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Evaluation in a severe asthma expert center improves asthma outcomes regardless of step-up in asthma therapy

Camille Bègne, Aurélien Justet, Clairelyne Dupin, Camille Taillé

► **To cite this version:**

Camille Bègne, Aurélien Justet, Clairelyne Dupin, Camille Taillé. Evaluation in a severe asthma expert center improves asthma outcomes regardless of step-up in asthma therapy. *Journal of Allergy and Clinical Immunology: In Practice*, 2020, 8, pp.1439 - 1442.e2. <10.1016/j.jaip.2019.10.026>. <hal-03491067>

HAL Id: hal-03491067

<https://hal.science/hal-03491067v1>

Submitted on 22 Aug 2022

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1 **Evaluation in a severe asthma expert center improves asthma outcomes**
2 **regardless of step-up in asthma therapy**

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5 Camille Bègne, MD¹, Aurélien Justet, MD^{1,2}, Clairelyne Dupin, MD¹,
6 and Camille Taillé, MD, PhD ^{1,2}.

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8 ¹ Service de Pneumologie et Centre de Référence Constitutif des Maladies Pulmonaires
9 Rares, Hôpital Bichat, Groupe Hospitalier Universitaire AP-HP Nord - Université de Paris,
10 Paris, France

11 ² INSERM UMR 1152, LabEx Inflammex, Paris, France

12
13 **Corresponding author:**

14 Prof Camille Taillé, Service de pneumologie, Hôpital Bichat,
15 46 rue Henri Huchard, 75018, Paris, France.

16 E-Mail: camille.taille@aphp.fr.

17 Phone: +33 1 40 25 68 02.

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19 **Word count:** 1238 words

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21 **Conflict of interest:**

22 CT has received fees from GSK, AstraZeneca, Novartis, Teva, Sanofi and Roche (consultancy,
23 advisory boards) and was an investigator in trials involving GSK, AstraZeneca, Novartis,
24 Sanofi, Roche and Boehringer Ingelheim.

25 CB, AJ and CD have no conflict of interest to disclose.

26
27 **Funding:** No funding source was received for this study.

28 **CLINICAL IMPLICATIONS STATEMENT**

29 We report the French experience of our severe asthma expert center and confirm that a
30 pluridisciplinary assessment at a one-day hospital stay results in improvements in severe
31 asthma disease management, avoiding treatment step-up in a small but clinically significant
32 proportion of patients.

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34 **Key-words:** *Severe asthma; Asthma center; Asthma treatment; Health care organization;*
35 *Asthma control; Disease management; Therapeutic patient education.*

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52 To the editor

53 The landscape of severe asthma has undergone considerable changes thanks to a clear
54 and consensual definition of severe asthma,¹ the availability of several highly effective
55 biologic therapies, and the regular update of practical guidelines for the global care of
56 asthma during the past ten years.¹⁻² All have contributed to improving the disease and
57 reducing its burden. However, getting a severe asthma diagnosis remains a complex process,
58 including tackling of differential diagnosis, comorbidities and environmental triggers,
59 evaluating adherence and providing patient education. Severe asthma centers have been
60 developed in several countries to provide high expertise and dedicated support. The benefits
61 of such structures have been demonstrated to be associated with an improvement in asthma
62 control and quality of life and a reduction in healthcare use, regardless of asthma
63 phenotype.³⁻⁵ However, the improvement has been reported to therapeutic step-up, or to
64 optimization of comorbidities.⁵ The role of overall management, including education and
65 psychological support, has been suggested,⁵ but not investigated.

