Table C.11. Characteristics of the included studies in KQ 1d for FeNO use for ICS reduction or withdrawal

| 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) | Medication (Frequency, Dose, Duration, etc.) | Asthma Outcomes | | Test Findings (Mean, SD) | Conclusions |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Cabral, 2009 155 | Brazil, longitudinal nonrandomized, outpatient setting, medium risk of bias. | FeNO, N= 32 | Mean age 10.3 years (SD: 2.2).  65.6% males.  Moderate asthma: n=18, 12 males, age (mean +/-SD) 9.4 +/-1.9.  Severe asthma n=14, 9 males, age 11.4+/-2.1. | FeNO was then measured using an off-line single-breath exhalation technique by chemiluminescence using a fast-responding analyzer (NOA 280; Sievers Instruments Inc, Boulder, Colorado). The analyzer was calibrated with a certified 47-ppb NO source (White Martins, Brazil) and 0 NO filter (Sievers Instruments Inc) before each measurement. | 2 month run-in period, ICS were adjusted to equivalent doses of fluticasone administered with a metered-dose inhaler. During tapering, the dose of ICS was reduced by 25% every 2 weeks as long as the child remained stable. If the patient did not remain stable, the ICS dose was either maintained or increased according to physician discretion; oral corticosteroids were given as needed for exacerbations. | FeNO level was not associated with future risk for asthma exacerbations in any of our regression models. The only factor that was associated with subsequent exacerbations in these models was an indicator of baseline severity (severe vs moderate). Even after further adjustment for exacerbations, children with severe asthma had a 2.7-fold (95% CI, 1.1 to 6.6) increased odds of having an exacerbation in the following 2 weeks when compared with children with moderate asthma. | | Baseline  Moderate asthma (N=18):  29 ppb (SD: 13)  severe asthma (N=14)  50 ppb (SD: 20) | In children with moderate-to severe asthma undergoing ICS reduction, FeNO measured biweekly and expressed as a continuous variable or dichotomized, was not associated with future risk for exacerbations |
| Spirometry, N= 32 | We performed spirometry using a spirometer that features a brass pneumotach and combines a portable unit with a computer system (KoKo spirometer; PDS Inc, Ferraris Cardio- pulmonary Systems Group, Louisville, Colorado). Children were asked to refrain from using their reliever medications for at least 4 hours before testing if possible. | FEV1% pred Baseline  Moderate asthma:  94.2 (SD: 16.2).  Severe asthma:  50 (SD: 20). |
| Hojo, 2013 156 | Japan  longitudinal nonrandomized  outpatient setting, low risk of bias. | FeNO, N= 51 | Global Initiative for Asthma (GINA) step1 group: (N=27)  Mean age 50.2 years (SD: 8.8),  44% male,  8% ever smokers  BMI 23.7 Kg/m2 (SD: 2.8),  56% atopic.  Global Initiative for Asthma (GINA) step2 group: (N=24)  Mean age 48.9 years (SD: 11.3),  46% male,  5% ever smokers  BMI 22.9 Kg/m2 (SD: 1.9),  76% atopic. | Online NIOX-MINO (Aerocrine Ltd., Solna, Sweden) every 8 weeks for 48 weeks. | GINA step1 group: Budesonide 400 μg and salmeterol 100 μg.  GINA step2 group:  Salmeterol/ fluticasone 250 at 2 puffs. | Moderate or more severe exacerbations of asthma were experienced by 6 patients (22%) in the step1 group, but only 3 in step2 group. | | Baseline:  step1 group  44.5 (SD: 28.7)  step2 group  48.8 (SD: 31.1)  At 8 weeks:  step1 group  39.4 (SD: 25.5)  step2 group  No change  At 24 weeks:  step1 group:  No change  step2 group:  39.6 (SD: 23.6) | In adults with moderate asthma treated with either budesonide 400 μg and salmeterol 100 μg or salmeterol/ fluticasone 250 at 2 puffs, step down from medium to low dose was safely performed using a combined FeNO and ACT approach at 8 week intervals |
