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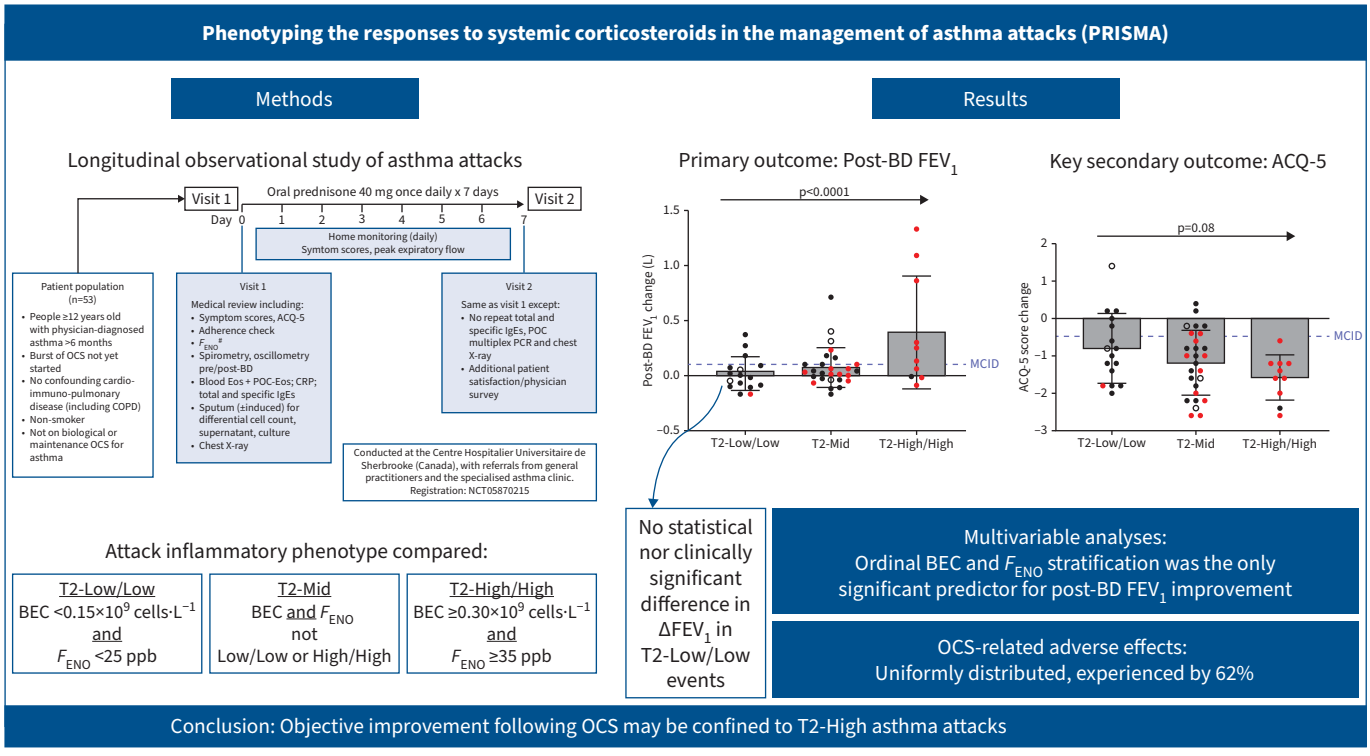

GRAPHICAL ABSTRACT Overview of PRISMA methods and findings. Type 2 (T2) inflammatory biomarkers (blood eosinophil count (BEC) and fractional exhaled nitric oxide (F_{ENO})) can effectively stratify acute asthma patients, predicting better clinical responses to oral corticosteroids (OCS) and thus supporting a personalised approach to asthma management. ACQ-5: Asthma Control Questionnaire-5; BD: bronchodilator; Eos: eosinophil; CRP: C-reactive protein; POC: point of care; FEV_1: forced expiratory volume in 1 s; MCID: minimal clinically important difference. #: F_{ENO} measurements taken using a NIOX VERO device (NIOX Group plc., Oxford, UK).

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Shareable abstract (@ERSpublications)
Type-2 inflammatory biomarkers (blood eosinophils and F_{ENO}) can stratify asthma attacks, predicting better clinical responses to oral corticosteroids, supporting a personalised approach to optimising treatment efficacy and reducing unnecessary exposure https://bit.ly/3EoL6QA

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Abstract

Background Asthma attacks are heterogeneous. It is not known whether the response to oral corticosteroids (OCS) in acute asthma varies according to type 2 (T2) inflammatory biomarkers, blood eosinophil count (BEC) and fractional exhaled nitric oxide (F_{ENO}). We aimed to explore the relationship between T2 biomarkers and response to OCS in acute asthma.

Methods We conducted a longitudinal observational study of people experiencing an asthma attack evaluated before and after a 7-day OCS course. The primary outcome was post-bronchodilator change in forced expiratory volume in 1 s (FEV_1) according to ordinal BEC-F_{ENO} three-group categories (T2-Low/Low: BEC $<0.15\times10^9$ cells·L^{-1} and F_{ENO} <25 ppb; T2-High/High: BEC $\geqslant0.30\times10^9$ cells·L^{-1} and F_{ENO} $\geqslant$35 ppb; T2-Mid: not meeting Low/Low or High/High criteria). A key secondary outcome was the change in Asthma Control Questionnaire-5 score. Exploratory outcomes included OCS-attributable adverse events.

Results 53 people were enrolled, with 16 (30%) T2-Low/Low, 27 (51%) T2-Mid and 10 (19%) T2-High/High asthma attacks. Post-bronchodilator FEV_1 changes increased with combined BEC-F_{ENO} elevation (p for interaction=0.007), peaking in the T2-High/High phenotype (0.390±0.512 L, p for trend<0.0001). Conversely, T2-Low/Low attacks showed nonsignificant FEV_1 changes (0.017±0.153 L). In univariable and multivariable analyses, only ordinal BEC-F_{ENO} stratification, not symptoms nor FEV_1, predicted subsequent post-bronchodilator FEV_1 improvement. All patients had improved Asthma Control Questionnaire-5 score, numerically peaking in the T2-High/High phenotype (−1.58±0.60, p for trend=0.08). All groups experienced similar OCS-attributable adverse events, with 33 patients (62%) reporting at least one event.

Conclusions We found that objective improvement following OCS is confined to T2-High events. As in chronic asthma, greater T2 burden identifies a distinct clinical and therapeutic trajectory, whereas OCS-related adverse events are uniformly distributed.

Introduction

Asthma is a common chronic respiratory disease affecting approximately 400 million people in the world. It is characterised by the occurrence of exacerbations or attacks: acute events of increased respiratory symptoms or deterioration of baseline lung function that require a change in treatment [1]. Although attacks are loosely defined, episodes requiring ⩾3 days of oral corticosteroids (OCS) and/or hospitalisation are qualified as severe. Severe asthma attacks generate morbidity, healthcare utilisation and avoidable deaths [1, 2]. Despite their significance, the standard of care in acute asthma has not changed in the last decades, with guidelines recommending a "one-size-fits-all" treatment approach with OCS for exacerbation symptoms lasting more than 48 h to reduce hospital admission and relapses, without evidence on other important outcomes [2, 3].

