current Smokers,BMI 28.5 (SD: 4.7),67.7% ICS-treated.Partly controlled (N = 115)Mean age 51 years (SD: 17),41% male,28.7% current smokers,BMI 27.5 (SD: 5.1),79.1% ICS-treated.Uncontrolled (N = 60)Mean age 46 years (SD: 15),40% male31.7% current smoker,BMI 28.0 (SD: 5.0),60% ICS-treated. | using a portable NO analyzer (NIOXMINO Airway Inflammation Monitor, Aerocrine, Solna,Sweden) at a flow of 50 mL/sec. | FeNO cutoff >22 ppb provided best predictor of not well-controlled in steroid-naive non-smokers, however, FeNO cutoff >27 ppb provided best predictor of NOT well-controlled in steroid-treated non-smokers.  | Well controlled: 16 (13 to 20)Partly controlled: 27 (19 to 44) Uncontrolled: 59 (23 to 111) FeNO cutoff >22 ppb provided best predictor of not well-controlled in steroid-naive non-smokers:Sensitivity: 0.87Specificity: 0.81PPV: 0.90NPV: 0.76AUC: 0.899 (0.778 to 0.967)FeNO cutoff >27 ppb provided best predictor of not well-controlled in steroid-treated non-smokers:Sensitivity: 0.64Specificity: 0.94PPV: 0.95NPV: 0.60AUC: 0.844 (0.775 to 0.899) | FeNO had AUC of 0.790 for the identification of not well-controlled asthma (using ACT). FeNO values >30 ppb presented positive predictive values (PPV) > 0.85 with the exception of smokers treated with inhaled corticosteroids. |
| EBC pH, N= 274 | EBC was collected using a commercially available device (EcoScreen, Viasys, Germany). Subjects rinsed their mouth with distilled water and performed tidal breathing for 15 min while wearing a nose clip. EBC pH was measured using a commercially available pH meter (Model 3510, Jenway, Essex, UK), immediately after the collection of condensate. Stable pH was achieved after deaeration of the EBC with argon (350 mL/min for 10 min). | Well controlled: 7.44 (7.34 to 7.57)Partly controlled: 7.25 (7.12 to 7.36) Uncontrolled: 7.14 (7.05 to 7.21)  |
| Asthma Control Questionnaire (ACQ) , N= 274 | Juniper’s Asthma Control Questionnaire (ACQ) was used. | Well controlled: 0.57 (0.29 to 0.86)Partly controlled: 1.86 (1.14 to 2.71)Uncontrolled: 3.43 (2.57 to 4.00) |
| Asthma Control Test (ACT) , N= 274 |  | Well controlled: 23 (22 to 24)Partly controlled: 18 (17 to 19)Uncontrolled: 14 (11 to 17) |
| Kwok, 2008 67 | United States, cross sectional,inpatient setting, high risk of bias. | FeNO, N= 90 | Mean age 8.9 years (7.9-9.8),67% male. | Chemiluminescence analyzer (NIOX MINO) through several visits in 81% of patients.The initial measurement was performed before or after the initial administration of b-adrenergic agonists, but always before the administration of corticosteroids. | There was no difference in the median FeNOconcentrations among subjects with mild, moderate, orsevere acute asthma exacerbations (P = 0.65) | The mean change in FeNO concentrations from the start to the end of treatment was 0.24 ppb (-1.45 to 1.94). | In children 2–18 years old seen in an urban ED for acute asthma exacerbation, measurement of FeNO was difficult for a large proportion of children and did not correlate with other measures of acute severity |
| Leblanc, 2013 68 | Portugal, longitudinal non randomized, outpatient setting, medium risk of bias. | FeNO, N=185 | Mean age 37.48 years (SD: 14.88), 21.6 % males  | Measured by chemiluminescence analysis, using NIOX instrument (Aerocrine; Sweden).FeNO evaluation a cut-off value of 35 ppb was used (15) with higher levels reflecting a greater probability of airway eosinophilic inflammation | FeNO change with asthma severity (based on FEV1) | The mean values of FEV1 were 85.5% (SD of 21.6%) for patients with low probability of inflammation (FeN0<35) and 84.8% (SD of 16.0%) for those with FeN0≥35.Among patients with FeNO < 35 ppb, 66% had FEV1 > 89% and 52% had asthma control test score > 19. | Among patients with partially and controlled asthma, 60% had FeNO less than 35.  |
| Spirometry, N=232 | Spirometry values, FEV1 and FEF25-75%, were expressed as 3-level variables: percent predicted less than 60%, between 60 and 80% and greater than 80% |
| Score registration of the Asthma Control Test, N=232 | Divided into 3 different groups: less or equal to 19 (uncontrolled asthma), 20 to 24 (partially controlled) and equal to 25 (well controlled asthma). A second ana lysis was performed dividing ACT™ score in 2 groups (score ≤19 and >19) |
| Lex, 2007 69 | Germany, longitudinal nonrandomized, outpatient setting, medium risk of bias. | FeNO, N=85 | Mean age 11 years (5-16) male 52%. | Measured by online chemiluminescence analyzer (NOA280, Sievers Instruments, Boulder, CO), at 50 ml/sec, Steroid prior to test was 49.4%, bronchodilators withheld prior to test was 9.4%. | FeNO was significantly elevated in those with exercise induced bronchoconstriction (EIB) defined as reduction of FeV1 > 15% vs those without. The cut off level of FeNO 25 ppb resulted in the best combination of sensitivity and specificity to predict exercise c induced bronchoconstriction. | With EIB (N=12) 51.3 ppb (31.1 to 67.3) vsWithout EIB (N= 73) 20.2 ppb (10.9 to 42.3). Sensitivity 100%Specificity 58%PPV 28%NPV 100%AUC 0.796 | In children with atopic asthma, FeNO was significantly elevated in those with exercise induced reduction of FeV1 (> 15%) with NPP 100% and PPV 28%. NPV and PPV for reported asthma symptoms within 2 weeks preceding the study were 96% and 26%. Thus, FeNO can be used to exclude EIB in atopic child |
| Spirometry, N= 85 | Patients were asked to withhold ß2-agonists for at least 12 hr; inhaled steroids were not withdrawn prior to testing. After measuring specific airway resistance (sRaw,tot) by body plethysmography, baseline spirometry was performed.  | FEV1 and FVC were significantly elevated in those with exercise induced bronchoconstriction (EIB) vs those without EIB, however, FEV1/FVC ratio was lower in patients with EIB vs without EIB.  | With EIB (N=12)FEV1% pred 95.2 (88 to 105.3)FVC % pred 86.1 (78.1 to 98.1)FEV1/FVC % pred 116.2 (111.1 to 123)Without EIB (N= 73)FEV1% pred 101.9 (95 to 114)FVC % pred 94.7 (85 to 105.6)FEV1/FVC % pred 114.9 (108.1 to 263.2). |
| Asthma symptoms in 2 weeks preceding exercise challenge, N= 38 |  |  | Asthma symptoms in 2 weeks preceding exercise challenge has a higher specificity but lower sensitivity, NPV and PPV to predict exercise induced bronchoconstriction (reduction of FEV1 >15%) than FeNO.  | sensitivity 83%specificity 62%PPV 26%NPV 96% |
| Mahut, 2010 70 | France, longitudinal nonrandomized, outpatient setting, low risk of bias. | FeNO, N=200 | Mean age 16 years (12-38), male 52.5% current smoker 0%, atopy 82% | Measured by online chemiluminescence analyser (ENDONO 8000; SERES, at 50-250 ml/sec, Steroid use prior to test was 82.5% | FeNO did not correlate with ACQ /short-ACQ nor was influenced by severity classes. |  | In adults and children stable and on treatment (mostly ICS), FeNO did not correlate with ACQ or short ACQ. |
