Linee guida GINA 2019 sull'asma grave: key points

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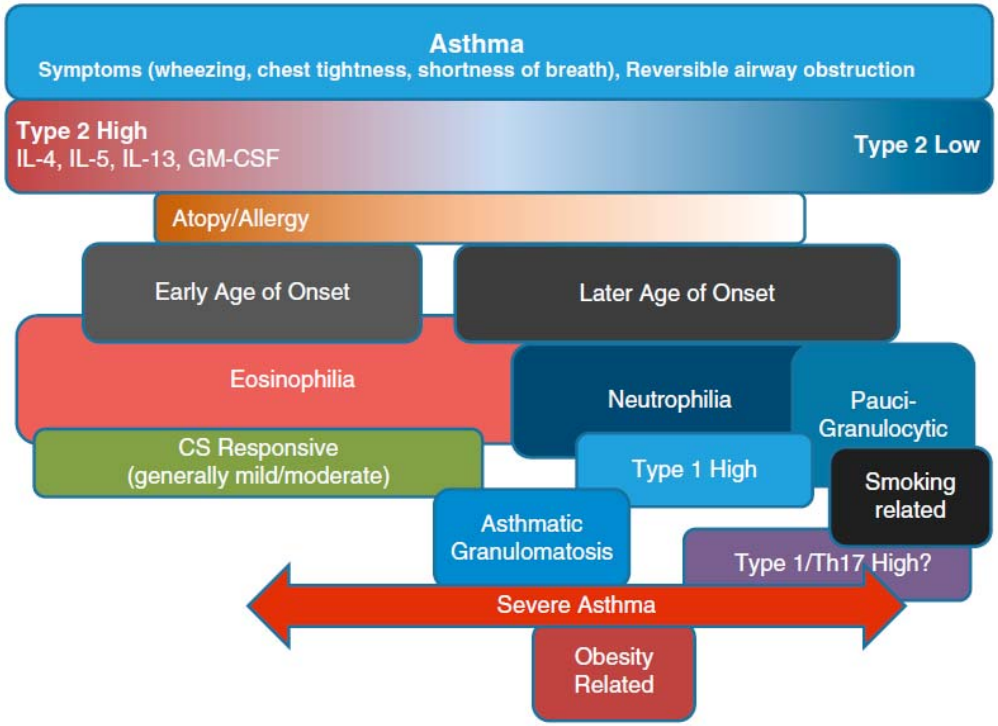
Definizione asma grave

