

Online Supplement

Lung function measurement

Lung function measurements were performed with a spirometer (Vmax Encore 22, Viasys Healthcare, Palm Springs, CA) according to international recommendations [E1]. The spirometer was calibrated daily. Post-bronchodilator measurements were taken 15 min after inhalation of salbutamol (400 µg). Finnish reference values were used [E2].

Conditions included as comorbidities

Hypertension, depression, painful condition (daily use of analgesic medication), coronary heart disease, treated dyspepsia, diabetes, thyroid disorders, rheumatoid arthritis and other inflammatory polyarthropaties and systematic connective disorders, anxiety and other stress-related & somatoform disorders, irritable bowel syndrome, cancer, treated constipation, stroke and transient ischemic attack, chronic kidney disease, diverticular disease of intestine, atrial fibrillation and other cardiac arrhythmias, peripheral vascular disease, heart failure, prostate disorders, glaucoma, epilepsy, dementia, schizophrenia/non-organic psychosis or bipolar disorder, psoriasis, inflammatory bowel disease, migraine, bronchiectasis, Parkinson's disease, multiple sclerosis, viral hepatitis and chronic liver disease. Alcohol problems, anorexia or bulimia, misuse of psychoactive substance, hearing loss and blindness or low vision were left out because presence of these conditions could not be assessed based on patients' self-report.

References of Online supplement

E1. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright P, van der Grinten CP, Gustafsson P, Jensen R, Johnson DC, MacIntyre N, McKay R, Navajas D, Pedersen OF, Pellegrino R, Viegi G, Wanger J, ATS/ERS Task Force. Standardisation of spirometry. *Eur Respir J* 2005; 26: 319-338.

E2. Viljanen AA, Halttunen PK, Kreuz KE, Viljanen BC. Spirometric studies in non-smoking, healthy adults. *Scand J Clin Lab Invest Suppl* 1982; 159: 5-20.

Table S1. Exclusion and inclusion criteria.

Inclusion criteria	
•	A diagnosis of new-onset asthma made by a respiratory specialist
•	Diagnosis confirmed by at least one of the following objective lung function measurements <ul style="list-style-type: none"> ▪ FEV₁ reversibility in spirometry of at least 15 % and 200 ml ▪ Diurnal variability ($\geq 20\%$) or repeated reversibility ($\geq 15\%/60$ l/min) in PEF follow-up ▪ A significant decrease in FEV₁ (15%) or PEF (20%) in response to exercise or allergen ▪ A significant reversibility in FEV₁ (at least 15% and 200 ml) or significant mean PEF change in response to a trial with oral or inhaled glucocorticoids
•	Symptoms of asthma
•	Age ≥ 15 years
Exclusion criteria	
•	Physical or mental inability to provide signed informed consent
•	Diagnosis of asthma below the age of 15 years
•	Patients with suspected or co-existing COPD <ul style="list-style-type: none"> ▪ post-bronchodilator FEV₁/FVC < 0.7 and >10 smoked pack years* ▪ post-bronchodilator FEV₁/FVC < 0.7 and current or former smoker but missing pack years
•	Missing data on IL-6 and/or hsCRP

* For some analyses these patients fulfilling the criteria of asthma-COPD overlap syndrome (ACOS) were included as a separate group for comparison.

Table S2. Characteristics of patients with and without systemic inflammation when smokers are excluded.