In chronic asthma, the treatment paradigm is evolving towards targeting "treatable traits" [4]. This framework relies on clinical characteristics that predict greater risk [5] and better treatment response [2]. The most noteworthy application is the targeted use of anti-inflammatory medications in asthma characterised by a type 2 (T2) inflammatory phenotype [6]. This trait is identified using simple, noninvasive and accessible tests such as the blood eosinophil count (BEC) and fractional exhaled nitric oxide (F_{ENO}) [2].

In acute asthma, several studies have documented the heterogeneity of attacks according to sputum, blood, exhaled air and microbiomic profiles [7–16]. Importantly, inflammatory phenotypes are often dynamic and indistinguishable from the point of view of initial symptoms or lung function [8]. We found no available report on the differential corticosteroid responsiveness according to inflammatory phenotypes. This is an important gap in knowledge, considering that corticosteroid toxicities appear after the lifetime equivalent of only four bursts (⩾1000 mg cumulative dose) of prednisone, *i.e.* four severe asthma attacks [17]. Biomarker-guided management could avoid harm from the inappropriate use of OCS and/or antibiotics due to overuse or without proper consideration of their potential risks and side effects [18].

We aimed to explore the relationship between T2 inflammatory biomarkers and treatment response to OCS in people with asthma experiencing a severe attack. We hypothesised that clinical trajectories following anti-inflammatory treatment improve based on the presence of inflammation, not symptoms.

Methods

Study design

The protocol of this observational longitudinal study of asthma attacks has been registered with ClinicalTrials.gov (NCT05870215) and published elsewhere [19]. The study was conducted at the Centre Hospitalier Universitaire de Sherbrooke (Canada), recruiting from general practitioners and the specialised asthma clinic.

Patient population

We included participants ⩾12 years old with physician-diagnosed asthma of >6 months' duration, with an objective diagnosis of asthma as defined by the Global Initiative for Asthma (GINA) [1] and experiencing a severe asthma attack. In agreement with the GINA recommendations [1], the decision to initiate OCS in patients with an asthma attack was defined by at least two criteria: 1) ⩾48 h of exacerbation symptoms not resolving despite increased use of inhaled reliever therapy and 2) physician or patient decision to initiate a burst of OCS. All participants provided written informed consent statements. Ethical approval was granted by the Research Ethics Committee of the CIUSSS de l'Estrie–CHUS, Sherbrooke, Quebec, Canada (#2023-4687). Exclusion criteria are listed in the supplementary methods.

Patients were assessed before (visit 1) and after a 7-day OCS course (visit 2) with home monitoring in between. On day 0 of the asthma attack (visit 1), patients were reviewed for eligibility, consented and prescribed oral prednisone (40 mg for 7 days). Evaluations in visits included clinical questionnaires, lung function, F_{ENO} and sputum/blood samples and have been described elsewhere (supplementary methods) [19].

Outcome measures

The primary outcome was the change in the post-bronchodilator (BD) forced expiratory volume in 1 s (FEV_1) between visits, a comparison based on ordinal BEC-F_{ENO} three-group categories: T2-Low/Low: BEC $<0.15\times10^9$ cells·L^{-1} and F_{ENO} <25 ppb; T2-High/High: BEC $\geqslant0.30\times10^9$ cells·L^{-1} and F_{ENO} ⩾35 ppb; and T2-Mid: not meeting Low/Low or High/High criteria. These ordinal categories were informed from randomised controlled trial datasets [20–22].

Secondary outcomes were the change in Asthma Control Questionnaire-5 (ACQ-5) scores between visits according to T2 inflammatory status and the proportion of patients achieving a minimal clinically important difference (MCID) ⩾0.1 L for post-BD FEV_1 or ⩾0.5 points for ACQ-5 [23, 24].

Exploratory outcomes and *post hoc* analyses have been described previously [19], with their methodology included in the supplementary material.

Statistical analysis

Descriptive statistics were computed as frequencies and percentages for categorical data and mean±SD or median and interquartile range (IQR) for continuous data. Demographics were compared across ordinal T2-Low/Low, T2-Mid and T2-High/High categories using ANOVA trend (Jonckheere-Terpstra) tests for

continuous variables and Chi-squared trend (Mantel–Haenszel) tests for categorical variables. No imputation methods were used. Listwise deletion was applied for concerned analyses.

We employed one-way ANOVA trend tests to assess the change in post-BD FEV_1 (primary outcome) and ACQ-5 (key secondary outcome) across the three biomarker-defined groups. A Chi-squared trend test was used to compare the proportion of patients achieving a MCID or reporting adverse events between groups.

For our primary analysis, assuming a two-sided α error of 0.05, a (T2-High/High+T2-Mid):T2-Low/Low event ratio of 1:1, and a mean±SD population difference in post-BD FEV_1 change of 100±100 mL, n=46 would provide 90% power to detect the difference in our primary outcome on an unpaired two-sample t-test. We aimed for a target of n=50 participants with visit 1 and visit 2 completed.

Exploratory analyses included regression models between T2 biomarkers and other clinical, microbiological and radiological parameters at visit 1 and the primary outcome expressed continuously (linear regression) or as ⩾MCID (logistic regression). Multiple linear regression models were performed for confounders associated ($p<0.05$) with post-BD FEV_1. The nonlinear relationship between baseline BEC and the change in post-BD FEV_1 across F_{ENO} categories was explored using generalised additive model smoothing, with cubic splines (three knots) to visualise nonlinear trends in ΔFEV_1 as a function of BEC. Separate smoothed curves were generated for F_{ENO} categories (<25 ppb and ⩾25 ppb) to highlight potential differences in trends. Longitudinal changes in home-monitored parameters (peak flow and symptom scores) were evaluated with a linear mixed-effects analysis. Agreement between venous BEC and point-of-care (POC) BEC was evaluated using intraclass correlation plus Bland–Altmann methods. All statistics were analysed with a two-sided α of 0.05. Statistical analyses were performed with R v4.2.3 (www.r-project.org) and GraphPad Prism (GraphPad Software, San Diego, CA, USA). The REDCap codebook, R code and statistical outputs are available at https://github.com/simoncouillard/PRISMA.

Additional details on the statistical analysis are provided in the supplementary methods.

Results

Between September 2022 and April 2024, we enrolled 59 patients experiencing an asthma attack prior to the initiation of OCS. Six patients were excluded after applying exclusion criteria. All 53 included patients completed both study visits, with 43 completing the post-attack virtual survey (supplementary figure S1). No severe inhaler technique issue was observed/corrected at visit 1.