| Asthma Control Diary (ACD) and Asthma Control Questionnaire (ACQ), N= 200 |  | There was a good agreement between ACD and the weekly telephonic ACQs questionnaires when considering weekly assessments separately as well as the multiple assessments per patient. |  |
| Martins, 2008 71 | Portugal, longitudinal nonrandomized, outpatient setting, high risk of bias. | FeNO, N=54 | mean age 7.8 years (SD: 1.1), Males 57.4%, atopy; 38.9% sensitized to at least one aeroallergen, 22.2% had positive skins prick tests for grass and/or olive tree pollen and 35.2% positive for house-dust mites. | FeNO measurement was read after the spirometry was performed, using a portable analyzer, Niox® Mino (Aerocrine, Sweden), in which the expiratory flow rate is maintained at 50 mL/s.  | The correlation between FeNO and FEV1, FEV1/FVC and ΔFEV1 was weak and not statistically significant (rho -0.189, -12.8 and 0.038 respectively).Comparing the children who had at least one wheezing and/or respiratory difficulty episode in the six months prior to the evaluation with those who were complaint-free during the same period, we find statistically significant differences for the ΔFEV1 (8% median [p25-75%: 3.25-16.5%] versus 4.5% median [p25-75%: 3-7%] respectively; p=0.04). We also find statistically significant differences for the FeNO (23 ppb median [p25-75%: 12-31.75 ppb] versus12 ppb median [p25-75%: 9-21.25 ppb] respectively; p=0.02). | The mean FEV1 value (a percentage of the theoretical value) was 100% (SD:14), the ΔFEV1 (a variation percentage in relation to the base value) was 8.1% (SD: 7.3) and the con-centration of nitric oxide in exhaled air (FeNO) in parts per billion (ppb) was 20.8 ppb (SD: 14.7).Comparing the children who needed to use a bronchodilator in the six months prior to the evaluation with those who had no need of this medication, we find statistically significant differences for the FeNO: 27 ppb median [p25-75%: 19.75-34.25 ppb] versus 11 ppb median [p25-75%: 9-18.75 ppb] respectively; p<0.0001. | In children, FeNO levels could differentiate those who had exacerbations and needed bronchodilators in the previous 6 months. |
| Spirometry, N=54 | The spirometer used was a Vitalograph® Compact (Buckingham, UK). 200μg of salbutamol were administered for the bronchodilation challenge. |
| McCormack, 2013 72 | United States,longitudinal nonrandomized,outpatient setting, low risk of bias. | FeNO, N= 150 | Mean age 11 years (5-17),57% Male,91% Black,43.3% ex-smokersWeight 28.0 Kg (SD: 5.0),60% ICS-treated,90% Atopy. | FeNO level was measuredat baseline, 3, 6, 9, and 12 months using the online Niox MINO (Aerocrine Inc) according to the ATS guidelines. | FeNO level was not a strong predictor of asthma-related health-care use in the subsequent 3 months; however, lung function was a better predictor than FeNO.ED visit in the past 12 months n: 111 patients.Acute visit in the 12 months follow period: 237 in 78 patients.ED visit in the 12 months follow period: 125 in 58 patients.Hospitalizations: 7 in 5 patients. | Baseline: 32 ppb (16-61) | In high risk children (minorities in urban areas with persistent asthma and atopy) on controller medication, FeNO every 3 months was not a significant predictor of acute visits, ED visits, unscheduled doctor visits, or hospitalization in adjusted analysis. |
| Spirometry, N= 150 | Spirometry was performed at baseline, 3, 6, 9, and 12 months according to ATS guidelines using a KoKo spirometer (nSpire Health Inc) and National Health and Nutrition Examination Survey reference equations for calculating % predicted values. | FEV1 Baseline: 94.4% pred (SD: 17.7)FEV/FVC Baseline: 80.7 % pred (SD: 9.6). |
| Menzies, 2008 73 | United Kingdom, longitudinal nonrandomized,outpatient setting, low risk of bias. | FeNO, N=267 | Mean age 51.6 years (SD: 1.1),46% male,0% ever smokers,0% current smokers. | Online chemiluminescence analyzer (NIOX MINO) through one time visit during 3 months period. | Exacerbations experience at 3 months: 14 patientsExacerbations experience in the 12 months before the visit: 72 patientsRoyal College of Physicians symptom score of 0 was identified as a significant negative predictor for exacerbations in the 12 months (P = 0.008) and 3 months (P = 0.005) before the clinic visit but not for the 3 months after the visit (P = 0.45)  | Exacerbation group: 31.3 ppb (SD: 8.3).No exacerbation group: 28.0 ppb (SD: 1.7) (P: 0.66) | In adults with asthma, FeNO was measured and correlated with exacerbations 12 months before and 3 months after. Levels of FeNO were significantly lower in frequently exacerbating patients receiving higher doses of maintenance ICS compared with patients with mild disease who were corticosteroid naive. Measurement of FeNO was an insensitive method (sensitivity, 66.7%; specificity, 51.9% at a cutoff value of 20 ppb) for identifying patients who subsequently exacerbated. |
| Spirometry, N= 267.  | Was performed in accordance with American Thoracic Society/European Respiratory Society guidelines to determine forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), and FEV1/FVC. | Exacerbation group: 85 % pred (SD: 5.9).No exacerbation group: 86.7% pred (SD: 1.3) (P: 0.75). |
| Meyts, 2003 74 | Belgium, cross-sectional, outpatient setting, high risk of bias. | FeNO, N=73 | Good asthma control (defined if both day- and night-time symptoms were absent, if the frequency of short-acting beta2-agonist use was less than four times during the past 2 weeks, and if the FEV1 of a well-per ) (N= 21) median age 10.9 years, atopy 76%.Acceptable asthma control (N= 31) median age 10.9 years, atopy 83.9%.Insufficient asthma control (N= 21) median age 10.7 years, atopy 85.7%. | Exhaled air was led via a Teflon tubing system to the chemiluminiscence analyzer (Ecophysics CLD 700 AL MED, Durnten, Switzerland). Air was continuously sampled at a sampling rate of 0.700 ml/min. Response time of the analyzer was 1 sec; detection limit for NO was 1 part per billion (ppb). | Percentages of change in FEV1 (median (quartiles)) After salbutamol administration were 2% (0-7) for group 1, 2% (2–8%) for group 2, and 8% (6–14%) for group 3. These percentages differed significantly between all three groups (P¼ 0.005), between groups 1 and 3(P¼ 0.002), and between groups 2 and 3 (P¼ 0.006). | Good asthma control: baseline FEV1% 101 (SD: 15), FVC% 105 (SD: 11).FeNO median 11 ppb (quartiles 9-21).Acceptable asthma control: baseline FEV1% 94 (SD: 15), FVC% 103 (SD: 14).FeNO median 15 ppb (quartiles 11-26).Insufficient asthma control: baseline FEV1% 91 (SD: 15), FVC% 103 (SD: 14).FeNO median 28 ppb (quartiles 19-33). | In children with asthma seen in outpatient settings, FeNO differentiates those with insufficient, acceptable and good control (defined if both day- and night-time symptoms were absent, if the frequency of short-acting beta2-agonist use was less than four times during the past 2 weeks, and if the FEV1 of a well-per ) (28 ppb, 15 ppb, 11ppb; p<0.01). |