Aspetti clinici

Ottimizzazione trattamento

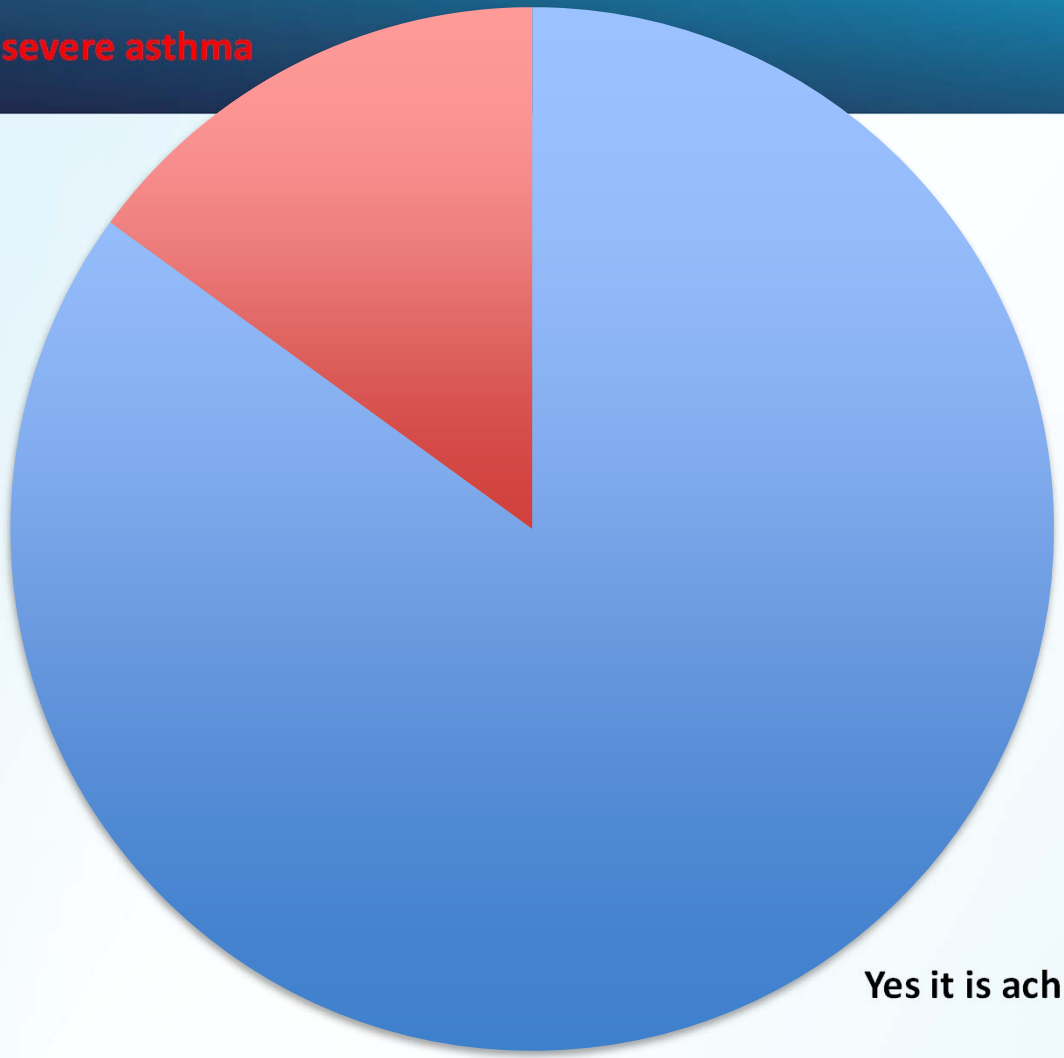
Farmaci biologici

Evolving Concepts of Asthma



(Marc Gauthier, Anuradha Ray, and Sally E. Wenzel AJRCCM 2015)

No it is not achievable: severe asthma



Severe if achieved only at maximal traetment regimens

Yes it is achievable: poor control asthma

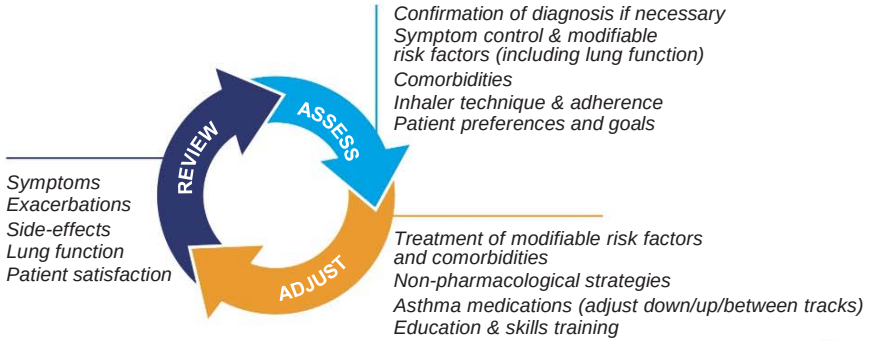
(ERS/ATS)

Severe asthma[144] is a subset of difficult-to-treat asthma (Box 3-15). It means asthma that is uncontrolled despite adherence with maximal optimized high dose ICS-LABA treatment and management of contributory factors, or that worsens when high dose treatment is decreased.[144] At present, therefore, 'severe asthma' is a retrospective label. It is sometimes called 'severe refractory asthma'[144] since it is defined by being relatively refractory to high dose inhaled therapy. However, with the advent of biologic therapies, the word 'refractory' is no longer appropriate.

Asthma is not classified as severe if it markedly improves when contributory factors such as inhaler technique and adherence are addressed.[144]

Adults & adolescents 12+ years

Personalized asthma management
Assess, Adjust, Review
for individual patient needs



CONTROLLER and PREFERRED RELIEVER
(Track 1). Using ICS-formoterol as reliever reduces the risk of exacerbations compared with using a SABA reliever

STEPS 1 – 2	STEP 3	STEP 4	STEP 5
As-needed low dose ICS-formoterol	Low dose maintenance ICS-formoterol	Medium dose maintenance ICS-formoterol	Add-on LAMA Refer for phenotypic assessment ± anti-IgE, anti-IL5/5R, anti-IL4R Consider high dose ICS-formoterol

