Table C.5. Characteristics of the included studies in KQ 1c (Algorithm using FeNO to guide drug therapy NON-RCTs)

| 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 | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Griese, 2000 57 | Germany, prospective nonrandomized, outpatient setting, low risk of bias. | FeNO, N=74 | Mean age 9.7 years (range 4-16),  76.1 % males,  100 % atoptic. | 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. | Step wise approach system. | 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). | In children, FeNO values above 13 ppb weakly correlated with the changes in asthma therapy and had modest sensitivity of 0.67 and a specificity of 0.65 to predict a step up in therapy. | |
| 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). |
| Laforce, 2014 116 | United States, observational, outpatient setting, high risk of bias. | FeNO, N =50 | Mean age 35.1 years (SD: 15.81),  40 % male,  BMI 27.4 kg/m2 (SD: 6.2),  30% ex-smoker, | Measurement was obtained (NIOX MINO, Aerocrine AB, Solna, Sweden) | 94% were on short acting B-agonists, 40% on long acting B-agonists combined with anti-inflammatory medication, and 16% on leukotriene receptor antagonists. | Asthma medication changes based on FeNO results. | No medication change (64%),  added medication or increased medication dose (20%), and  Subtracted medication or decreased medication dose (16%). | Treatment decisions made in a single office visit based on a single FeNO test in 50 asthmatics led to change in therapy (augmentation in 20% and reduction in 16%) and were estimated to reduce cost by $629 per patient per year. |
| Asthma control test (ACT) scores, N =50 |  | FeNO values by ACT scores | ACT scores ≤19= FeNO 40.3 ppb (SD: 50.84).  ACT scores ≥19=  FeNO 26.1 ppb (SD: 21.96). |
| Spirometry, N = 50 |  | FeNO values by FEV1 | ≤80% Predicted=  FeNO 41.1 ppb (SD: 46.92).  >80% Predicted=  FeNO 41.1 ppb (SD: 46.92). |
| Malerba, 2008 117 | Italy, longitudinal nonrandomized study, medium risk of bias. | FeNO, N= 14 | Mean age 43.9 years (SD: 10.1),  43% male,  Weight 67.2 Kg (SD: 10.8),  43% ever smokers,  0% current smokers  100% Eosinophilic phenotype. | Online chemiluminescence nitric oxide analyzer (Ecomedics AG CLD88; Ecomedics. Durnten, Switzerland), at a flow of 50 mL/sec, through several visits during 12 months period, 4 weeks washout. | 12 months of Inhaled corticosteroids in a stepwise fashion according to FeNO and sputum eosinophilia values. | There is a significant positive correlation between FeNO and sputum Eosinophilia (r= 0.49, P < 0.01 at baseline; r= 0.53, P < 0.01 at 3 months; r= 0.28, P < 0.01 at 6 months). Also, there is a significant positive correlation between FeNO and sputum eosinophilia mean difference at 6 months (r = 0.41, P < 0.01) but not at 3 months (r = 0.06, P = 0.39).  Mean number of exacerbations was significantly lower compared  to baseline (3 vs 9 exacerbations,  P < 0.001). | Baseline:  57 ppb (SD: 33)  At 3 months:  26 ppb (SD: 16)  At 6 months:  17 ppb (SD: 8)  At 12 months:  22 ppb (SD: 10) | Adults with mild-moderate persistent asthma treated based on FeNO and sputum eosinophils had fewer symptoms and exacerbations  compared with the previous year in which they were treated conventionally |
| Spirometry, N= 14 | Spirometry and maximal fill flow-volume curve were obtained using a pneumotachograph with volume integrator (CAD/ Net system 1070; Medical Graphics Corporation; St. Paul, MN). Static lung volumes were measured by means of the multibreath nitrogen washout method. | FEV1 baseline:  99% pred (SD: 20)  At 3 months:  101% pred (SD:17)  At 6 months:  103 % pred (SD:15)  At 12 months:  105 % pred (SD:12)  FEV1/FVC Baseline:  91 % pred (SD:11)  At 3 months:  91 % pred (SD:10)  At 6 months:  93 % pred (SD:10)  At 12 months:  95 % pred (SD:7) |