As shown in table 1, 16 patients (30%) had protocol-defined T2-Low/Low, 27 patients (51%) had T2-Mid and 10 patients (19%) had T2-High/High events. In addition to greater T2-related biomarker levels, including sputum eosinophils, the T2-High/High group had significantly more male patients, a greater prevalence of nasal polyposis, a previous history of T2-High status in the past 12 months, post-BD FEV_1 reversibility, lower pre- and post-BD FEV_1/forced vital capacity (FVC) values and lower forced expiratory flow at 25–75% of FVC ($FEF_{25–75\%}$). In contrast, the T2-Low/Low group had significantly greater symptoms suggestive of dysfunctional breathing pattern (Nijmegen score ⩾23 points) [25]. Notably, there were no differences between groups regarding GINA treatment step, ACQ-5, post-BD FEV_1, Δpost-BD FEV_1 compared to the best value in the previous 12 months, chest X-ray bronchial abnormalities/plugs, or frequency of viral or bacterial infections or use of antibiotics. Additional baseline characteristics are shown in supplementary table S1.

The primary outcome analysis of post-BD FEV_1 change (in litres) at day 7 showed progressively greater FEV_1 changes from T2-Low/Low (0.017±0.153 L, n=16) to T2-Mid (0.071±0.180 L, n=27) to T2-High/High (0.390±0.512 L, n=10; p for trend<0.0001) (figure 1a). Within the T2-Low/Low group, the difference in post-BD FEV_1 between visit 1 and visit 2 was not statistically significant or clinically relevant (mean paired difference 0.016 L, 95% CI −0.059–0.093 L; p=0.645) (supplementary table S6).

In the secondary outcome of ACQ-5 change at day 7, ordinal BEC-F_{ENO} categorisation showed a nonsignificant numerical trend towards greater ACQ-5 across groups (T2-Low/Low −0.80±0.93 points, T2-Mid −1.19±0.87 points, T2-High/High −1.58±0.61 points; p=0.08) (figure 1b).

Post-BD FEV_1 improved beyond the MCID (⩾0.1 L), with significant statistical trends with ordinal BEC-F_{ENO} three-group categorisation (T2-Low/Low 18% (n=3), T2-Mid 33% (n=9), T2-High/High 60% (n=6); p=0.04). Similar statistical trends were found when FEV_1 changes were graded from poor to excellent (<1×MCID, 1–<2×MCID, 2–<3×MICID, ⩾3×MCID) according to ordinal categorisation (p=0.02) (supplementary table S2).

TABLE 1 Baseline characteristics according to T2-Low/Low, T2-Mid and T2-High/High inflammatory phenotypes.

	T2-Low/Low	T2-Mid	T2-High/High	p-value for trend
Patients (n)	16	27	10	
Age (years)	47.3±16.0	50.1±15.8	50.3±12.4	NS
Sex				<0.001
Female	13 (81.3)	20 (74.1)	1 (10.0)	
Male	3 (18.8)	7 (25.9)	9 (90.0)	
Body mass index (kg·m^{-2})	30.2±9.30	30.9±8.15	27.7±4.55	NS
Smoking status				NS
Never	14 (87.5)	19 (70.4)	8 (80.0)	
Former	2 (12.5)	8 (29.6)	2 (20.0)	
Duration of asthma (years)	22.3±19.5	19.6±14.8	9.90±12.3	NS
Prior severe asthma attacks (past 12 months) (n)	1.94±2.59	1.30±1.49	1.50±1.65	NS
ACQ-5 score, scale 0–6	3.36±1.02	3.51±1.17	2.92±0.844	NS
GINA step				NS
1–3	5 (31.3)	4 (14.8)	1 (10.0)	
4	4 (25.0)	9 (33.3)	2 (20.0)	
5	7 (43.8)	14 (51.9)	7 (70.0)	
ICS/LABA	15 (93.8)	25 (92.6)	9 (90.0)	NS
Total daily ICS dose (µg fluticasone equivalent)	922±734	839±366	975±448	NS
Adherence (% prescriptions renewed last year)	71.9±29.6	78.4±34.0	88.3±28.7	NS
Chronic sinusitis				NS
Absent	8 (50.0)	14 (51.9)	5 (50.0)	
Past	1 (6.3)	2 (7.4)	3 (30.0)	
Current	7 (43.8)	11 (40.7)	2 (20.0)	
Nasal polyps				0.001
Absent	15 (93.8)	19 (70.4)	4 (40.0)	
Past	1 (6.3)	4 (14.8)	1 (10.0)	
Current	0 (0)	4 (14.8)	5 (50.0)	
Obstructive sleep apnoea	8 (50.0)	6 (22.2)	2 (20.0)	NS
Dysfunctional breathing likely on Nijmegen[#]	10 (62.5)	9 (33.3)	1 (10.0)	0.006
Charlson score	0.875±1.36	1.15±1.32	0.800±0.789	NS
Post-BD FEV_1 (L)	2.68±0.588	2.42±0.678	3.19±0.881	NS
Post-BD FEV_1 (% predicted)	91.7±11.8	79.8±14.9	85.2±14.4	NS
FEV_1 reversibility[¶] (mL)	95±122	162±161	314±186	0.001
Post-BD FVC (L)	3.51±0.743	3.31±0.929	4.46±1.01	0.04
Post-BD FVC (% predicted)	96.9±11.6	86.8±16.3	94.6±13.2	NS
Post-BD FEV_1/FVC (%)	76.8±6.71	73.7±7.16	71.3±7.05	0.048
$FEF_{25-75\%}$ (% predicted)	74.3±26.8	57.7±22.4	50.2±14.0	0.006
R_5–R_{19} (kPa·L^{-1}·s^{-1})	0.09±0.09	0.11±0.12	0.10±0.05	NS
AX (kPa·L^{-1})	2.27±1.84	2.69±2.86	1.84±0.694	NS
ΔFEV_1 (attack *versus* prev.) (L)	0.0142±0.371	−0.145±0.237	−0.157±0.457	NS
ΔFVC (attack *versus* prev.) (L)	−0.008±0.423	−-0.287±0.302	−0.376±0.627	0.045
Previously T2-High[+]				0.002
Yes	2 (12.5)	8 (29.6)	7 (70.0)	
No	11 (68.8)	10 (37.0)	1 (10.0)	
Unknown	3 (18.8)	9 (33.3)	2 (20.0)	
Chest X-ray findings				NS
No bronchial abnormalities	3 (18.8)	5 (18.5)	3 (30.0)	
Bronchial thickening	5 (31.3)	7 (25.9)	3 (30.0)	
Possible plug	4 (25.0)	5 (18.5)	0 (0)	
Definitive plugs/atelectasis	3 (18.8)	10 (37.0)	4 (40.0)	
Missing	1 (6.3)	0 (0)	0 (0)	
Total IgE (IU·mL^{-1})	127±186	243±375	970±1630	0.02
F_{ENO} (ppb)	12.1±4.50	21.8±14.0	70.4±21.5	<0.001
Blood eosinophils (×10^9 cells·L^{-1})	0.08±0.02	0.30±0.22	0.73±0.28	<0.001
Sputum eosinophils (%)	0.6±0.9	11.8±23.9	33.3±29.7	<0.001
Sputum neutrophils (%)	58.2±28.4	67.1±26.8	37.2±22.6	NS
Virus-associated exacerbation on multiplex PCR[§]	8 (50.0)	12 (44.4)	3 (30.0)	NS
Rhinovirus infection	4 (25.0)	7 (25.9)	2 (20.0)	NS
Bacteria-associated exacerbation[f]	2 (12.5)	3 (11.1)	3 (30.0)	NS
Antibiotic treatment	2 (12.5)	4 (14.8)	2 (20.0)	NS