RELIEVER: As-needed low-dose ICS-formoterol

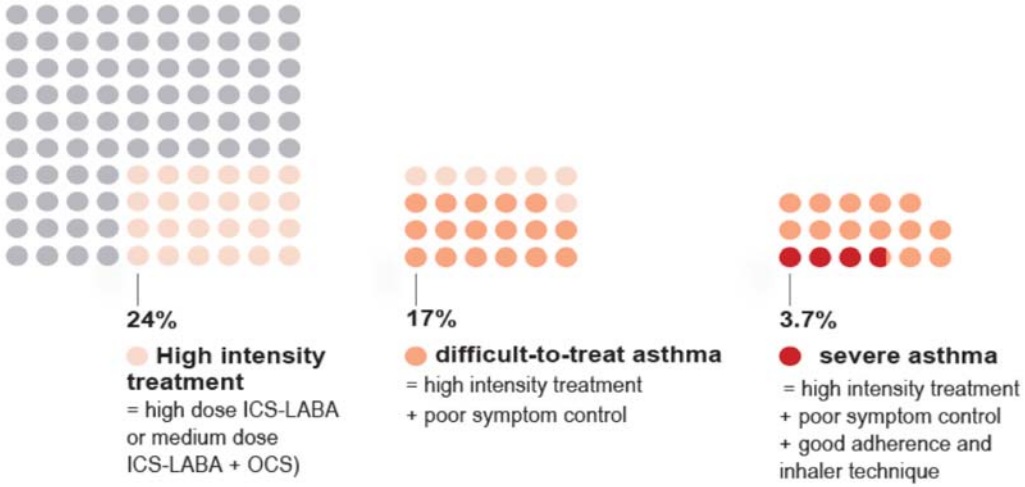
CONTROLLER and ALTERNATIVE RELIEVER
(Track 2). Before considering a regimen with SABA reliever, check if the patient is likely to be adherent with daily controller

STEP 1	STEP 2	STEP 3	STEP 4	STEP 5
Take ICS whenever SABA taken	Low dose maintenance ICS	Low dose maintenance ICS-LABA	Medium/high dose maintenance ICS-LABA	Add-on LAMA Refer for phenotypic assessment ± anti-IgE, anti-IL5/5R, anti-IL4R Consider high dose ICS-LABA

RELIEVER: As-needed short-acting β2-agonist

Other controller options for either track				
	Low dose ICS whenever SABA taken, or daily LTRA, or add HDM SLIT	*Medium dose ICS, or add LTRA, or add HDM SLIT*	*Add LAMA or LTRA or HDM SLIT, or switch to high dose ICS*	*Add azithromycin (adults) or LTRA; add low dose OCS but consider side-effects*

What proportion of adults have severe asthma?



Data from Hekking et al, JACI 2015

ICS: inhaled corticosteroids; LABA: long-acting beta$_2$-agonist; OCS: oral corticosteroids

GP OR SPECIALIST CARE

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DIAGNOSIS: *"Difficult-to-treat asthma"*