| Sputum eosinophilia (sEOS), N =14 | Subjects were pretreated with inhaled salbutamol (200 ug by metered-dose inhaler), and 10 min later hypertonic (4.5%) sterile saline nebulized solution was inhaled for three periods of 5 min at most by means of an ultrasonic nebulizer (Ultraneb 2000; DeVilbiss; Somerset, PA). The subjects were instructed to cough sputum into containers. If any symptom occurred, nebulization was discontinued.  The cutoff for an abnormal result was defined when sEos count was > 3% as percentage cells. | Count at Baseline: 27% (SD: 27)  At 3 months:  13% (SD: 15)  At 6 months:  4% (SD: 3)  At 12 months:  3% (SD: 3) |
| Malerba, 2012 118 | Italy,  longitudinal nonrandomized,  inpatient setting | FeNO, N= 14 | Mean age 44.9 years,  42.9% male  42.9% ex-smokers,  Mean weight 67.2 Kg,  64.3% atopic | Using an online high-resolution chemiluminescence nitric oxide analyzer (Ecomedics AG CLD88; Ecomedics; Dumten, Switzerland). Values of FeNO included from 4 to 20 ppb were considered within normal limits. | Median beclomethasone equivalent:  At baseline: 500 ug  At 6 months: 750 ug  At 12 months: 500 ug. | No changes were observed in the frequency of clinical asthma exacerbations (3, 4 and 3 exacerbations at baseline, 6 month, and 12 month visit, respectively). | FeNO (ppb) at Baseline: 20.7  At 6 months: 26.1  At 12 months: 19.8 | Titration of ICS based on FeNO and sputum eosinophils in adults with mild-to-moderate persistent asthma was associated with reduction in symptom scores and ICS dosage. |
| Spirometry, N= 14 | Spirometry and maximal full flow-volume curve were obtained using a pneumotachograph with volume integrator (CAD/ Net system 1070; Medical Graphics Corporation, St. Paul, MN, USA). | FEV1 % pred at baseline: 99.5  At 6 months: 98  At 12 months: 100  FEV1/FVC % pred at baseline: 94  At 6 months: 92  At 12 months: 93 |
| Methacholine challenge test (PD20), N= 14 | The methacholine challenge was performed as a dose-response curve by increasing (doubling) doses of methacholine chlorohydrate (starting with 12.5 ug) every 3 min. The test was stopped when the highest dose (1.600 ug) was tolerated, or if a fall> 20% in forced expiratory volume in the first second FEV1 from baseline (saline solution) was induced after methacholine inhalation. A methacholine challenge result was considered positive if the PD20 was < 1.600 ug. | PD20 (ug) at baseline: 714.5  At 6 months: 995.8  At 12 months: 877 |
| Sputum Eosinophilia count (sEos), N= 14 | After baseline spirometry measurements, subjects were pretreated with inhaled salbutamol (200 ug by metered-dose inhaler), and 10 min later hypertonic (4.5%) sterile saline nebulized solution was inhaled for three periods for a maximum of 5 min by means of an ultrasonic nebulizer (Ultraneb 2000; DeVilbiss; Somerset, PA, USA). The cut-off for an abnormal result was defined when sEos count was> 3% as percentage cells. | sEos count (%) at baseline: 2.7  At 6 months: 3.6  At 12 months: 1.9 |
| symptom score, N =14 | Obtained from diary cards. Mean daily symptom scores (dyspnea, wheezing,  cough, daytime and nighttime awakenings, each scored  0 to 3. | Mean score at baseline: 10  At 6 months: 8.5  At 12 months: 8 |
| Wan, 2014 119 | Taiwan, Cross section study, high risk of bias. | FeNO, N= 140 | mean age 6 years,  56.6% males,  100% were on ICS. | Measured by (MINO device) once every three months for one year. | ICS (Flixotide 50 g; 2 puffs) with or without Singulair (5 mg orally per day). | FeNO levels decreased in 86.4% patients and increased in 13.6% patients, which were correlated with the changing of C-CAT (≥20 ppb, ≤19 ppb). | Baseline  32.31 ppb (SD: 13) | In Children with Asthma who received ICS, FeNO can be used to detect response to treatment. |
| International Study of Asthma and Allergies in Childhood questionnaire (ISAAC) , N= 140 |  | Baseline  18.13 (SD: 2.10). |

ACT: Asthma control test; FEF25–75: forced expiratory flow at 25–75% of forced vital capacity; 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; PD20: provocation dose causing a 20% decline in FEV1; PEF: he peak expiratory flow; R: correlation coefficient; SD: standard deviation.