Data presented as mean±SD or n (%), unless otherwise stated. Nonsignificant (NS) characteristics defined by p⩾0.05. T2: type 2; ACQ-5: Asthma Control Questionnaire-5; GINA: Global Initiative for Asthma; ICS/LABA: inhaled corticosteroid/long-acting β-agonist; BD: bronchodilator; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; $FEF_{25-75\%}$: forced expiratory flow at 25–75% of FVC; R_5–R_{19}: difference of resistances measured at 5 Hz and 19 Hz; AX: reactance area; ΔFEV_1: change in post-BD FEV_1 at visit 1 compared to best value in previous (prev.) 12 months; F_{ENO}: fractional exhaled nitric oxide. [#]: Nijmegen questionnaire score ⩾23; [¶]: change of post-BD FEV_1 at visit 1, following the administration of 400 µg salbutamol after a 15-min wait period; [+]: defined as a blood eosinophil count ⩾0.15×10^9 cells·L^{-1} and/or F_{ENO} ⩾25 ppb in the previous 12 months; [§]: defined as a positive molecular testing at visit 1; [f]: defined as a positive sputum culture confirmed within 2–3 days after visit 1.

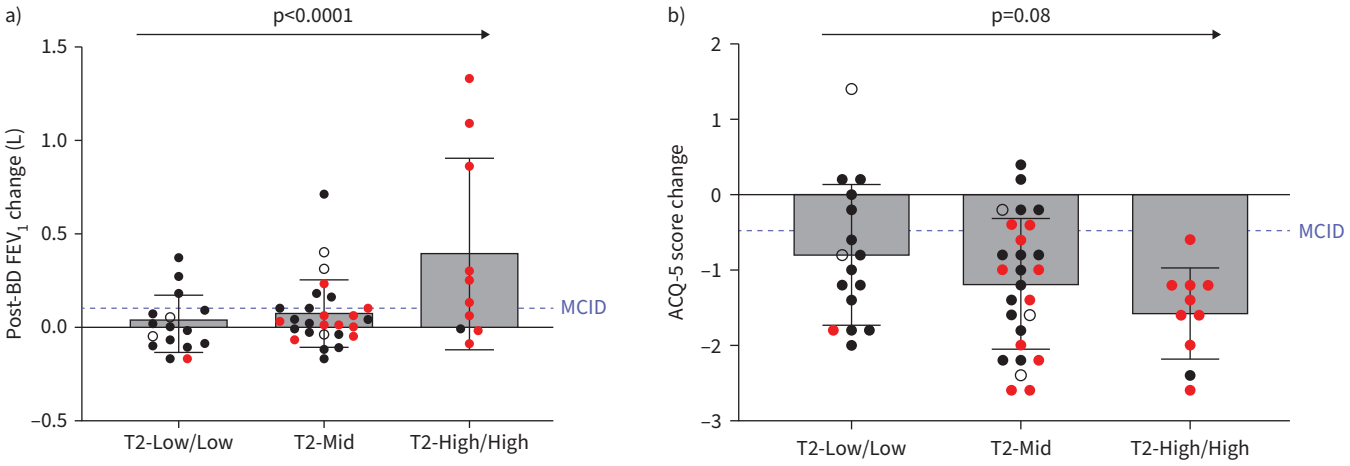

FIGURE 1 Change in a) post-bronchodilator (BD) forced expiratory volume in 1 s (FEV_1) in litres (primary outcome) and b) mean Asthma Control Questionnaire-5 (ACQ-5) score (key secondary outcome), according to ordinal biomarker stratification. Ordinal blood eosinophil count (BEC)-fractional exhaled nitric oxide (F_{ENO}) categories: T2-Low/Low, BEC <0.15×10^9 cells·L^{-1} and F_{ENO} <25 ppb (n=16); T2-Mid, not meeting Low/Low or High/High criteria (n=27); T2-High/High, BEC ⩾0.30×10^9 cells·L^{-1} and F_{ENO} ⩾35 ppb (n=10). Red dots represent patients with sputum eosinophils ⩾3%, black dots represent patients with sputum eosinophils ⩽2% and empty circles represent patients for whom sputum samples were unavailable or invalid. MCID: minimal clinically important difference.

ACQ-5 improved beyond the MCID (⩽−0.5 points) with nonsignificant trends (T2-Low/Low 68% (n=11), T2-Mid 74% (n=20), T2-High/High 100% (n=10); p=0.09) but ordinal categorisation responses achieved statistical significance across BEC-F_{ENO} three-group categorisation (p=0.04) (supplementary table S3).

The exploratory univariate prediction of changes in post-BD FEV_1 (litres) is illustrated in figure 2a. Significant predictors included BEC, F_{ENO}, BEC×F_{ENO} interaction, sputum eosinophils, a T2-High status for peak biomarker values in the previous 12 months, FEV_1 (per 10% decrease of predicted value) and ΔFEV_1 (per 10% decrease compared to best value in previous 12 months). Symptom scores (ACQ-5) were not predictive. In multivariable analyses, the only independent predictor for change in post-BD FEV_1 (litres) was the ordinal BEC-F_{ENO} three-group categorisation (mean difference 0.13 L per step, 95% CI 0.01–0.25; p=0.039) (figure 2b). The spline curve of the specific model testing BEC×F_{ENO} interaction is shown in supplementary figure S3 demonstrating the significant positive interaction (p for interaction=0.007).

In logistic regression to predict FEV_1 improvements ⩾0.1 L, the ordinal BEC-F_{ENO} three-group categorisation was also the only independent predictor (odds ratio 2.50, 95% CI 1.04–6.67; p=0.049) (supplementary figure S4a). The receiver operating characteristic curve showed an area under the curve of 77.6% (95% CI 64.8–90.4%), suggesting good accuracy of the multivariable model to predict post-BD FEV_1 improvements ⩾0.1 L based on ordinal BEC-F_{ENO} three-group categorisation and FEV_1 % predicted (supplementary figure S4b). Changes in other exploratory clinical and lung function variables are presented in the supplementary table S4. These showed no differences between groups for modified Medical Research Council or visual analogue scale score changes. There were significant changes of $FEF_{25–75\%}$ (p=0.0006), absolute peak expiratory flow (PEF) (p=0.005) and PEF % (p=0.031) across T2 categorisation.