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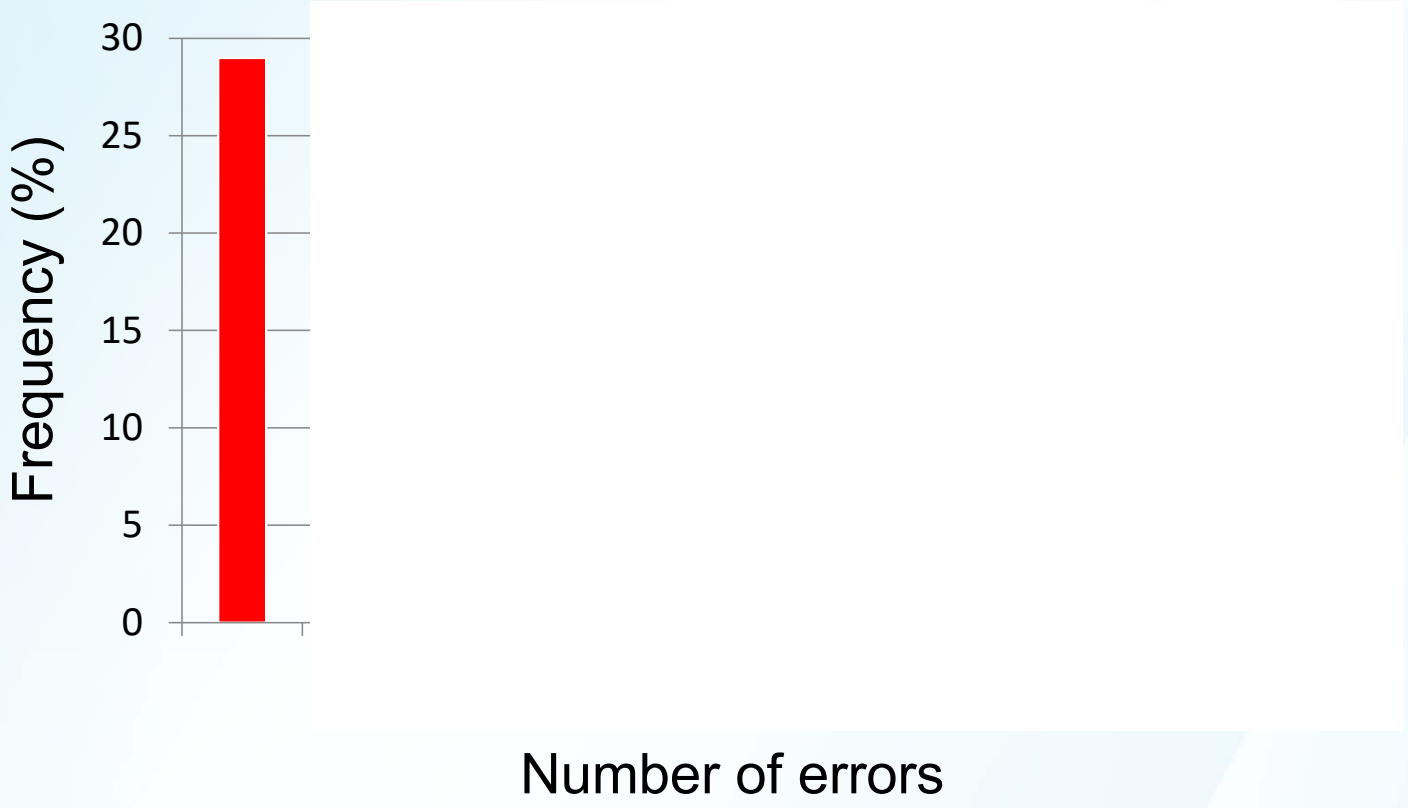
- Medication side effects
- Anxiety, depression and social difficulties

Key

decision, filters

intervention, treatment

Inhalers. Handling errors is associated with increased asthma symptoms



(Giraud et al. ERJ 2002)

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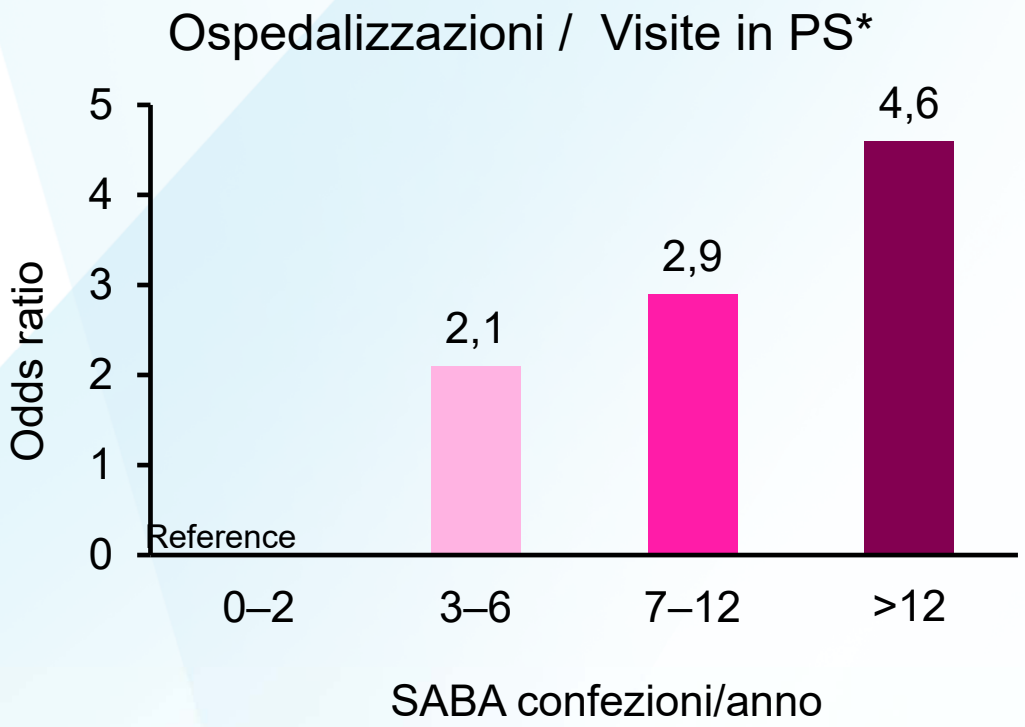
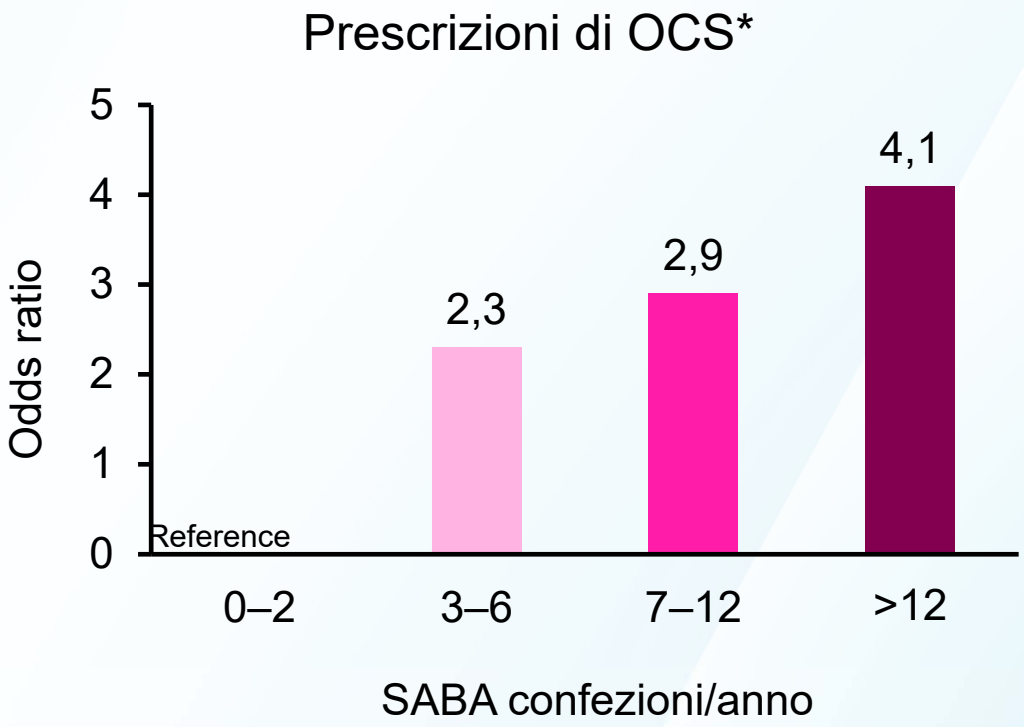
decision, filters