| Spirometry, N= 73 | All subjects underwent baseline and postbronchodilator (20 min after 400 micro.g salbutamol administration with pMDI and Volumatic1 spacer) flow-volume measurements, using the IOS digital (Jaeger, Germany). |
| Michils, 2008 75 | Belgium, longitudinal nonrandomized, outpatient setting, low risk of bias. | FeNO, N=341 |  | FeNO was measured before any forced expiratory maneuvers using a daily calibrated LR 2000 chemoluminescence analyzer (Logan Research Ltd, Rochester, UK) with on-line measurement of a single exhalation at flow rate of 50 mL.s-1 (ATS/European Respiratory Society standard). | In non-severe asthma, an optimal control was documented at the first visit in 164 pairs (out of 415). Loss of optimal control at visit two is considered as a positive event. This occurred in 39 occasions. In the whole population, anFeNO increase, 30% makes a loss of optimal control unlikely (NPV 82%).In steroid naïve patients, an initial FeNO level. 35 ppb predictsasthma control optimization in two out of three cases (PPV68%). In ICS-treated patients, asthma control is unlikely to become optimal after treatment increase if FeNO was 35 ppb at the first visit (NPV 88%). FEV1 never predicted optimization. | ICS naïve patients:49.8 ppb (24 to 103.5).ICS dose ≤500 microg: 27 ppb (11.7 to 62.1), ICS >500 microg: 20.5 ppb (9 to 46.7),  | In unselected population of adults with persistent asthma, FeNO correlated with ACT and need for control optimization. This correlation was reduced in those of high dose ICS. |
| Spirometry, N= 341 | Spirometry was performed using a Zan 300 spirometer (Zan1, Oberthulba, Germany). Pre-bronchodilator FEV1 was used as an index of airway caliber.  | ICS naïve patients:FEV1%: 88.9 (SD:18.5) ICS dose ≤500 microg: FEV1%: 90.1+/-15.1, ICS >500 microg: FEV1%: 84.1 (SD: 19) |
| Asthma Control Questionairre (ACQ), N= 341 |  | ICS naïve patients:2 (0 to 5.2).ICS dose ≤500 microg: 0.8 (0 to 4.8).ICS >500 microg: 1.3 (0 to 5.2). |
| Michils, 2009 76 | Belgium, longitudinal nonrandomized, outpatient setting, medium risk of bias. | FeNO, N= 470 | Nonsmokers (n= 411)Mean Age 41 years (SD: 16), male 47.4%, atopic 85.1%.Smokers (n=59); mean age 38 years (SD: 11), male57.6%, atopic 91.5%. | Measured by online chemoluminescence analyzer (Logan Research Ltd, Rochester, UK) at a flow rate of 50 mL/sec (American Thoracic Society (ATS)/European Respiratory Society (ERS) standard). | FeNO exhibits high operating characteristics in both nonsmoking and smoking groups. The cut-off valuesfor decreases inFeNO which had the highest NPVs for establishing control were 30% in nonsmokers and 20% in smokers. When considering the subgroup of smoking patients treated with >500 mg equivalents BDP.day-1, FeNO was no longer significant in assessing an improvement of asthma control. As for improvement assessment, FeNO exhibited analogous operating characteristics in nonsmoking and smoking patients. With a cut-off value at 30% change, a high NPV was observed in both groups. When considering the subgroup of smoking patients treated with >500 mg equivalents BDP.day-1, FeNO operating characteristics in assessing asthma control worsening are less significant. | Baseline FeNO:Nonsmokers: 33.7 (14.3 to 79.2), smokers: 18.1 (6.9 to 47.5). | Correlation between FeNO and ACQ were noted in smokers and nonsmokers on ICS. |
| Asthma control questionnaire (ACQ), N= 470 | Asthma control was assessed using a French translation of the short version of the ACQ of Juniper et al. | ACQ score: Nonsmokers: 1.5 (0 to 5), smokers: 1.7 (0 to 5.3). |
| Spirometry, N= 470 | FEV1: Nonsmokers: 85.6 (SD: 15.7), smokers: 86.2 (SD:17.9). |
| Nayak, 2013 28 | India,cross section study,inpatient setting, medium risk of bias. | FeNO, N= 100 | Asthmatics (N=55):Mean age 45.2 years (12-82),41.8% male,51% On inhalational steroids.Controls (N=45):Mean age 48.5 years (16-76),48.9% Male. | Three FeNO measurements were recorded for each subject using chemiluminescence NO-analyser and the procedure was performed as per standard recommendation. FeNO level of < 8.0 ppb was taken as normal. | The FeNO levels were not significantly lower in steroid treated cases as compared with steroid naïve cases. | asthmatics: 16.5 ppb (SD: 10.3)Controls: 5.5 ppb (SD: 2.7).Steroid-treated cases (N=28): 15.7 ppb (SD: 9.8).Steroid-naive cases (N=27): 17.3 ppb (SD: 10.9).Correlation of FeNO with severity of asthma in steroid-treated cases:Mild asthma: 6.3 ± 2.6Moderate asthma: 15.1 ± 9.7Severe asthma: 18.8 ± 9.7.Correlation of FeNO with severity of asthma in steroid-naïve cases:Mild asthma: 11.9 ± 8.3Moderate asthma: 20.7 ± 8.2Severe asthma: 28.9 ± 11.3 | In patients with bronchial asthma, FeNO levels significantly correlate with the severity of asthma and the levels reduce with steroid therapy. |
| Nittner-Marszalska, 2013 77 | Poland,longitudinal nonrandomized,outpatient setting, low risk of bias. | FeNO, N=72 | Pregnant asthmatics with a median age 29 years (18-38),0% male,0% current smokers,73.6% atopy. | Flow of 50mL/sec, using an online chemoluminescence analyzer (NIOX, Aerocrine, Stockholm, Sweden), in a fasting status every month for 6 months. | No asthma exacerbation experience. It is defined as an episode of increasing asthma symptoms requiring a change of corticosteroids treatment.  | 31.6 ppb (7.3 to 129.8). | Pregnant asthmatics women underwent monthly FeNO and there was a weak correlation between FeNO and ACT and wide variation in FeNO values. Results were the same in atopic and non-atopic women. Levels did not significantly differ in women who lost control from values during control. |
| Spirometry, N=72 | Spirometry (Master Scope, Jeager, Germany) was performed according to the recommendations of the American Thoracic Society and the European Respiratory Society | FEV1 97.1% pred (55 to 135). |
| Ozier, 2011 78 | France. longitudinal cohort study, medium risk of bias. | FeNO (EndoNO), N= 90 | controlled asthma (N= 62)mean age of 38.5, 32% males, 77.4% atopic, 23% ever smoked.uncontrolled asthma (n=28): mean age of 44.8 years, 46% males,82.1 atopic, 32% ever smoked.  | chemiluminescence device EndoNO (SERES, France) on-line at a flow rate of 50 ml/s and a pressure of 10 cm H2O |  | FeNO (EndoNO) cutoff of 22 ppb (n=89) can predict the persistence of asthma control with:Sensitivity 77.7%, specificity 62.9%, PPV 47.7%, NPV 86.7%. | In Adults, FeNO can predict the persistence of asthma control in controlled patients and may can be used in asthma management since it can accurately be measured by means of hand-held devices. |
| FeNO (MINO) , N= 90 | Electrochemical device NIOX MINO (Aerocrine AB, Sweden). | FeNO (MINO) cutoff of 31 ppb (n=78) can predict the persistence of asthma control with:Sensitivity 60%, specificity 66%, PPV 45.4%, NPV 77.8%. |
| Asthma control questionnaire (ACQ) , N= 90 | All clinical and the functional items were equally weighted and averaged (each quoted from 0-6). | Well controlled: 0.62 Non-well controlled2.48 |