Day 0 to 7 trajectories of peak flow values (PEF) and symptom scores according to T2 phenotypes showed significant improvement of both parameters over time (figure 3), with the interaction between time and the T2-High/High group being statistically significant (p=0.017) for PEF trajectories.

In our exploration of POC BEC, the device failed to deliver a valid reading for 52 (49%) of 106 potential determinations. Under this caveat, laboratory BEC and POC BEC showed excellent reliability (intraclass correlation coefficient 0.98, 95% CI 0.96–0.99; p<0.001), with a fixed bias estimate of 0.012×10^9 cells·L^{-1} (95% CI −0.001–0.025×10^9 cells·L^{-1}) (supplementary figure S5).

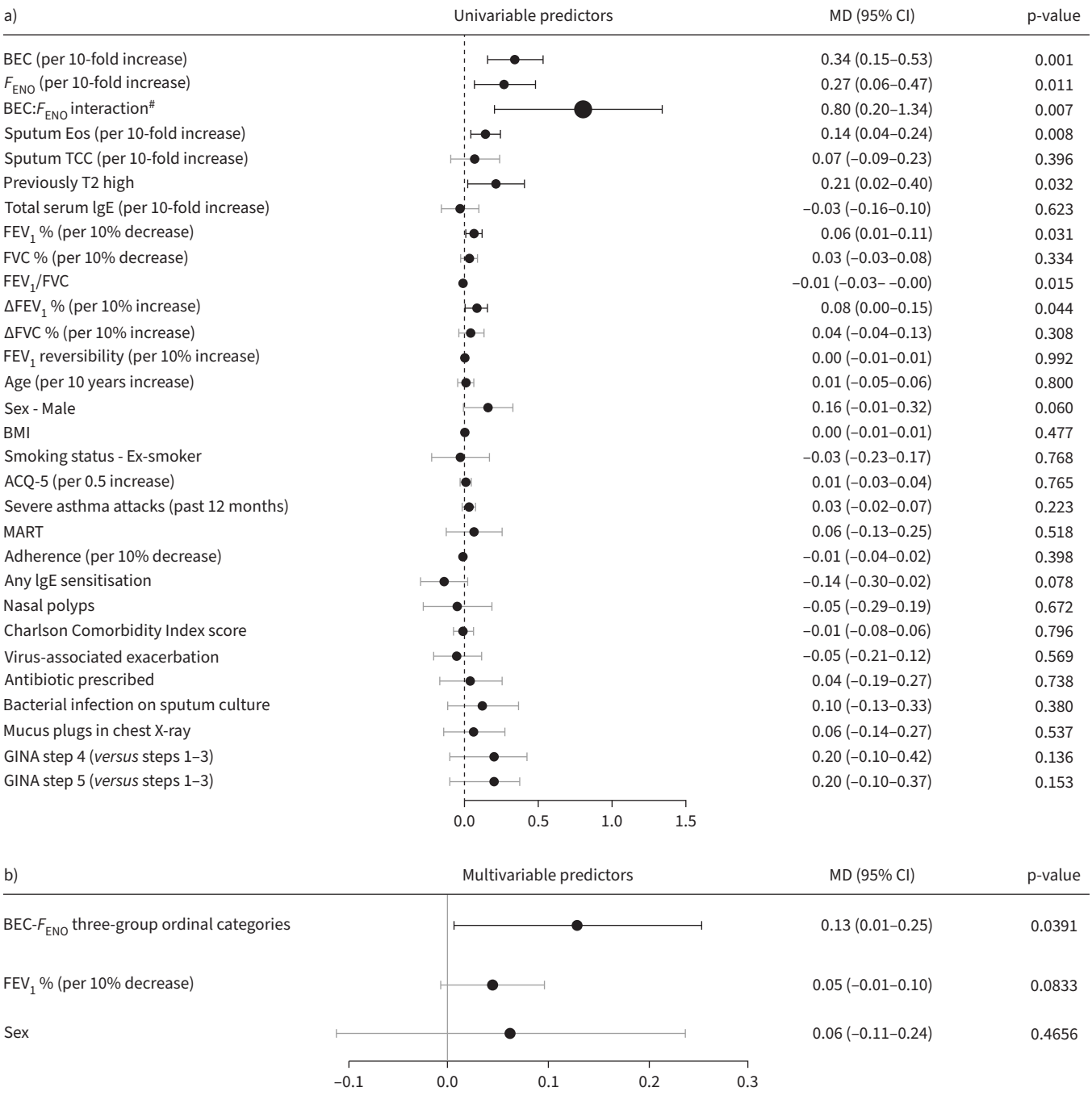

FIGURE 2 Univariate and multivariable analysis of predictors of change in post-bronchodilator forced expiratory volume in 1 s (FEV_1). Data are presented as the mean difference (MD) and error bars represent the 95% confidence intervals. Grey error bars indicate nonsignificant predictors. a) Forest plot presenting the univariable predictors for changes in post-bronchodilator FEV_1 (litres). The predictors include various biomarkers, asthma-related metrics and demographic factors. b) Forest plot presenting the MD of a significant improvement in FEV_1 for various predictors as determined by a multivariable regression model. BEC: blood eosinophil count; F_{ENO}: fractional exhaled nitric oxide; Eos: eosinophil; TCC: total cell count; Previously T2 high: defined as BEC $\geqslant 0.15\times10^9$ cells·L^{-1} and/or F_{ENO} $\geqslant$25 ppb in the previous 12 months; FVC: forced vital capacity; ΔFEV_1: change in FEV_1 at visit 1 compared to best value in previous 12 months; ΔFVC: change in FVC at visit 1 compared to best value in previous 12 months; BMI: body mass index; ACQ-5: Asthma Control Questionnaire-5; MART: maintenance and reliever therapy; GINA: Global Initiative for Asthma. #: interaction term was included to assess the combined effect of biomarkers.

The overall incidence of OCS-attributable adverse events was comparable between the groups, with 33 patients (62%) reporting at least one event. The incidence of at least one event that qualified as severe (grade 3–4) was rare (n=3, 6%) (table 2). The most frequent adverse events reported were insomnia,