66 Among the 175 patients referred by pulmonologists for severe asthma in our expert
67 center between 2014 and 2016 and attending a systematic evaluation during a one-day visit
68 after screening by an asthma specialist, 119 patients were retrospectively studied (Online
69 Repository Data, Figure E1). All had already received high ICS doses and LABA when referred
70 to this visit. As put forward by Mc Donald et al.,⁶ this pluridisciplinary assessment was aimed
71 at confirming the diagnosis of asthma and severity, but also establishing asthma phenotypes,
72 managing comorbidities and refining the management plan. All patients underwent medical
73 evaluation and explorations (CT scan, lung function tests, blood samples),² and attended an
74 individual interview with a nurse involved in therapeutic education to ensure a proper use of
75 inhaler technique and to provide personalized written action plan. They were also referred to

76 a dietitian, a psychologist, a tobaccologist or a social worker, when needed. All medical
77 reports were then discussed by the pluridisciplinary team to confirm the diagnosis of severe
78 asthma on the basis of asthma history and symptoms, pulmonary function tests and CT scan,
79 to list aggravating factors and to propose treatments to improve asthma control. A biologic
80 medicine was prescribed when treatment of comorbidities was optimized and disease
81 understanding was deemed to be suitable with appropriate self-management. We excluded
82 10 patients (5.7%) in whom another diagnosis than asthma was made. Patients with a 12
83 month-follow up were retrospectively distributed into the three following groups according
84 to the medical decisions made by the pluridisciplinary team during the follow-up:

- 85 - Group 1 (N=49) comprised patients who were prescribed a step 5 asthma therapy, such as
86 OCS, omalizumab, bronchial thermoplasty or had a change in a step 5 treatment during
87 the follow-up.
- 88 - Group 2 (N=16) comprised patients undergoing at least one comorbidity intervention
89 without any prescription of a step 5 treatment or any change in the 5 step treatment
90 during the follow-up.
- 91 - Group 3 (N=54) comprised patients who neither benefited from asthma treatment step-
92 up nor from comorbidity intervention during the follow-up.

93 Patients in Group 1 were proposed the following changes in their step 5 treatments:
94 omalizumab (N=25), azithromycine (N=8), bronchial thermoplasty (N=10), OCS (N=4) and
95 azathioprine (N=2). The following scheduled medical interventions were offered in patients
96 in Group 2: pulmonary rehabilitation (N=3), nocturnal ventilation for OSA (N=4), smoking
97 cessation (N=1), psychiatric care (N=1), nutritional follow-up by dietitian (N=1), sleeve
98 gastrectomy (N=1) and hyperventilation treatment (N=7).

99 All baseline characteristics, including asthma control and annual rate of exacerbations
100 were not significantly different among the groups (TABLES I and II). From the first evaluation
101 at 6 months, the proportion of patients achieving an ACT score ≥ 20 increased in the 3
102 groups, then continues to progress at 12 months, group 3 demonstrating the largest
103 proportion (increased from 11 to 20% à 6 months and 29.5% at 12 months) of controlled
104 patients. This was associated with a decrease in daily dose of OCS and hospitalizations rate
105 (TABLE II). No significant changes on FEV1 were observed (TABLE II).

106 These results on a team-based care approach are close to those previously observed in
107 other health care systems,³⁻⁵ showing similar extend in ACT changes⁵ and reduction in asthma
108 exacerbation,³⁻⁵. We also confirm that severe asthma diagnosis was reviewed in a sizable part
109 of the cohort⁴, although the majority of patients were referred by lung specialists.

110 Many challenges remain in the management of severe asthma before prescribing
111 biological therapies. In this context, it is relevant to point out that a small but clinically
112 significant proportion of patients in Group 3 improved without any add-on therapies (step-
113 up treatment and medical interventions) after a 12-month period. This effect 'patient care'
114 may explain a part of the dramatic effect observed in the placebo arm in some randomized
115 studies.⁷ More importantly, this emphasizes the role of information and patient education to
116 improve inhalation technique and adherence, increase confidence in treatments and action
117 plan use and highlights the importance of a pluridisciplinary and expert evaluation, which
118 may give benefits before considering a biologic. Indeed, as patients were mainly referred for
119 treatment step-up, we can consider that a biologic prescription may have been avoided in
120 about 10 patients in group 3 and 2 in group 2 (13.4% of the study population).