| Papakosta, 2011 79 | Greece,longitudinal nonrandomized,outpatient setting, medium risk of bias. | FeNO, N= 160 | Adults with newly diagnosed asthma Mean age 39.7 years (SD: 16.6),35% male. | FeNO was measured at an expiratory flow rate of 50ml/s by a chemiluminescence analyzer (CLD 88sp; ECOMEDICS AG, Duernten, Switzerland) according to the latest American Thoracic Society / European RespiratorySociety (ATS/ERS) recommendations. |  | Baseline: 25.97 ppb (SD: 25.68)At 4–12 weeks after initiation of treatment: 17.0 ppb (SD: 14.77).CompletelyControlled group (N=37)Baseline:20.52 ppb (SD:24.97)At 4–12 weeks after initiation of treatment (N = 48): 19.23 ppb (SD: 18.18).Partly controlled (N=85) Baseline: 24.39 ppb (SD: 20.58)At 4–12 weeks after initiation of treatment:15.39 ppb (SD: 12.72)Uncontrolled (N= 38) Baseline:34.78 ppb (SD: 33.92).At 4–12 weeks after initiation of treatment (N = 13): 21.04 ppb (SD: 14.66) | In adults with newly diagnosed asthma, patients with uncontrolled asthma had statistically higher FeNO values than patients with partly controlled (p = .038) and completely controlled asthma (p = .016). ACT score was found to have a negative correlation with FeNO. |
| Spirometry, N= 160 | FEV1 was measured by an electronic spirometer (Wright Ventilometer, Clement Clarke International, LondonEngland). | Baseline: FEV1 88.18% pred (SD: 14.17)At 4–12 weeks after initiation of treatment: FEV1 92.63 % pred (SD: 12.34)Completelycontrolled(n = 37): Baseline: FEV1 0.28 % pred (SD: 14.60)At 4–12 weeks after initiation of treatment (N = 48):FEV1 95.07 % pred (SD: 13.01)Partly controlled  (N= 85): Baseline FEV1 88.74 % pred (SD: 13.19)At 4–12 weeks after initiation of treatment (N = 99): FEV1 92.23 % pred (SD: 11.79)Uncontrolled  (N = 38):Baseline FEV1 84.89 % pred (SD: 15.62)At 4–12 weeks after initiation of treatment (N = 13):FEV1 86.71 % pred (SD: 12.57). |
| Asthma Control Test (ACT) score, N= 160 | The ACT questionnaires administered to the patients of this study had been formally translated into Greek. Patients were classified into three groups based on ACT scores (9): completely controlled (ACT score = 25), partly controlled (ACT score range = 20–24), and uncontrolled (ACT score range = 5–19). | Baseline: 21.27 ± 3.74At 4–12 weeks after initiation of treatment: 23.00 ± 2.19(P < 0.001) |
| Plaza, 2013 80 | Spain,longitudinal nonrandomized, outpatient setting, low risk of bias. | FeNO, N= 381 | Mean age 44.3 years (SD: 14.86),43% male,66.4% atopy. | Flow of 50mL/sec, using a NioxMino® portable equipment (Aerocrine, Sweden)  | The combination of FeNO and ACQ-7, showed 75% specificity and a 85.2% positive predictive value to identify patients with not well controlled asthma.The area underthe ROC curve was 0.8754 for FeNO and ACQ-7 combined,and 0.544 for sole FeNO. | Baseline: 44.18 ppb (SD: 29.82)At 1 month: 26.8 ppb (SD: 20.82). | In adults with not well controlled persistent asthma and a positive bronchodilator test, adding FeNO to ACQ-7 increased the detection of not well controlled asthma following maintenance therapy adjustment by 14.8%. |
| Spirometry, N= 381 | Spirometry was performedaccording to the European Respiratory Society/AmericanThoracic Society guidelines using the predicted values forMediterranean populations. | FEV1 Baseline: 79% pred (SD: 18.8)At 1 month: 85.3% pred (SD: 16.6). |
| ACQ-7 score, N= 381 | The questionnaire contains 7 items comprising 6 multiple choice test questions on the frequency of asthma symptoms and the use of rescue medication within the prior 7 days, and the FEV1 percent of predicted value. The total ACQ-7 score, computed from its 7 items, ranges from 0 (maximum control) to 6 (minimum control), and a 0.75 point threshold was chosen toconsider controlled asthma | Baseline: 2.21 (SD: 0.81)At 1 month: 1.10 (SD: 0.78). |
| Quaedvlieg, 2009 81 | Belgium, cross section, outpatient setting, low risk of bias. | FeNO, N= 134 | Well controlled group (N=31): mean age 40 years (SD: 13), Male 52%, Ever smokers 32%, current smokers 3%, atopy 90%.Borderline group (N=32): mean age 47 years (SD: 12), Male 50%, Ever smokers 0%, current smokers 25%, atopy 69%.Uncontrolled group (N=71): mean age 42 years (SD: 12), Male 49%, Ever smokers 20%, current smokers 20%, atopy 69%. | measured by an online chemoluminescence analyser (NIOX, Aerocrine, Stockholm, Sweden), at one visit, at a flow rate of 50 mL/s, in accordance with the recommendations of the ATS/ERS task force. Corticosteroid use and bronchodialtors withhold prior to test in each group were 64%, 62%, 65% and 100%, 100%,100%, prospectively. | There is no FeNO significant difference between the three groups. | Controlled mean 47.9 ppb (11.4 to 130), borderline mean 30.6 ppb (2.8 to 222), uncontrolled mean 50.2 ppb (4.1 to 244). | In adults with asthma mostly on ICS, FeNO did not differentiate well controlled/borderline controlled/well-controlled based on ACQ.  |
| A bronchial responsiveness (methacholine challenge test), N= 134 | Measured by a modified Cockroft’s method. Inhaled tidal breathing for 2 min fourfold increasing concentrations of methacholine chloride from 0.06 to 16 mg/mL. The aerosol was generated by a jet nebulizer (Hudson,Temecula, CA, USA).  | Uncontrolled asthmatics had a greater BHR to methacholine than controlled asthma. | PC20 in controlled mean 6.3 mg/ml (0.17 to 16), borderline mean 3.9 mg/ml (0.05 to 16), uncontrolled mean 1.6 mg/ml (0.06 to 16).  |
| Sputum eosinophilia, N= 134 | induced by inhalationof a hypertonic saline (NaCl 4.5%) combined withadditional salbutamol delivered by an ultrasonicnebulizer (Ultra-Neb 2000, De Vilbiss, Somerset, PA,USA) with an output set at 0.9 mL/min. Sputum was weighed and homogenized by adding three volumes of PBS, vortexed for 30 s and centrifuged at 800 g for 10 min at 41C. | Uncontrolled asthmatics had a greater sputum eosinophilia than controlled and borderline asthma. | Controlled mean 0.4% (0 to 31.2), borderline mean 1.4% (0 to 26), uncontrolled 5.6% (0 to 93.4). |
| Spirometry, N= 134 | Electronic spirometer connected in real time to a computer (Spirobank, MIR, Rome, Italy). All manoeuvres were repeated three times and the best FEV1 value was selected by the software program (Winspiro, MIR). |  | FEV1 (% pred); controlled mean 101 (SD: 11), borderline mean 88 (SD: 13), uncontrolled mean 81 (SD: 27).FEV1/FVC (%); controlled mean 80.6 (SD: 4.5), borderline mean 76.5 (SD: 6.5), uncontrolled mean 79 (SD: 21). |
| Asthma Control Questionnaire (ACQ), N= 134 | The ACQ score from the six-item Juniper ACQ questionnaire deleting the FEV1 from the original questionnaire (0 = totally controlled and 6 = severely uncontrolled).  |  | Controlled ACQ < 0.75, uncontrolled ACQ > 1.5, borderline ACQ 0.75-1.5. |