| Spirometry, N= 51 | Spirometry was measured every  8 weeks. | FEV1% pred at baseline:  step1 group  72.6 (SD: 9.7)  step2 group  76.5 (SD: 16.2)  At 48 weeks:  step1 group:  76.4 (SD: 13.5)  step2 group:  79.4 (SD: 12.4) |
| Asthma control test (ACT), N= 51 | ACT was measured every 8 weeks | Baseline  Step1 group:  23.1 (SD: 1.4)  Step2 group:  22.2 (SD:1.6) |
| Jones, 2001 157 | New Zealand, longitudinal nonrandomized, outpatient setting, low risk of bias. | FeNO, N=77 | Mean age 42.9 years (range 18-74),  38.9% male,  15.6% ex-smokers,  0% current smoker. | Measured by calibrated chemiluminescence analyzer with online measurement of single exhalations according to a standard protocol, with the exception of flow rate (250 ml/s) | Corticosteroid treatment was stopped following a 2- to 4-wk run-in during which the maintenance dose remained unchanged. | The loss of control group (LOC) (N=60) experienced a 2.16-fold increase in FeNO between first and last visit, which was significantly greater than the 1.44-fold increase for the no LOC group (p< 0.01).  There were also significant differences between LOC and no LOC groups for the decrease in FEV, (p<0.01), the increase in sputum eosinophils  (p= 0.04). | | Loss of control mean difference: 2.16 (1.88 to 2.48).  No loss of control  mean difference: 1.44 (1.13 to 1.82) | In adults, both single measurements and changes of FeNO (10 ppb, 15 ppb, or an increase of > 60% over baseline) had positive predictive values that ranged from 80 to 90% for predicting and diagnosing loss of asthma control after ICS withdrawal. |
| Spirometry, N=77 | Spirometry was measured using a rolling seal spirometer. | Loss of control FEV1 mean difference  -11.9 (-15.2 to -8.7).  No loss of control  FEV1 mean difference  -1.1 (-3.3 to 1.2). |
| Sputum eosinophils, N=77 |  | Loss of control  mean difference  14.3 (8.0 to 20.6).  No loss of control  mean difference  3.3 (-1.5 to 8.0) |
| Liu, 2010 158 | United States, longitudeinal nonrandomized, outpatient setting, medium risk of bias. | FeNO, N= 21 | Mean age 29.7 years (18-40),  14% male,  0% current smoker. | Measured by online NIOX (Aerocrine), flow rate per referenced guidelines, steroid priot to test was 100%, | 6 months of stepwise fluticasone weaned from 220 ug twice daily to 220 ug once daily. | There is a linear increase pattern for FeNO associated with dose titration. However, FeNO was not a significant time-dependent predictor for the exacerbation. | |  | Adults with moderate persistent asthma undergoing withdrawal of ICS had significant but heterogeneous rise in FeNO. |
| Exhaled breath condensate (EBC), N= 21 |  | For EBC pH, no significant trend was observed during titration, however, the fall in EBC pH was greater in the 6 subjects who had an exacerbation than in the 7 who did not. | | Mean difference EBC PH in exacerbation vs non exacerbation: -0.58 (SD: 0.7) vs 0.16 (SD: 0.13). |
| Spirometry, N= 21 |  | There is a significant linear decrease pattern for FEV1 during dose titration. However, FEV1 was not significant time-dependent predictor for the exacerbation. | |  |
| Obase, 2013 159 | Japan,  RCT, unclear risk of bias. | FeNO, N= 29 | Step-down group (N= 15)  Mean age 46.5 years.  Continued group (N= 14)  Mean age 45.3 years | Flow of 50 mL/sec, using an online nitric oxide analyzer (NOA 280i; Sievers Instruments, Inc., Boulder, CO) in one visit several times. | Budesonide/ formoterol  Step-down group:  Baseline  538 mcg/day (424–653)  At 8 weeks  331 mcg/day (285–376)  Continued group:  Baseline  500 mcg/day (385–615)  At 8 weeks  500 mcg/day (385–615) |  | | Step-down group:  Baseline  51.0 (38.5 to 63.4)  At 8 weeks:  65.7 (36.0 to 95.4)  Continued group:  Baseline  50.9 (33.9 to 67.9)  At 8 weeks:  45.0 (25.9 to 64.1) | Adults newly diagnosed asthma received budesonide/ formoterol for 8 weeks or more then randomized to continue or step-down group. In both groups, pulmonary function indicators and symptoms did not change. FeNO level decreased significantly in the dosage-continued group (from 50.9ppb to 45.0ppb), and increased significantly in the step-down group (from 51.0ppb to 65.7ppb). |