	Without systemic inflammation	With systemic inflammation	p value
n	47	49	
Age (years)	53,6 (13,6)	61,9 (13,1)	0,003
BMI	26,7 (3,9)	29,7 (4,4)	0,001
Δ BMI during follow-up	+0,7 (2,5)	+1,4 (3,1)	0,254
Male gender n (%)	14 (29,8 %)	12 (24,5 %)	0,648
Smokers (incl. ex) n (%)	0	0	
Pack years	0	0	
≥ 1 co-morbidity n (%)	10 (21,3 %)	20 (40,8 %)	0,049
Number of other drugs in use ^a	1 (0-2)	2 (0-4)	0,086
Blood neutrophils ($10^9/l$)	3,6 (2,5-4,3)	3,8 (3,0-4,9)	0,070
Blood eosinophils ($10^9/l$)	0,16 (0,09-0,28)	0,15 (0,10-0,28)	0,774
FeNO (ppb)	12,5 (6-18)	11 (5-22)	0,956
Total IgE (kU/l)	61 (24-187)	61 (26-157)	0,947
pre-bd FEV ₁ (%)	91 (14)	88 (20)	0,288
post-bd FEV ₁ (%)	94 (13)	91 (20)	0,364
post-bd FEV ₁ /FVC (ratio)	0,77 (0,07)	0,75 (0,10)	0,921
AQ20 (no of YES)	3 (1-7)	4 (2-8)	0,275
ACT score	22 (20-25)	22 (19-24)	0,152
Uncontrolled asthma n (%)	11 (23,4 %)	12 (24,5 %)	$>0,999$
Controlled asthma n (%)	24 (51,1 %)	20 (40,8 %)	0,413
Daily ICS users n (%)	40 (85,1 %)	40 (81,6 %)	0,786
ICS daily dose ^b	550 (400-950)	800 (800-1000)	0,004
Daily LABA users n (%)	19 (40,4 %)	27 (55,1 %)	0,160
≥ 2 OCS bursts/2 yrs n (%)	6 (13 %)	7 (14,6 %)	$>0,999$

Continuous variables are shown as mean (SD) or median (25-75 percentiles). Systemic inflammation is defined as IL-6 $>1,55$ pg/ml and/or hsCRP $>4,12$ mg/l.

ICS=inhaled corticosteroid, OCS=oral corticosteroid, ACT=Asthma control test, AQ20= Airways questionnaire 20. LABA=long-acting β_2 -agonist.

^aNumber of drugs in use for other indication than asthma or allergy.

^bBudesonide equivalents (μ g).

Table S3. Comorbidities present in patients with 1 vs ≥2 comorbidities.

	1 comorbidity n=47	≥2 comorb n=51	ACOS n=30	p value
Hypertension n (%)	15 (31,9 %)	37 (72,5 %)***	16 (53,3 %)	<0,001
Type 2 diabetes n (%)	1 (2,1 %)	21 (41,2 %)***	6 (20 %)***	<0,001
Coronary heart disease n (%)	2 (4,3 %)	13 (25,5 %)***	6 (20 %)	0,015
Any psychiatric disease n (%)	3 (6,4 %)	21 (41,2 %)***	3 (10 %)***	<0,001
Depression n (%)	2 (4,3 %)	12 (23,5 %)*	3 (10 %)	0,016
Thyroid disorder n (%)	6 (12,8 %)	6 (11,8 %)	4 (13,3 %)	0,977
Painful condition n (%)	4 (8,5 %)	11 (21,6 %)	4 (13,3 %)	0,185
Systemic rheumatic disease n (%)	0	5 (9,8 %)	1 (3,3 %)	0,066
Treated dyspepsia n (%)	2 (4,3 %)	11 (21,6 %)*	3 (10 %)	0,031

*, ** and *** indicates p<0,05, 0,01 and p<0,001, respectively, when compared to patients with one comorbidity.

*** indicates p<0,001 in comparison to patients with ≥2 comorbidities.

Table S4. Predictors of medium ICS dose at follow-up.

	OR	95 % CI	p-value
Age at onset > 40 years	0,690	0,229-2,081	0,510
Male gender	1,030	0,341-3,106	0,959
Baseline FEV₁ post-bd < 80 %	9,040	2,342-34,884	0,001**
Waist circumference > 80/94 cm (female/male) at follow-up	1,328	0,299-5,890	0,709
FEV₁/FVC post-bd < 0,75 at follow-up	3,590	1,211-10,646	0,021*
Every 10 pack years smoked at follow -up	1,070	0,540-2,119	0,847
IL-6 > 1,55 pg/ml at follow-up	1,472	0,475-4,561	0,503
Blood neutrophils > 3,9x10 ⁹ /l	2,248	0,744-6,791	0,151
Blood eosinophils > 0,2x10 ⁹ /l	1,031	0,330-3,220	0,957
ACT score			
16-20	5,819	1,724-19,644	0,005**
5-15	0,836	0,101-6,899	0,868

Medium ICS dose refers to 401-800 µg daily dose of budesonide equivalent. FEV₁=forced expiratory volume in 1 second, post-bd=post-bronchodilator, FVC=forced vital capacity, ACT=asthma control test. * and ** indicates p<0,05 and p<0,01, respectively, in comparison to patients with low ICS dose or no ICS in use (budesonide equivalent 0-400 µg).