| Raj, 2014 82 | India, longitudinal cohort study, outpatient setting, medium risk of bias. | FeNO, N= 243 | mean age of 8.3 years, 76% males, 100% atopic (positive to at least one allergen). | measurement was done using NIOX MINO (Aerocrine AB, Solna, Sweden), 81% were on inhaled steroids, | Pulmonary score did not correlate with acute exacerbation FeNO (r=0.1, Spearman correlation, P=0.29).FeNO cutoff = 20 ppb during exacerbation had a sensitivity of 44%, specificity of 68.7%, AUC of 0.59. | Baseline (n=185)Median 15 ppb (9-26)Personal best (n=218)Median 8 ppb (5-12)During exacerbation (n=143) Median 17.7 ppb (12-25.3). | In children with acute exacerbation of asthma, FeNO during exacerbation was not higher than that during follow up but was significantly higher than personal best. FeNO during acute exacerbation did not correlate with the severity of acute exacerbation and could not diagnose or predict exacerbation. |
| Spirometry, N= 243 | Spirometry was done using portable spirometer (Superspiro MK2, Micro Medical Ltd, UK) |  |
| Pulmonary score, N= 243 | Each parameter is rated on a 0-3 scale, with a maximum total score of 9. Mild, moderate, and severe acute exacerbations were defined as pulmonary score of 0-3, 4- 6, and 7-9, respectively. |
| Ricciardolo, 2016 83 |  Italy, cross sectional, outpatient setting, high risk of bias. | FeNO, N=363 | Mean age 46.28 years (SD: 17.11), 41.3 % males, BMI 25.31 kg/m2 (SD: 5.18),81.3% atopic (allergy). | Measured with a chemiluminescence analyser(Eco Medics CLD88 sp, Duernten, Switzerland) beforespirometry; the detection limit of the apparatus was 1-5parts per billion (ppb), as required by ATS guidelines | Compared to controlled and partly controlled asthmatic, poorly controlled asthmatics showed the highest FeNO values (p < 0.001), with a probability almost four times greater to have pathological values compared to controlled asthmatic patients (p = 0.002). | Poorly controlled asthmatic median: 42.90 ppb, 25th-75th:19.63 to 77.15).(OR: 3.71, 95%CI: (1.74 to 7.89); p = 0.002) | FeNO assessment in clinical practice may be a useful tool for monitoring asthmatics as it is associated with several clinical factors, including asthma control. |
| Spirometry, N=363 | Spirometry was performed using a computer-assisted spirometer (Pulmolab 435-spiro 235, Morgan, England, ---predictive values ECCS 1993), with optoelectronic whirl flowmeter. |
| Robroeks, 2007 84 | Netherlands, cross sectional study, outpatient clinic, high risk of bias. | FeNO, N= 64 | mean age 10.7 years (SD: 0.4),mean weight 38 Kg (SD: 2).  | Measured at one visit using offline chemoluminescence analyzer nitric oxide monitor (NIOX; Aerocrine AB, Solna, Sweden) at an exhalation flow rate of 50 ml/sec.  | Compared to FEV1, FeNO, IFN-g and IL-4 were significant indicators of an asthma diagnosis, with odds ratios ranging from 1.03 for FeNO to 5.21 for IL-4 in EBC.  | FeNO at 30ppb: OR: 3.32;95% CI: 1.05 to 10.5.FeNO at 20 ppb:OR: 2.26; 95%CI: 0.92 to 5.55. | FeNO, 8-isoprostane, IFN-gamma and IL-4 were significant indicators of asthma control with a sensitivity of 82%, specificity of 80%, and area under the curve was 0.761. |
| exhaled breath condensate (EBC), N= 64 | The acidity of EBC was immediately measured in non-deaerated samples (Radiometer, type PHM201, Zoetermeer, the Netherlands) and EBC was rapidly frozen at 80 1C using dry ice, and was stored at 80 1C until analysis. Then, cytokines (IFN-g, TNF-a, IL-2, -4, -5, -10) were assayed with flow cytometry (CBA, BD Biosciences, San Diego, CA, USA). |
| Rosias, 2004 85 | Netherlands, longitudinal nonrandomized, outpatient setting, medium risk of bias. | FeNO, N=23 | Mean age 10.6 years (SD: 2.8), weight 35.4 Kg (SD: 12.3). | FeNO was measured by means of NIOX(Aerocrine, Solna, Sweden) according to the criteria of the American Thoracic Society. At a constant flow rate at 50 ml/sec, guided by a balloon meter. The mean FeNO value of three consecutive measurements was used for analysis.  | The correlate ons found between FeNO and preFEV1 (r ¼ 0.59, P< 0.05), and FeNO and ACQ score (r¼ 0.48, P¼ 0.06). | FeNO median 23.1 (SD: 5).FEV1% pred; Pre-FEV1: 96.4% (SD:16.2), Post-FEV1: 103.2%(SD: 16.7). | In children with mild to moderate persistent asthma on ICS, FeNO weakly correlated with asthma control questionnaire (p=0.06). |
| Spirometry, N= 23 |  |
| Sato, 2009 86 | Japan, cross sectional, inpatient setting, medium risk of bias. | FeNO, N=78 | Non-exacerbation group (N=62): mean age 60.4 years (SD: 14.1), male 43.5%, atopic% 54.8, BMI 21.7 (SD: 8.6), current smoker 12.9%, ever smoker 19.4%.Exacerbation group (N=16): mean age 64.6 years (SD: 7.2), male 37.5%, atopic% 56.3, BMI 21.9 (SD: 7.8), current smoker 6.3%, ever smoker 18.8%. | Using an online collection apparatus using chemiluminescence (280A Sievers Nitric Oxide Analyzer, Boulder, CO, USA) according to the ATS (American Thoracic Society) guidelines. | The area under the curve (AUC) of the cut-off points of the secondnode, as the combination of the ACT score ≤23 and thepercentage of predicted FEV1 ≤91.8% (AUC 0.678, 95% CI0.513 to 0.833) are the most predictive factors in comparison with those of the first node, as the ACT score ≤23 (AUC 0.613, 95% CI 0.453 to 0.773), or those of the third node, as the combination of the ACT score ≤23, and the percentage of predicted ≤91.8% and FeNO≥36.7 ppb (AUC 0.625, 95% CI 0.453 to 0.797). | FeNO: non-exacerbation group: 42.8 (SD: 30.6), exacerbation group: 47.1 (SD: 40.2). | In adults with mild to moderate asthma, clinically stable for 3 months on ICS, FeNO did not accurately predict future exacerbations over a year (AUC 0.501 (0.341–0.661), sensitivity 0.44, specificity 0.57. |
| Spirometry, N=78 | When clinically stable for at least 2 months, asthmatic patients were instructed to continue all their medications, except to withhold inhaled long-acting ß2-agonists for 24 hours and inhaled albuterol sulfate for 6 hours before testing. Spirometry was performed  | Baseline FEV1%Non-exacerbation group: 92.7 (SD: 15.8), exacerbation group: 83.3 (SD: 17). |
| ACT, N=78 | using a CHESTAC-8800 (CHEST, Tokyo,Japan). | ACT score: non-exacerbation group: 23.6 (SD: 2.2), exacerbation group: 23.4 (SD: 1.8). |
| Shirai, 2008 87 | Japan, cross sectional, outpatient setting, high risk of bias. | FeNO, N= 105Classified by 5-item ACT questionnaire score. (Totally controlled =25, well controlled = 20-24, uncontrolled= 5-19). | Total controlled (N=45)Median age 54 years (35-62), male 42.2%, ever smoker 24.4%, current smoker 8.9%.Well controlled (N=28)Median age 57 years (43-67), male 32.1%, ever smoker 23.1%, current smoker 14.3%.Uncontrolled (N=32)Median age 49 years (36-62), male 32%, ever smoker 37.5%, current smoker 12.5%. | Measured by online nitric oxide analyzer (Sievers NOA 280i; Sievers, Boulder, Colorado) at 50 ml/sec. | FeNO were significantly lower in the totally controlled asthma group than in the uncontrolled asthma group. ACT score was negatively correlated with FeNO, however, it was a weak correlation (r= -0.310). | Total controlledMedian 53 (44.5 to 64.5).Well controlledMedian 61.9 (33.5 to 105.6).UncontrolledMedian 72.1 (45.9 to 142.8). | In adults with asthma on ICS for 3 months, ACT ability to differentiate controlled from uncontrolled was improved with FeNO |