| Spirometry, N= 29 | Dry spirometer (CHESTAC-33; CHEST MI, Tokyo, Japan), which meets the 1994 American Thoracic Society (ATS) recommendations  for diagnostic spirometry | FEV1Step-down group:  Baseline  98.8 (84.2 to113.3)  At 8 weeks:  105.2 (94.9 to 115.5)  Continued group:  Baseline  94.0 (80.6 to 107.3)  At 8 weeks:  92.0 (76.8 to 107.3) |
| Asthma control test (ACT) , N= 29 | In general, patients with a score below 0.75 have adequately controlled asthma; those with a score above 1.0 do not have well-controlled asthma. On the seven-point scale of the ACQ, a change of 0.5 in the score is the smallest that can be considered clinically important. In this study, we set a score of 0.5 or less as confirmation of adequate asthma control by ICS/LABA at baseline and after 8 weeks of treatment. | Step-down group:  Baseline  24.3 (23.6 to 25.0)  At 8 weeks:  22.9 (20.2 to 25.6)  Continued group:  Baseline  23.8 (22.8 to 24.8)  At 8 weeks:  24.0 (22.4 to 25.6) |
| Asthma Control Questionnaire (ACQ) , N= 29 | Patients with a score below 0.75 have adequately controlled asthma; those with a score above 1.0 do not have well-controlled asthma. On the seven-point scale of the ACQ, a change of 0.5 in the score is the smallest that can be considered clinically important. In this study, the score set of 0.5 or less as confirmation of adequate asthma control by ICS/LABA at second entry and 8 weeks after randomization. | Step-down group:  Baseline  0.04 (-0.02 to 0.10)  At 8 weeks:  0.31 (-0.07 to 0.68)  Continued group:  Baseline  0.13 (0.03 to 0.22)  At 8 weeks:  0.25 (-0.05 to 0.55) |
| Asthma Quality of Life Questionnaire (AQLQ) , N= 29 | The questionnaire consists of 32 questions within four domains: symptoms, activity limitation, emotional function and environmental stimuli. | Step-down group:  Baseline  6.66 (6.43 to 6.88)  At 8 weeks:  6.34 (5.84 to 6.85)  Continued group:  Baseline  6.76 (6.56 to 6.96)  At 8 weeks:  6.57 (6.16 to 6.99) |
| Pijnenburg, 2005 160 | Netherlands, longitudinal nonrandomized, low risk of bias. | FeNO, N=37 | Group1 (without relapse) (N=28): mean age 12.2 years (range 7.3-16.9),  75% atopic,  Daily dose of ICS 400 (100-400), mean weight 10.2 Kg (range 7.3-14.2).  Group2 (With relapse) (N=9):  Mean age 12.3 years (range 10.0-15.8),  88% atopic,  daily dose of ICS 200 (100-400), mean weight 14.8 Kg (range 8.5-25.8). | FeNO was measured online with an expiratory flow of 50 ml/s according to ATS and ERS guidelines. NO was continuously sampled with a sampling flow of 175 ml/min and analyzed by a chemiluminescence analyzer (Sievers 280 NOA, Boulder, CO, USA). The analyzer was calibrated weekly using 0 and 115 ppb NO certified gases (BOC, Herenthout, Belgium). | Baseline FeNO was measured at t = 22 and t = 0 weeks. FeNO was monitored 2, 4, 12, and 24 weeks after withdrawal of ICS. | | Two and four weeks after withdrawal of steroids geometric mean FeNO in children who were about to relapse was higher than in those who did not relapse: at 2 weeks (ratio 2.3; 95% CI 1.2 to 4.1; p = 0.01) and at 4 weeks (ratio 2.6; 95% CI 1.3 to 5.1). | Group1  Baseline:  10.5 (7.3 to 14.2).  At 2 weeks  15.7 ppb  At 4 weeks  15.9 ppb  Group2  Baseline:  14.8 (8.5 to 25.8).  At 2 weeks  35.3 ppb  At 4 weeks  40.8 ppb | In children, FeNO measurements 2 and 4 weeks after discontinuation of ICS predicted those who relapsed. Value of 49 ppb at 4 weeks after discontinuation had the best sensitivity (71%) and specificity (93%) for asthma relapse. |