121 Our findings also highlight the importance of asthma training courses for all healthcare
122 professionals, in order to provide a pluridisciplinary management of severe asthma

123 patients. It is noteworthy to mention that there are no asthma nurses in France, contrarily in
124 UK, for example. Such an approach meets patient expectations as they often ask for some
125 explanation on disease and treatment,⁸ express concern about potential side effect of
126 medications,¹ and claim to access consistent quality care by a specialized severe asthma
127 team.⁹ All this highlights the need for building up healthcare networks in order to shorten
128 times for care management, optimize prescribing of costly biotherapies, and facilitate a
129 pluridisciplinary collaborative setting in asthma management.

130 Of course, this study has a monocentric retrospective design, which may seem like a
131 drawback is strength actually, as this study reflects the routine clinical practices in an expert
132 asthma center. Although already well-described,⁶ organization of specialized centers
133 depends on local health care systems, human and material resources. We also acknowledge
134 that Group 1 and Group 2 were heterogeneous and somewhat artificial: Group 1 gathered
135 patients receiving various drug types and those undergoing bronchial thermoplasty, and
136 Group 2 gathered patients undergoing a variety of interventions. As a result, the benefit
137 seems to be low in Group 1 and Group 2. However, the aim of the study was not to assess
138 effect of step 5 treatments. The reduction in OCS consumption in some patients may have
139 been masked by introduction of OCS in 4 patients in Group 1. Finally, the data on asthma
140 exacerbations and hospitalizations were based on self-report, as in the Dutch study⁴ and
141 may suffer a recall bias. Similarly, during patient education sessions self-management skills
142 of the disease are taught in order to avoid hospitalizations. This means a better disease
143 patient knowledge of the disease, but not necessarily a better asthma control.

144 In conclusion, a systematic assessment of severe asthma by a pluridisciplinary team in an
145 expert center improves severe asthma control in a small but clinically significant part of the
146 patients, sometimes without any step up in asthma treatments. This study highlights the

147 importance of setting up specialized asthma center to provide an appropriate environment
148 for optimizing overall patient care before considering biologic prescription.

149

150 **ACKNOWLEDGMENTS**

151 The authors are grateful to Prof Bruno Crestani, Dr Mada Ghanem, Dr Pierre Le Guen, Dr
152 Laure Tabèze, Dr Raphaël Borie, Dr Marie-Christine Dombret, Dr Catherine Neukirch and all
153 collaborators from the Respiratory Diseases Department involved in severe asthma care, and
154 to Mrs Brigitte Bourdillat for help in English editing.

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189 **TABLE I.** Demographic and clinical baseline characteristics of the population (N=119)
 190 according to the medical decision-making by a pluridisciplinary team at the end of a one-day
 191 visit

Characteristics	All (N=119)	Group 1 (N=49)	Group 2 (N=16)	Group 3 (N=54)	P value
Demographics					
Age (y) ^a	50.8±1.3	49.2±2.0	47.4±2.8	53.0±2.0	NS
Sex: female	80(67.2%)	31(63.3%)	13(81.3%)	36(66.7%)	NS
BMI (kg/m ²) ^a	26.9±0.6	27.2±0.8	27.7±2.0	26.3±0.7	NS
Current smokers	13 (11%)	5 (10.2%)	3 (18.75%)	5 (9.2%)	NS
Former smokers	34 (28.5%)	17 (34.6%)	3 (18.75%)	14 (26%)	NS
Asthma history					
Age of asthma onset (y) ^a	26.5±1.8	20.5±2.6	25.8±5.4	32.0±2.7*	.013
Asthma treatment					
LAMA	37(31.1%)	15(30.5%)	5(31.0%)	17(31.5%)	NS
Omalizumab	12(10.1%)	6(12.2%)	1(6.2%)	5(9.2%)	NS
Montelukast	60 (50.4%)	32(65.3%)	7(43.8%)	21(38.9%)*	.023
Azithromycin	15(12.6%)	5 (10.2%)	1(6.2%)	9(16.5%)	NS
Daily oral corticoids	31(26.1%)	14(28.6%)	2(12.5%)	15(27.8%)	NS
Dose of prednisone (mg/d)	18.0±2.0	20.4±2.0	45.0±15.0	13.0±1.3	NS
Comorbidities					
Atopy	64(53.8%)	36(73.5%)	9(56.3%)	19(35.1%)*	.0005
GERD	60(50.4%)	27(55.1%)	9(56.3%)	24(44.4%)	NS