| Spirometry, N= 105 |  | No significant differences were seen in %FEV1 and FEV1/ FVC between three groups. ACT score was positively correlated with %FEV1 but not with FEV1/FVC, however, it was a weak correlation FEV1% pred (r 0.219). | FEV1 % predTotal controlledmedian 93.4 (84.5 to 105.4).Well controlledmedian 87.9 (76.0 to 94.3).Uncontrolledmedian 86.4 (71.8 to 95.9).FEV1/FVCTotal controlledmedian 78.0 (66.9 to 84.9).Well controlledmedian 73.4 (66.4 to 80.6).Uncontrolledmedian 73.2 (62.9 to 84.5). |
| Szefler, 2008 88 | United States, RCT, outpatient setting, low risk of bias. | FeNO monitoring, N= 276. (guideline-based care and FeNO) | Mean age 14.4 years (SD: 2.1), 52.9% males, Race: Black 66%, Hispanic 22%, other or mixed 11%. | Measured by a rapid-response chemiluminescent analyzer (flow rate 50 mL/s; NIOX System, Aerocrine, Sweden) according to the guidelines of the American Thoracic Society. | Maximum days with symptoms, which was our primary endpoint, did not differ between treatment groups over the study period (p=0·78).Control levels did not differ between groups. lung function, fraction of exhaled NO, and adherence did not differ between groups during the study; however, despite the level of control achieved, fraction of exhaled NO was less than 20 ppb in only 190 (35·6%) of 534 participants on at least 80% of visits during the treatment period. | 306/534 patients (57·3%) had their asthma under good control (control level=1) for at least 80% of visits.In 122/534 patients (22·8%), asthma control was at level 3 or 4 for at least 20% of visits. (22·1% of FeNO monitoring Group and 23·6% of control group). | Patients aged 12–20 years with persistent asthma randomized to guideline based treatment vs treatment modified by FeNO (for 46weeks). Both groups had similar days with symptoms, and exacerbation rate. FeNO group had higher ICS doses. |
| Control (guideline based care only), N=270 | Mean age 14.4 years (SD: 2.1), 52.6% males, Race: Black 61%, Hispanic 23%, other or mixed 16%. |  |
| van der Valk, 2012 89 | Netherlands, Switzerland and Italy, longitudinal nonrandomized,outpatient setting, medium risk of bias. | FeNO, N=27 | Moderate exacerbations (N=18): Mean age 11.7 years (SD: 2.5),44.4% male,Weight 43.8 Kg (SD: 11.8).Severe exacerbations (N=9):Mean age 10.1 years (SD: 2.1),22.2% male,Weight 37.6 Kg (SD: 11.1). | Fractional exhaled nitric oxide was measured daily using a handheld airway inflammation monitor (NIOX MINO, Aerocrine, Solna, Sweden), along with daily symptom scores for 30 weeks at home |  | Moderate exacerbations (N=18): 21 ppb (14 to 32).Severe exacerbations (N=9): 19 ppb (10 to 40). | In Children with asthma receiving daily measurements of FeNO, slope and trends can predict exacerbations |
| Spirometry N=27 |  | Moderate exacerbations (N=18): FEV1 86.7% pred (SD: 16.6)Severe exacerbations (N=9): FEV1 78.7% pred (SD: 24.3). |
| van Vliet, 2015 90 | The Netherlands, longitudinal nonrandomized,outpatient setting, low risk of bias. | FeNO, N =96 | Age mean (range) 10 (6-17), 52 % males, 76 % atoptic asthma | FeNO was measured online using a NIOX analyzer (Aerocrine, Solna, Sweden) according to American Thoracic Society/European Respiratory Society (ATS/ERS) criteria. A standard flow rate of 50 ± 5 ml/sec was required for a correct maneuver. | Performance of, FeNO in prediction of asthma exacerbation | Estimate (95% CI)-0.011 (−0.029 to 0.007) | In asthmatic children on ICS, FeNO measured every 2 months did not predict exacerbations even when combined with inflammatory markers and clinical characteristics. |
| ACQ Questionnaire, N=96 | The ACQ was used to assess asthma control at the clinical visits. The cut-off points used for level of asthma control were: ACQ ≥ 0.75 (controlled asthma); 0.75< ACQ ≤1.5 (partly controlled); and ACQ >1.5 (uncontrolled asthma). | Performance of asthma clinical characteristics (ACQ score) in prediction of asthma exacerbation | Estimate (95% CI)0.082 (- 0.424 to 0.589) |
| spirometry, N=96 | Performed by means of the ZAN 100 spirometer, according to ATS/ERS standards (nSpire Health GmbH, Oberthulba, Germany).Recorded parameters included: FEV1, forced vital capacity (FVC) and maximum expiratory flow at 50% of FVC (MEF50) | Performance of (Bronchodilator response, delta FEV1 % predicted value) in prediction of asthma exacerbation | Estimate (95% CI)−0.047 (−0.104 to 0.011) |
| Visitsunthorn, 2014 91 | Thailand, cross-sectional study, outpatient setting, high risk of bias. | FeNO, N=114 | Mean age 12.3 years (SD: 3.5), 61.4% males, BMI 20.21 (SD: 4.65), atopy 100%. | Measured by means of an electrochemical technique (ECO medics, CLD 88 sp, chemiluminescence NO-analyzer with optional ultrasonic flow meter). Carried out according to the manufacturer’s and American Thoracic Society/European Respiratory Society (ATS/ERS) recommendations, requires a single-breath on-line measurement with the mouthpiece in place. | The FeNO levels and log FeNO in patients with different asthma control status  | uncontrolled groupFeNO 39.15 ppb (2.40 to 192.30), partly controlled group FeNO 24.90 ppb (2.20 to 85.70)controlled group FeNO 19.20 ppb (5.10 to 108.90).The mean+ SD of Log FeNO in controlled group 1.295+0.31, partly controlled group1.298+0.41uncontrolled group1.417+0.49  | In children with asthma (mostly mild persistent), FeNO levels differentiated controlled, partly controlled and uncontrolled in those not on ICS (trend was not statistically significant in those on ICS) |
| Spirometry, N= 114 | Spirometry was performed using the standard method.  |
| Visitsunthorn, 201792 | Thailand, prospoctive study, inpatient setting, low risk of bias. | FeNO, N = 70 | Overall Median age 12.6 year, 65.7% males, 100% atopics (allergic rhinitis).18.6% develop asthma exacerbation (AE) vs 81.4%.\* AE episode had to include at leastone of the following: PEFR <20% of predicted; use of a beta-2 agonist for ≥2 days; use of systemic corticosteroids or an increase from a stable maintenance dose for ≥ 3 days; hospitalization or emergency-room visit that necessitated administration of systemic corticosteroids. | A single breath FeNO measured every 3 month using a CLD 88 ChemiluminescenceNitric Oxide Analyser with optional ultrasonicflow meter (ECO Medics, Dürnten, Switzerland) according to the(ATS/ERS).  | Baseline FeNO levels, FEV1 bronchodilator reversibility and FEF25–75% bronchodilator reversibility were significantly higher in 18.6% patients with AE within the next 12 months than in 81.4% those without AE. FeNO of 31 ppbprovided optimal sensitivity and specificity for AE prediction than FEV1 reversibility and FEF25–75%. | Baseline level in AE vs without AE:FeNO (ppb): 35.6 vs 16.5.FEV1:7 vs 4FEF25–75%: 34 vs 14FeNO of 31 ppb for AE prediction:Sen 92.3%Spe 75.4%PPV 46.2%NPV 97.7% | Baseline FeNO level was significantlyhigher in asthmatic patients who experienced an asthma excaerbation within the next 12 months. The optimal cutoffpoint of FeNO level for the prediction of an AE is31 ppb. |