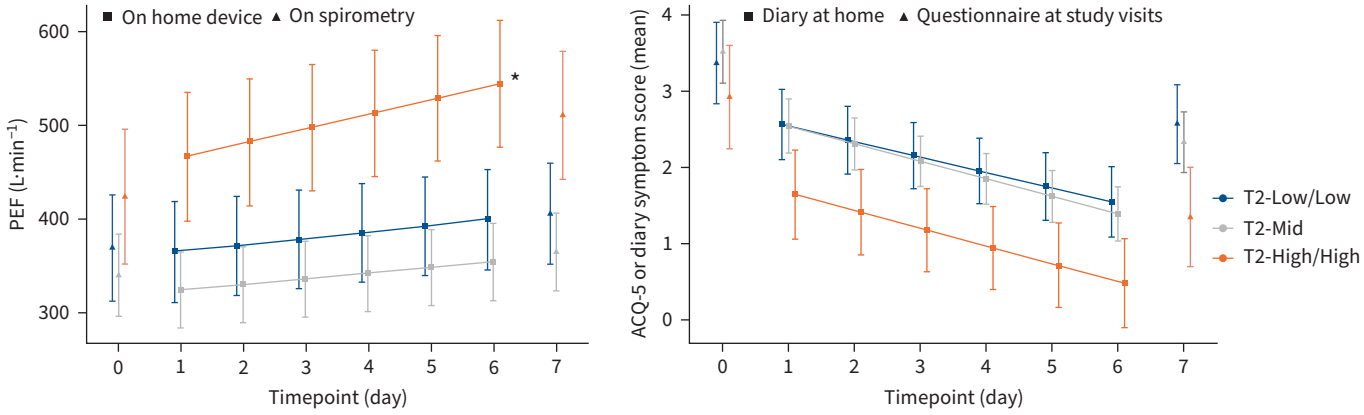

FIGURE 3 Peak expiratory flow (PEF) values and symptoms score trajectories analysis according to ordinal blood eosinophil count (BEC)-fractional exhaled nitric oxide (F_{ENO}) three-group categories. a) Mean PEF values and b) Asthma Control Questionnaire-5 (ACQ-5) and symptom scores measured over 7 days, stratified by ordinal BEC-F_{ENO} three-group categories. The T2-Low/Low group is shown in blue, the T2-Mid in grey and the T2-High/High group is shown in orange. *: p<0.05 for interaction between T2-High/High group and time on linear mixed effect modelling. PEF values are represented for both home device measurements (solid lines and squares) and spirometry measurements at study visits (triangles). ACQ-5 and symptoms scores values are represented for both home measurements (solid lines and squares) and at study visits (triangles). Error bars represent the standard error of the mean.

changes in appetite, dyspepsia and tremors. The severe events were more frequently changes in mood, tremors and changes in appetite (supplementary table S5).

The 90-day web-based surveys showed no significant difference in the ACQ-5 since visit 1 nor in the frequency of subsequent severe exacerbations. At follow-up, 23 of 53 patients (43%) were using biologicals, with use in the T2-High/High group (5 out of 10, 50%) and T2-Mid group (14 out of 27, 52%) only slightly more likely than in the T2-Low/Low group (4 out of 16, 25%) (p=0.15). The T2-Low/Low group only received tezepelumab (4 out of 4, 100%), whereas the T2-Mid and T2-High/High groups predominantly received dupilumab and tezepelumab (Chi-squared p=0.08).

In prespecified sensitivity analyses, univariate regression showed numerical trends towards males gaining more post-BD FEV_1 than females (mean difference 0.16, 95% CI −0.01–0.32; p=0.06) (figure 2a). However, the disaggregated statistical outputs according to sex generally showed that T2 inflammatory responsiveness occurred in both sexes (https://github.com/simoncouillard/PRISMA). Owing to the absence of transgender and the limited number of non-Caucasian patients (n=3, 5%), we did not conduct further sensitivity analyses.

Post hoc analyses for the primary outcome showed progressively greater % predicted post-BD FEV_1 changes (p for trend<0.029) from T2-Low/Low to T2-High/High (supplementary figure S6). Post-BD FVC improved significantly in absolute values (p=0.03) (supplementary figure S6a) with a trend in percentage change (p=0.06) (supplementary figure S6b). Post-BD FEV_1/FVC likewise showed a trend towards improvement (p=0.06) (supplementary figure S7). Pre-BD FEV_1 differences were significant in both absolute changes (p<0.0001) (supplementary figure S8a) and percentage changes (p=0.001) (supplementary

TABLE 2 Adverse events related to oral corticosteroid use in the total population and according to T2 groups

	Overall	T2-Low/Low	T2-Mid	T2-High/High	p-value
Patients (n)	53	16	27	10	
Any adverse event	33 (62.3)	10 (62.5)	18 (66.7)	5 (50.0)	0.696
Any mild adverse event	32 (60.4)	10 (62.5)	18 (66.7)	4 (40.0)	0.4
Any severe adverse event	3 (5.7)	1 (6.3)	1 (3.7)	1 (10.0)	0.76

According to an adaptation of the Common Terminology Criteria for Adverse Events 5.0.1 [26]. See supplementary methods and supplementary table S4. Data are presented as n (%), unless otherwise stated. T2: type 2.

figure S8b). *Post hoc* analyses for the primary outcome according to sputum eosinophils showed that high sputum levels (⩾3%) were associated with greater improvements in post-BD FEV_1 (p=0.005) (supplementary figure S9).

An analysis of the individual domains of the ACQ-5 questionnaire revealed that T2-High/High patients experienced the greatest improvements in night-time symptoms (mean −2.10±1.10 points; p=0.0246) and activity limitations (mean −1.90±1.10 points; p=0.0368).

Following OCS treatment, significant reductions were observed in biomarkers across the T2 subgroups (supplementary table S6), with the T2-High/High group exhibiting the largest reduction in BEC (p<0.0001), F_{ENO} (p=0.0003) and sputum eosinophils (p<0.0001).

Discussion

Prospective evaluation of severe asthma attacks before and after OCS highlights the utility of T2 inflammation biomarkers (BEC and F_{ENO}) to identify distinct clinical trajectories. Comparison based on ordinal BEC-F_{ENO} three-group categories of T2 inflammatory burden showed significantly greater lung function improvements and a strong trend towards better symptom control in T2-High attacks. In contrast, 30% of attacks qualified as T2-Low/Low, achieving nonsignificant post-BD FEV_1 changes below the MCID. Importantly, dual biomarker stratification outperformed symptom-, X-ray-, microbiology- and FEV_1-based parameters in univariable and multivariable models predicting lung function improvements. Finally, we found that the side-effects of OCS were reported uniformly, indicating a disconnect between therapeutic trajectories and toxicity.

The observed heterogeneity in clinical trajectories of asthma attacks challenges traditional management of these events. Indeed, using a symptom-based decision to initiate OCS when symptoms had not abated within ⩾48 h of increased inhaled therapy, we followed GINA recommendations [1]. These recommendations are based on clinical trials reported prior to 1993, at a time where regular inhaled corticosteroids (ICS) were not firmly mandated, anti-inflammatory reliever therapy was not an option and T2 inflammatory biomarkers were not clinically accessible [3]. Our prospective observational study was not designed to question the decrease in clinical relapse observed in the previous century's trials of OCS. However, it does imply that these clinical responses may have been driven by T2-High/High attacks, that the percentage of T2-Low/Low attacks may have increased with the advent of widespread use of ICS, or a combination of both. The statistical and clinical robustness of our carefully designed observational study's findings underscore the potential for personalised treatment in acute asthma to minimise unnecessary exposure and side-effects. It also complements the recently published ABRA study [27] and strengthens the evidence for biomarker-guided management in obstructive lung disease exacerbations.