Chronic rhinosinusitis	58(48.7%)	26(53.1%)	10(62.5%)	22(40.7%)	NS
Nasal polyps	39(32.7%)	15(30.6%)	3(18.8%)	21(38.9%)	NS
OSA	13(10.9%)	6(12.2%)	3(18.8%)	4(7.4%)	NS
Anxiety	29(24.4%)	14(28.6%)	3(18.8%)	12(22.2%)	NS
Depression	16(13.4%)	7(14.3%)	1(6.2%)	8(14.8%)	NS
HVS	40(33.6%)	15(30.6%)	10(62.5%)	15(27.8%)	NS
Cardiovascular disease	28(23.5%)	11(22.4%)	3(18.8%)	14(25.9%)	NS
Diabetes and/or dyslipidemia	23(19.3%)	7(14.3%)	1(6.3%)	15(27.8%)	NS
Lung function testing					
FEV1 (% pred)	71.0±2.2	66.6±3.0	82.0±6.5	72.0±3.0	NS
FEV1 post BD (% pred)	78%	73%	90%	78%	NS
FEV1/FVC (%)	62.0±1.4	59.0±2.3	71.5±1.5	63.3±2.0	NS
RV (% pred) ^a	148±4.2	147±7.0	144±6.0	149±6.0	NS
RV/TLC ^a	53.0±3.1	47.0±3.6	60.0±9.0	53.0±5.0	NS
Max blood eosinophil count (/mm ³) ^{a,b}	532±101	613±160	597±207	596±160	NS

192 Data are expressed as n (%). ^a mean±SD. ^b Higher blood eosinophil count in the previous 12 months

193 *BD*, bronchodilator; *FEV1*, forced expiratory volume in one second; *FVC*, forced expiratory volume; *GERD*,

194 gastroesophageal reflux disease; *HVS*, hyperventilation syndrome; *LAMA*, Long-acting muscarinic

195 antagonists; *OSA*, obstructive sleeping apnea; *NS*, not significant; *RV*, residual volume; *TLC*, total lung

196 capacity. Allergy was defined by an allergen driven asthma confirmed by a skin prick test and/or a specific

197 IgE >0.35 ku/l, and/or food allergy and/or atopic dermatitis. *HVS* was diagnosed in our center by a

198 hyperventilation test.

199

200 **TABLE II.** Comparison of asthma control, frequency of exacerbations and
 201 asthma-related hospital admissions, the use of oral corticosteroids, and lung
 202 function over the 12-month follow-up in the analysis population according to
 203 the medical decision-making by a pluridisciplinary team