| Spirometry, N= 70 | Spirometry was performed at first visit and every 3 months by standard method. FEV1 and FEV1/FVC ratio were expressed as absolute values and percentage of predicted values. |
| Voorend-van Bergen, 2015 93 | The Netherlands,RCT, outpatient setting, high risk of bias. | FeNO, N= 266 | FeNO Group (n=92)Mean age 10.3 years (SD: 2.9), 67 % males, 100 % atoptic.Web based mointoringgroup (n =91)Mean age 10.6 years (SD: 2.8), 66 % males, 100 % atoptic.Standard careGroup (n=89 )Mean age 10.2 years (SD: 3.2), 69 % males, 100 % atoptic. | FeNO was measuredonline on the NIOX chemiluminescence analyzer or NIOX MINO (Aerocrine, Stockholm, Sweden) according toguidelines, offline, Assessed using an electronic spirometer(Masterscreen, Jaeger, Würzburg, Germany) andexpressed as percentage predicted or z-score according to= GLI2012 | Mean difference was higher in web group than other groups. | FeNO change from baseline over time expressed as ratio of geometric means;FeNO group 1.40Web group 1.64Standard care group 1.18 | RCT of children with atopic asthma compared web-based monthly monitoring ACT vs FeNO and ACT every 4 months vs standard care. There was no statistically significant difference in terms of ACT or asthma free days. Lower ICS use was in the web based approach. QALYs and costs were not statistically significant |
| Spirometry, N= 229 |  | FEV1 % pred mean difference was higher in standard care group than other groups. | FeNO group 0.16Web group -0.10Standard care group 0.26 |
| Asthma Control Test, N= 269 | Used the Dutch, translated and linguistically validated version of the ACT (MAPI-research institute, Lyon, France) in children from the age of 12 years, and the C-ACT for children aged 4–11 years | Mean difference was higher in web group than other groups. | FeNO group 0.12Web group 1.73Standard care group 0.37 |
| Warke, 2004 94 | Ireland, cross sectional, outpatient setting, high risk of bias. | FeNO, N=133 | Median age 9.9 years (range 5-14), 53.3% male. | Measured by online chemiluminescence analyzer (NOATM 280, Sievers Instruments Inc., Boulder, Colorado). The flow rate was 50 ml/s and this corresponded to a mouth pressure of 17 cm H2O. | FeNO levels (median [IQR] ppb) were significantly elevated in children who had recent symptoms compared with those without recent symptoms. The difference between medians was 8.6 ppb (95% CI for the difference 1.8 to 13.9, p = 0.004). However, there was a significant difference in FeNO levels between the controlled and uncontrolled group (difference between medians 17.9 ppb [95% CI for difference 0.1 to 22.8], p=0.03). | Recent symptoms (n = 101) 14.6 ppb [6.5 to 45.3]) vs those without recent symptoms (n=32) 6.0 ppb [3.2 to 17.4]. | In children, FeNO levels differed significantly between the controlled and uncontrolled asthmatics and between the three treatment decision subgroups (up, down, or unchanged). |
| Spirometry, N=133 | Performing a forced expiratory maneuver (MicroLab 3300 spirometer, Micro Medical Ltd., Gillingham, UK). |  |
| Yamashita, 2015 95 | Japan.longitudinal cohort study, outpatient setting, high risk of bias. | FeNO, N=37 | uncontrolled asthma (N= 18)mean age of 49.2, 33.4% males, 16.6% current smokers.controlled asthma (N= 19)mean age of 52.2, 23.3% males, 5.3% current smokers. | NIOX MINO© (Aerocrine AB, Solna, Sweden), at a constant flow rate of 50 mL/s. | Using a FeNO cut-off level of 34 ppb yielded a sensitivity of 76.5% and specificity of 73.7% for the achievement of full asthma control. AUC = 0.86. | uncontrolled 60.7ppb (SD35).controlled: 24.9 ppb (SD 14.5) | Using a FeNO cut-off level of 34 ppb yielded a sensitivity of 76.5% and specificity of 73.7% for the achievement of full asthma control. |
| Gold standard, N=37 | A positive indication of airway reversibility after inhalation of a short-acting β2 agonist, response to a provocative concentration of methacholine, or sputum eosinophil counts >3% or FeNO levels >22 parts per billion (ppb). Mild asthma was defined as a forced expiratory volume within 1 s (FEV1.0 predicted) of >80% at the first diagnosis of asthma. |  |
| Yang, 2015 96 | Korea, longitudinal nonrandomized, outpatient setting, medium risk of bias. | FeNO, N=145 | Mean age 10.58 years (SD: 2.60), males 71%, BMI 19.15 (SD: 3.75), atopy 100% | FeNO was measured by an NO analyzer with electrochemical sensors (NIOX MINO; Aerocrine AB, Solna, Sweden), according to the ERS/ATS guidelines. Constant flow rate of 50 mL/s. FeNO was measured twice and a third measurement was performed if there is a more than 10% difference between first 2 measurements. | H-FeNO (mean (95% CI, ppb) (No loss of asthma control vs loss of asthma control)R21FeNO (% ) mean (95% CI) (No loss of asthma control vs loss of asthma control) | 32.98 (29.70 to 36.63) vs 59.82 (55.60 to 64.35)22.80 (16.41 to 29.19) vs 58.10 (53.45 to 62.75) | In patients aged 8-16 years with atopic asthma serially monitored over 2 years, loss of asthma control was predicted by the highest FeNO of serial measurements and the rate of FeNO > 21 ppb. |
| Spirometry, N=145 | Lung function tests were performed with spirometer (Vmax SensorMedics, Yorba Linda, CA, USA) in accordance with ERS/ATS recommendations | L-%FEV1mean (95% CI) (No loss of asthma control vs loss of asthma control)L-FEV1/FVC (%)mean (95% CI) (No loss of asthma control vs loss of asthma control) | 84.40 (80.34 to 88.46) vs 78.03 (75.41 to 80.64)79.63 (77.12 to 82.13) vs 74.16 (72.32 to 76.00) |
| Yavuz, 2012 97 | Turkey,longitudinal nonrandomized,outpatient setting, low risk of bias. | FeNO, N= 76 | Mean age 8.7 years (SD: 1.4),61.8% male. | Using an online NIOX-MINO; Aerocrine, Stockholm, Sweden at a flow of 50mL/sec. The mean value of three consecutive measurements was used for analysis. Bronchodilators withheld prior to FeNO test in 39.5 %. | A C-ACT score of 22 or less had 69% sensitivity and 77% specificity in determining not well-controlled asthma, whereas a FeNO value of 19 ppb or higher had 61% sensitivity and 59% specificity in patients who completed 3 visits. | **Baseline:**Well controlled asthma (N=40): 16 ppb (13–22)Not well controlled asthma (N=36): 20 ppb (13–28).**At 1 month:**Well controlled asthma (N=45): 18 ppb (12 to 26.5).Not well controlled asthma (N=19): 23 ppb (16 to 31).**At 2 months:**Well controlled asthma (N=39): 16 ppb (13 to 26)Not well controlled asthma (N=12): 21.5 ppb (14 to 69). | In children, multivariate analysis revealed that a C-ACT score of 22 or less (odds ratio, 8.75; 95% Cl, 4.35–17.59) and a FeNO of 19 ppb or greater (odds ratio, 2.60; 95% Cl, 1.07–6.29; P .03) were significant indicators for not well-controlled asthma. |