Our findings align with existing evidence suggesting that T2 inflammatory biomarkers are more important than symptoms and allergies to predict asthma treatment responses [2, 6]. In acute asthma, Pizzichini *et al.* [16] investigated the time course of symptoms, FEV_1 and inflammatory changes in sputum and blood samples from 10 patients experiencing a severe asthma exacerbation that was treated with prednisone for 10 days. After initiating treatment, improvements in symptoms, FEV_1, BEC and serum eosinophil cationic protein levels were observed within the first 24 h, while sputum eosinophils decreased at 48 h. A correlation was reported between the decreases in sputum eosinophils and FEV_1 change, but not with baseline eosinophil values. Similarly, Maneechotesuwan *et al.* [15] analysed serum cytokines in 28 consecutive patients with acute asthma treated with OCS for 1 week at an emergency department. These authors characterised the immunological profile of "paradoxical responders", defined by the effect of OCS on BEC. Both studies relied on specialised measurements. In contrast, the current GINA strategy recommendation is to base OCS prescription on symptoms with or without lung function tests. In our study, the assessment of acutely symptomatic patients relied on clinically accessible biomarkers, in addition to spirometry and other tests. The differential improvement observed in asthma attacks using T2 biomarkers is noteworthy because these were available in 100% of patients, reinforcing the feasibility of incorporating underlying biological assessments into clinical decision-making processes across the range of disease severities [13, 28].

Our finding that BEC and F_{ENO} were synergistic predictors of FEV_1 improvement is biologically plausible, given that each biomarker captures distinct components and compartments of the T2 immune response. Indeed, blood eosinophils reflect the systemic pool of interleukin-5 and circulating effector cells, whereas F_{ENO} is indicative of T2 cytokine, chemokine and alarmin signalling within the airway compartment [29]. This mechanistic understanding reinforces the concept that taking both biomarkers together is the most effective strategy to stratify acute as well as chronic asthma [2, 5, 6, 22, 27, 30, 31]. Our observation that

the most impressive change in post-BD FEV_1 and other lung function parameters occurred in participants with greater dual biomarker elevation (BEC $\geqslant 0.30\times10^9$ cells·L^{-1} and F_{ENO} $\geqslant$35 ppb) further supports the phenotyping of asthma attacks using both BEC and F_{ENO}.

Notably, a substantial proportion of T2-Low/Low patients achieved meaningful symptom improvement despite limited changes in lung function, suggesting that withholding OCS in this group could deny some patients significant symptomatic relief. A potential explanation for this finding is regression to the mean. Additionally, alternative mechanisms such as resolution of viral infection, non-T2 inflammatory pathways or a placebo effect may have contributed. Domain-specific analysis of ACQ-5 showed significant reductions in night-time awakenings and activity limitations in the T2-High/High group, reflecting symptoms that are closely linked to improvements in lung function.

We acknowledge that our study has several limitations. First, being an observational study, it inherently carries the limitations of such designs. However, by ensuring that all patients received prednisone, all groups received active treatment. This suggests that differences between phenotypes may be even greater in a placebo-controlled biomarker-stratified trial, where placebo *versus* OCS differences would be smaller in T2-Low/Low than in T2-High/High events. Second, while we did not assess quality of life, we measured symptoms. Despite being underpowered for this outcome, we observed strong numerical trends that suggest meaningful clinical differences with greater T2 burden. Third, adverse effects were reported by patients through a directed questionnaire, which could have led to over-reporting and attribution bias. Fourth, we advocated for POC BEC but failed in most of our attempts with the tested device. Fifth, our 90-day post-attack visit was conducted virtually for people who had often benefited from background treatment escalation, meaning that the reported outcomes are likely confounded. Finally, the small sample size in the T2-High/High group represents an additional limitation that warrants caution in interpreting the findings. These limitations should be considered in further clinical studies of asthma attacks.

In conclusion, the PRISMA study identifies a novel utility for blood eosinophils and F_{ENO} to stratify people experiencing asthma attack. Indeed, we found that the T2-High groups experienced greater improvements in lung function and symptom control. The study also noted that the side-effects of OCS were uniformly reported across groups, supporting the incorporation of biomarker-driven approaches into routine acute asthma care to enhance outcomes and reduce the risks associated with OCS therapy. Future translational studies will elucidate the underlying mechanisms that drive the differential responses observed with T2 inflammatory biomarker stratification [19]. For example, our findings provide a strong rationale for a placebo-controlled non-inferiority study of prednisolone *versus* placebo in patients with T2-Low/Low attacks, as done successfully in COPD [27].

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Data availability: Data from this study may be shared if the investigators' proposed use of the data has been approved by the study principal investigator and an institutional research ethics committee. The REDCap codebook, statistical code and outputs for this study are available at https://github.com/simoncouillard/PRISMA.

The protocol of this observational longitudinal study of asthma attacks has been registered at ClinicalTrials.gov with identifier NCT05870215.

Ethics statement: Ethics approval was obtained from the research ethics committee of the CIUSSS de l'Estrie–CHUS, Sherbrooke, QC, Canada (#2023-4687).

Conflict of interest: C. Celis-Preciado has received an education scholarship from the Université de Sherbrooke, within the current work; outside the current work, he has received speaker honoraria from AstraZeneca, GlaxoSmithKline and Sanofi-Regeneron, and consultancy fees from AstraZeneca, GlaxoSmithKline and Sanofi-Regeneron. S. Leclerc reports speaker honoraria from AstraZeneca, outside of the submitted work. F.A. Vézina reports speaker honoraria from AstraZeneca, Sanofi-Regeneron, GlaxoSmithKline, Boehringer Ingelheim and Novartis, outside of the submitted work. P. Lachapelle reports speaker honoraria from AstraZeneca, Sanofi-Regeneron, GlaxoSmithKline, Boehringer Ingelheim and Novartis, and has received consultancy fees from AstraZeneca, GlaxoSmithKline and Sanofi-Regeneron, outside the submitted work. S. Couillard reports he has received unrestricted research grants from Sanofi-Genyme-Regeneron, bioMérieux and the Québec

Air-Intersectorialité-Respiratoire Network; he is the holder of the Association Pulmonaire du Québec's Research Chair in Respiratory Medicine; and he is a Clinical Research Scholar of the Fonds de Recherche du Québec, within the submitted work. Outside the submitted work, he reports unrestricted research grants from NIHR Oxford BRC, the Quebec Respiratory Health Research Network, the Fondation Québécoise en Santé Respiratoire, AstraZeneca, bioMérieux, Academy of Medical Sciences and the Association Pulmonaire du Québec; speaker honoraria from AstraZeneca, GlaxoSmithKline, Sanofi-Regeneron and Valeo Pharma; consultancy fees from FirstThought, AstraZeneca, GlaxoSmithKline, Sanofi-Regeneron, Access Biotechnology and Access Industries; sponsorship to attend/speak at international scientific meetings from AstraZeneca and Sanofi-Regeneron; is an advisory board member and holds stock options for Biometry Inc., a company which is developing a F_{ENO} device (myBiometry); and he advised the Institut National d'Excellence en Santé et Services Sociaux (INESSS) for an update of the asthma general practice information booklet for general practitioners. The remaining authors report no potential conflicts of interest.