	All	Group 1	Group 2	Group 3
ACT score				
ACT score				
Baseline	13.4±0.6	12.5±1.0	12.0±1.0	15.0±0.8
At 6 months	16.3±0.7	15.07±1.1	14.6±1.6	17.2±1.2
At 12 months	15.7±0.6	14.3±1.0	15.4±1.7	17.3±0.9
P value*	<0.05	<0.05	NS	<0.05
Distribution of ACT scores at baseline	(N=119)	(N=49)	(N=16)	(N=54)
ACT ≥20	10 (8.4%)	4 (8.1%)	0	6 (11.1%)
16≤ACT≤19	14 (11.7%)	5 (10.2%)	2 (12.5%)	7 (13%)
15≤ACT	95 (79.8%)	40 (81.6%)	14 (87.5%)	41 (76%)
Distribution of ACT score at 6 months	(N=112)	(N=47)	(N=15)	(N=50)
ACT ≥20	20 (17.8%)	9 (19%)	1 (6.2%)	10 (20%)
16≤ACT≤19	34 (30%)	11 (22.4%)	7 (43.7%)	16 (32%)
15≤ACT	58 (51.7%)	27 (57.4%)	7 (43.7%)	24 (48%)
P value **	<0.05	<0.05	<0.05	<0.05
Distribution of ACT score at 12 months	(N=119)	(N=49)	(N=16)	(N=54)
ACT ≥20	29 (24.3%)	11 (22.4%)	2 (12.5%)	16 (29.6%)
16≤ACT≤19	50 (42%)	15 (30%)	10 (62.5%)	25 (46.3%)
15≤ACT	40 (33.6%)	23 (47%)	4 (25%)	13 (24%)
P value*	<0.05	<0.05	<0.05	<0.0001
ACT score increased by ≥3 points				
At 6 months (N=112)	37 (33%)	15 (32%)	4 (26.6%)	18 (36%)
At 12 months (N=119)	51 (42.8%)	23 (47%)	5 (31.2%)	23 (42.6%)

	(N=119)	(N=49)	(N=16)	(N=54)
Annual Exacerbations rate				
Baseline	7.2±0.7	7.3±1.0	8.2±2.0	6.9±1.2
At 12 months	1.5±0.2	1.8±0.4	1.3±0.4	1.3±2.2
P value*	<0.001	<0.001	<0.05	<0.001
Annual hospitalizations rate	(N=119)	(N=49)	(N=16)	(N=54)
Baseline	0.40±0.07	0.40±0.12	0.30±0.15	0.30±0.11
At 12 months	0.10±0.03	0.10±0.06	0.06±0.06	0.10±0.06
P value*	<0.001	<0.05	NS	<0.05
Patients with hospitalizations for asthma	(N=119)	(N=49)	(N=16)	(N=54)
Baseline	30 (25.2%)	11 (22.4%)	5 (31.2%)	14 (26%)
At 12 months	10 (8.4%)	5 (10.2%)	1 (6.2%)	4 (7.4%)
P value*	<0.001	<0.05	NS	<0.05
Use of oral corticosteroids				
Daily dose of OCS, mg				
Baseline	16.4±7.3	19±2.0	22.5±3.5	15±5.6
At 12 months	12.6±5.5	11.2±4.5	5±0	12±5.4
P value*	<0.05	<0.05	NS	NS
Proportion of patients treated with daily OCS	(N=119)	(N=49)	(N=16)	(N=54)
Baseline	27(22.6%)	15 (30.6%)	2 (12.5%)	10 (27.7 %)
At 12 months	27(22.6%)	16 (32.5%)	2 (12.5 %)	9 (26 %)
P value*	NS	NS	NS	NS
FEV1, %				
Baseline	71.0±2	66.5±3	82.0±6	72.0±3
At 12 months	73.0±2	69.0±4	88.0±5	74.0±4
P value*	NS	NS	NS	NS

204 Results are expressed as mean±SD or as n (%). ACT, asthma control test; FEV1, forced expiratory
205 volume in one second; OCS, oral corticosteroids; SD, standard deviation. Exacerbation was self-
206 reported by the patient and defined as OCS treatment for more than 3 days, or a 50% increase
207 in daily OCS for more than 3 days, or an emergency department visit, or a hospital admission.

208 *Comparison of the changes was made separately for each group between the baseline and at
209 6 months for ACT ** or at 12 months*.

FIGURE E1