| Spirometry, N= 76 | Spirometry tests used ZAN100spirometry system (nSpire Health, Longmont, Colorado) | **Baseline:**Well controlled asthma (N=40): FEV1 96% pred (89 to 103)FEV1/FVC 90% pred (84 to 94)Not well controlled asthma (N=36): FEV1 84% pred (75 to 94)FEV1/FVC 85% pred (80 to 94).**At 1 month:**Well controlled asthma (N=45): FEV1 97% pred (89 to 102)FEV1/FVC 91% pred (85 to 95).Not well controlled asthma (N=19):FEV1 84% pred (74 to 94).FEV1/FVC 87% pred (80 to 94). **At 2 months:**Well controlled asthma (N=39):FEV1 93% pred (86 to 105)FEV1/FVC 89% pred (83 to 94).Not well controlled asthma (N=12):FEV1 78% pred (76 to 85).FEV1/FVC 83% pred (78 to 86). |
| Childhood Asthma Control Test (C-ACT), N= 76 | The official Turkish version of the C-ACT questionnaire was administered. Children and parents answered their respective parts of the test separately, and the sum of their scores was used for analysis. Absolute values for the C-ACT scores are demonstrated, and changes in C-ACT scores are expressed as a percentage of the initial value. | **Baseline:**Well controlled asthma (N=40): 24 (21 to 26) Not well controlled asthma (N=36): 19 (17 to 21)**At 1 month:**Well controlled asthma (N=45): 25 (23 to 26) Not well controlled asthma (N=19): 20 (16 to 23)**At 2 months:**Well controlled asthma (N=39): 24 (22 to 26) Not well controlled asthma (N=12): 23 (21 to 25). |
| Zeiger, 2006 98 | United States, RCT with cross-over, outpatient setting, unclear risk of bias. | FeNO, N= 99 | Range age (6-13) years, Male 59%.  | Measured by (78% online) NIOX Aerocrine AB – chemiluminescence,  | FeNO decreased after 16 weeks of fluticasone propionate (FB) 100 mg BID, and montelukast (MT) 5-10 mg once a day but the decrease was greater after fluticasone. Change in FeNO correlated with improvements in asthma control days (ASDs) in fluticasone but not with montelukast. | Baseline 39.5 ppb (34.2 to 44.7) FP 20.6 ppb (15.0 to 26.2)MT 30.9 ppb (25.5 to 36.2)FP-MT mean difference -10.3 ppb (-16.9 to -3.7).FeNO vs ACDsFP -0.21 (-0.33 to -0.08)MT -0.04 (0.17 to 0.09) | Change in FeNO level significantly predicted asthma control days in children treated with fluticasone (but not montelukast) |
| Spirometry, N= 126 |  | Fluticasone (FB) led to significant improvements in prebronchodilator FEV/FVC while montelukast (MT) associated with a significant but small decrease. However, greater improvements in prebronchodilator FEV1/FVC occurred after fluticasone (FB) than after montelukast (MT). | FEV1/FVC % baseline 126 80.1 (79.1 to 81.1) FP 82.2 (80.9 to 83.6)MT 79.0 (77.6 to 80.5)FP-MT mean difference 3.2 (2.3 to 4.1) |
| Asthma control questionnaire , N= 127 |  | Compared with baseline, both fluticasone (FB) and montelukast (MT) treatments were associated with significant improvements in ACQ scores, but better control was achieved with fluticasone. | Baseline 0.96 (0.89 to 1.03) FP mean 0.59 (0.50 to 0.69)MT mean 0.76(0.66 to 0.87) FP- MT mean difference -0.17(-0.27 to -0.07) |
| Zeiger, 2011 99 | United States,cross section study,outpatient setting, medium risk of bias. | FeNO, N= 325 | Group 1; 1st quartile of FeNO (7-19 ppb): (N=88)Mean age 37.2 years (SD: 14.5),25% Male,59.1% Allergic rhinitis30.7% Atopic dermatitis BMI 28.6 (SD: 7.9).Group 2; 2nd quartile of FeNO (20- 28 ppb): (N=77)Mean age 37.7 years (SD: 14.4),41.6% male,55.8% Allergic rhinitis,27.3% Atopic dermatitis,BMI 28.2 (SD: 6.6).Group 3; 3rd quartile of FeNO (29- 47 ppb): (N=79)Mean age 36.4 years (SD: 14.8),51.6% male,60.8% Allergic rhinitis,26.6% Atopic dermatitis,BMI 28.6 (SD: 6.5).Group 4; 4th quartile of FeNO (48- 215 ppb): (N=81)Mean age 31.4 years (SD: 14.8),42% male59.3% Allergic rhinitis,32.1% Atopic dermatitis,BMI 27.6 (SD: 6.5). | FeNO measurements were done using the NIOX MINO® handheld device (Aerocrine AB, Solna, Sweden) |  | Group 1: 15 ppb (7 to 19)Group 2: 25 ppb (20 to 28)Group 3: 37 ppb (29 to 47)Group 4: 72 ppb (48 to 215) | In atopic 12- to 56-year-old persistent asthmatics on ICS, higher FeNO levels significantly correlated with more SABA dispensing and oral steroids courses in the past year, lower FEV (1) % predicted levels, but not ACT score. |
| Spirometry, , N= 325 | Spirometry captured FEV1, FEV1% predicted, and FEV1/FVC using the KOKO electronic Pneumotach spirometer (Ferraris Respiratory, Louisville, CO, USA) by ATS standards and over-reading for quality assurance. Age, gender, and ethnicity appropriate prediction equations were used to calculate the percent of predicted FEV1. | FEV1Group 1: 89.4% pred (SD: 14.0)Group 2: 87.1 % pred (SD:14.1)Group 3: 84.8 % pred (SD:13.9)Group 4: 83.8 % pred (SD:16.8)FEV1/FVCGroup 1: 0.80 % pred (SD:0.08)Group 2: 0.77 % pred (SD:0.09)Group 3: 0.77 % pred (SD:0.08)Group 4: 0.74 % pred (SD:0.09) |
| Asthma Control Test (ACT) score, N= 325 | >19 controlled,16–19 not well controlled, and <16 very poorlycontrolled | Asthma control test: 3-level categories (%)**Group 1:** controlled: 61.4not well controlled: 18.2very poorly controlled: 20.5**Group 2:** controlled: 57.1not well controlled: 20.8very poorly controlled: 22.1**Group 3:** controlled: 75.9not well controlled: 15.2very poorly controlled: 8.9**Group 4**: controlled: 48.1not well controlled: 28.4very poorly controlled: 23.5Emergency department/urgent care (%)Group 1: 33Group 2: 28.6Group 3: 22.8Group 4: 38.3Hospitalization (%)Group 1: 2.3Group 2: 7.8Group 3: 0Group 4: 11.1 |

ACT: asthma control test; ACQ: Asthma control questionnaire; AUC: area under the curve; BHR: Bronchial Hyperreactivity; BMI: body mass index; CI: confidence interval; COPD: chronic obstructive pulmonary disease; EBC: Exhaled breath condensate; ED: emergency department; ERS/ATS recommendation: The European Respiratory Society/ American Thoracic Society recommendation; FEF: forced expiratory flow; FEF25–75: forced expiratory flow at 25–75% of forced vital capacity; Eos: Eosinophilia count; FeNO: fraction exhaled nitric oxide; FEV1: forced expiratory volume in the first second; FEV1% pred: forced expiratory volume in the first second percentage predicted; FVC: forced vital capacity; ICS: inhaled corticosteroid; IFN: Interferon; IgE: Immunoglobulin E; IL: Interleukin; IQR: interquartile range; LR: likelihood ratio; LTRA: Leukotriene receptor antagonist; NPV: negative predictive value; NR: Non-Reported; OR: odds ratio; PC15: provocation concentration causing a 15% fall in FEV1; PC20: provocation concentration causing a 20% fall in FEV1; PD15: provocation dose causing a 15% decline in FEV1; PD20: provocation dose causing a 20% decline in FEV1; PEF: he peak expiratory flow; PH: potential hydrogen; pMDI: pressurized Metered-Dose Inhaler; PPV: positive predictive value; R: correlation coeffieient; RCT: randomized clinical trial; ROC curve: receiver operating characteristic curve; SD: standard deviation; QALYs: Quality-Adjusted Life-Year.