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References

1 Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention (2024 update). 2024. Available from: https://ginasthma.org/
2 Pavord ID, Beasley R, Agusti A, *et al.* After asthma: redefining airways diseases. *Lancet* 2018; 391: 350–400.
3 Rowe BH, Spooner C, Ducharme F, *et al.* Corticosteroids for preventing relapse following acute exacerbations of asthma. *Cochrane Database Syst Rev* 2007; 3: CD000195.
4 Agusti A, Bel E, Thomas M, *et al.* Treatable traits: toward precision medicine of chronic airway diseases. *Eur Respir J* 2016; 47: 410–419.
5 Couillard S, Laugerud A, Jabeen M, *et al.* Derivation of a prototype asthma attack risk scale centred on blood eosinophils and exhaled nitric oxide. *Thorax* 2022; 77: 199–202.
6 Couillard S, Do W, Beasley R, *et al.* Predicting the benefits of type-2 targeted anti-inflammatory treatment with the prototype OxfoRd Asthma attaCk risk scaLE (ORACLE). *ERJ Open Res* 2022; 8: 00570-2021.
7 Baigelman W, Chodosh S, Pizzuto D, *et al.* Sputum and blood eosinophils during corticosteroid treatment of acute exacerbations of asthma. *Am J Med* 1983; 75: 929–936.
8 McDowell PJ, Busby J, Hanratty CE, *et al.* Exacerbation profile and risk factors in a type-2–low enriched severe asthma cohort: a clinical trial to assess asthma exacerbation phenotypes. *Am J Respir Crit Care Med* 2022; 206: 545–553.
9 Alfaro C, Sharma OP, Navarro L, *et al.* Inverse correlation of expiratory lung flows and sputum eosinophils in status asthmaticus. *Ann Allergy* 1989; 63: 251–254.
10 Fahya BJV, Kimb KW, Liub J, *et al.* Prominent neutrophilic inflammation in sputum from subjects with asthma exacerbation. *J Allergy Clin Immunol* 1995; 95: 843–852.
11 Ordoñez CL, Shaughnessy TE, Matthay MA, *et al.* Increased neutrophil numbers and IL-8 levels in airway secretions in acute severe asthma: clinical and biologic significance. *Am J Respir Crit Care Med* 2000; 161: 1185–1190.
12 Ghebre MA, Pang PH, Diver S, *et al.* Biological exacerbation clusters demonstrate asthma and chronic obstructive pulmonary disease overlap with distinct mediator and microbiome profiles. *J Allergy Clin Immunol* 2018; 141: 2027–2036.
13 McDowell PJ, Diver S, Yang F, *et al.* The inflammatory profile of exacerbations in patients with severe refractory eosinophilic asthma receiving mepolizumab (the MEX study): a prospective observational study. *Lancet Respir Med* 2021; 9: 1174–1184.
14 Diver S, Haldar K, McDowell PJ, *et al.* Relationship between inflammatory status and microbial composition in severe asthma and during exacerbation. *Allergy* 2022; 77: 3362–3376.
15 Maneechotesuwan K, Prapruetkit N, Chankham J, *et al.* Paradoxical eosinophilic and cytokine responses to oral corticosteroid treatment in patients with asthma exacerbations. *J Allergy Clin Immunol Glob* 2024; 3: 100238.
16 Pizzichini MM, Pizzichini E, Clelland L, *et al.* Sputum in severe exacerbations of asthma: kinetics of inflammatory indices after prednisone treatment. *Am J Respir Crit Care Med* 1997; 155: 1501–1508.
17 Blakey J, Chung LP, McDonald VM, *et al.* Oral corticosteroids stewardship for asthma in adults and adolescents: a position paper from the Thoracic Society of Australia and New Zealand. *Respirology* 2021; 26: 1112–1130.

18 Ramakrishnan S, Couillard S. Antibiotics for asthma attacks: masking uncertainty. *Eur Respir J* 2021; 58: 2100183.

19 Celis-Preciado CA, Leclerc S, Duval M, *et al.* Phenotyping the Responses to Systemic Corticosteroids in the Management of Asthma Attacks (PRISMA): protocol for an observational and translational pilot study. *BMJ Open Respir Res* 2023; 10: e001932.

20 Gomez LDP, Pavord I, Busse W, *et al.* Long-term effect of dupilumab on prevention of lung function decline in patients with uncontrolled moderate-to-severe asthma: ATLAS trial design. *ERJ Open Res* 2023; 9: 00417-2022.

21 Couillard S, Steyerberg E, Beasley R, *et al.* Blood eosinophils, fractional exhaled nitric oxide and the risk of asthma attacks in randomised controlled trials: protocol for a systemic review and control arm patient-level meta-analysis for clinical prediction modelling. *BMJ Open* 2022; 12: e058215.

22 Meulmeester FL, Mailhot-Larouche S, Celis-Preciado C, *et al.* Inflammatory and clinical risk factors for asthma attacks: a patient-level meta-analysis of control arms of 22 randomised trials. *Lancet Respir Med* 2025; in press [https://doi.org/10.1016/S2213-2600(25)00037-2].

23 Bonini M, Di Paolo M, Bagnasco D, *et al.* Minimal clinically important difference for asthma endpoints: an expert consensus report. *Eur Respir Rev* 2020; 29: 190137.

24 Tepper RS, Wise RS, Covar R, *et al.* Asthma outcomes: pulmonary physiology. *J Allergy Clin Immunol* 2012; 129: S65–S87.

25 Traister RS, Fajt ML, Landsittel D, *et al.* A novel scoring system to distinguish vocal cord dysfunction from asthma. *J Allergy Clin Immunol Pract* 2014; 2: 65–69.

26 National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) version [5.0.1]. Bethesda, MD, US Department of Health and Human Services, 2017. Available from: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

27 Ramakrishnan S, Russell REK, Mahmood HR, *et al.* Treating eosinophilic exacerbations of asthma and COPD with benralizumab (ABRA): a double-blind, double-dummy, active placebo-controlled randomised trial. *Lancet Respir Med* 2025; 13: 59–68.

28 Couillard S, Petousi N, Smigiel K, *et al.* Towards a predict and prevent approach in obstructive airways diseases. *J Allergy Clin Immunol Pract* 2023; 11: 704–712.

29 Couillard S, Shrimanker R, Chaudhuri R, *et al.* Fractional exhaled nitric oxide nonsuppression identifies corticosteroid-resistant type 2 signaling in severe asthma. *Am J Respir Crit Care Med* 2021; 204: 731–734.

30 Couillard S, Jackson DJ, Wechsler ME, *et al.* Work-up of severe asthma. *Chest* 2021; 160: 2019–2029.

31 Couillard S, Jackson DJ, Pavord ID, *et al.* Choosing the right biologic for the right patient with severe asthma. *Chest* 2025; 167: 330–342.