| Spirometry, N=37 | Flow-volume curves were obtained with a dry rolling seal spirometer (Jaeger, Wurzburg, Germany) according to ATS guidelines. After maximal inspiration, three reproducible loops with a maximum variability in FVC of 10% were obtained. FVC and FEV1 are expressed as percentage predicted. | Forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV1) before and after bronchodilation were measured at t = 22, 12 and 24 weeks. At t = 0 weeks, treatment with ICS was discontinued in patients with low symptom scores (below 14). | |  | Group1  Baseline FEV1% 100 (73-134)  FVC%  106 (80 to 139).  Post-bronchodilation: FEV1%  106 (80 to 139), Post-bronchodilation: FVC%  103 (66-127).  Group2  Baseline:  FEV1%  99 (88 to 109), FVC%  105 (87 to 118).  Post-bronchodilation:  FEV1%  107 (91 to 119), Post-bronchodilation:  FVC%  105 (78 to 118). |
| Prieto, 2003 161 | Spain,  longitudinal non randomized,  outpatient setting, high risk of bias. | FeNO, N=37 | Mean age 32.2 years, (range 28.7–35.6),  30 % males,  27% ex-smoker,  81% atopic. | Measured on-line by the restricted breath analysis according to the recommendations of the American Thoracic Society using a chemiluminescence analyzer (NiOx; Aerocrine; Solna, Sweden) | 2-week run-in of beclomethasone dipropionate, 500 to 1,000 ug or equivalent daily. Then, 12 weeks with ICS at half the previous dose. | | FeNO changes from the run-in period to the visit performed 2 weeks after the reduction of ICS. | FeNO ≥ 10 ppb  OR 1.89, 95% CI  (0.36 to 9.97). | In adults with asthma on high dose ICS that was reduced by 50%, FeNO values at baseline >15 ppb perdict reduction failure. |
| Spirometry, N =37 | Measured using a  calibrated pneumotachograph (Jaeger MasterScope; Erich Jaeger  GmbH; Wurzburg, Germany) according to standardized guidelines. |  |  |
| Tsurikisawa, 2012 162 | Japan, longitudinal nonrandomized, outpatient setting, low risk of bias. | FeNO, N= 90 | Exacerbation-free group (N=50); Mean age 49.1 years (SD:14.6), 34% male,  28% ever smoker, 74% atopic.  Exacerbation group (N=40); Mean age 50.9 years (SD:15.9), 37.5% male,  30% ever smoker,  60% atopic. | Mesured by online (80%) NO chemiluminescence analyzer (NOA model 280A, Sievers Instruments) at 70 ml/sec, steroid prior to test was 100%. | 12 months of the daily inhaled corticosteroid dose that reduced by half. | FeNO was lower in exacerbation-free compared with exacerbation group after treatment.  However, FeNO was a more significant predictor of success in ICS reduction than FEV1 (p = 0.028). | | Exacerbation-free group  25.6 ppb (SD: 12) Exacerbation group  43.4 ppb (SD: 27.3).  0.961, 95% CI (0.93 to 0.99). | In adult patients with moderate or severe asthma but no clinical symptoms of asthma for at least 6 months in whom ICS doses reduced by half, FeNO was a statistically independent predictor of success. |
| Spirometry, N= 90 | Measured by spirometer (Auto Spiro AS-303, Minato Medical Science, Osaka, Japan) after each inhalation. | FEV1 was higher in exacerbation-free group before and after treatment compared with exacerbation group, however, FEV1 was a less predictor of success in ICS reduction than FeNO (p = 0.03). | | Exacerbation-free group  85.9 % pred (SD: 20.9) to 91.1 % pred (SD: 15.1) Exacerbation group  79.6 % pred (SD: 21.3) to 84.1 % pred (SD: 16.7).  1.1, 95% CI (1.0-1.2) |

AST: American Thoracic Society;BMI: body mass index; CI: confidence interval; EBC: Exhaled breath condensate; ERS: European Respiratory Society; 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; OR: odds ratio; PH: potential hydrogen; RCT: randomized clinical trial; SD: standard deviation.