intervention, treatment

SABA and Clinical outcomes





*1. Global Initiative for Asthma. 2019 GINA Report, Global Strategy for Asthma Management and Prevention. http://www.ginasthma.org. Accessed 12 June 2019.; 2. Schatz M, et al. *J Allergy Clin Immunol.* 2006;117:995-1000.

Fatal asthma; is it still an epidemic?

Andrea Vianello[1], Marco Caminati[2*], Mariangiola Crivellaro[3], Rafi El Mazloum[4], Rossella Snenghi[4], Michele Schiappoli[2], Annarita Dama[2], Andrea Rossi[2], Giuliana Festi[2], Maria Rita Marchi[1], Chiara Bovo[5], Giorgio Walter Canonica[6] and Gianenrico Senna[7]

17 pz

Table 3 Clinical features of patients suffering from fatal asthma

Patient's initials	Atopy	Follow-up	Concomitant risk factors	Allergic sensitizations	Asthma treatment	History of Hospital/ER admissions
GP	Present	infrequent	Smoking, party, physical exercise	NR	Intermittent use fo SABA	any
JV	Present	NR	Physical exercise	NR	Intermittent use fo SABA	Any
LM	Present	Infrequent	Heavy smoker	Grass, mites, peach	Intermittent use fo SABA	In childhood 3 years in an high altitude hospital, recently several admission to ER for asthma exacerbations
SM	Present	Infrequent	Smoking	Mites	SABA as needed	Admission to ER for asthma exacerbation; treated with epinephrine and Oxigen supply
RB	Present	infrequent	Outdoor physical exercise, concomitant use of homeopathic remedies	Mites, Parietaria, grass	Intermittent use of SABA and short courses of ICS	Any
ST	Present	regular	Severe asthma in childhood	Mites, grass, alternaria	SABA as needed. Short courses of ICS	Any
AR	Present	infrequent	Dinner	Grass, mites alternaria	Intermittent use of ICS-LABA and SABA as needed	Any
SH	NR	NR	NR	NR	NR	NR
MP	Present	infrequent	NR	Grass, Alternaria	ICS-LABA, short courses of oral steroids	Any
AV	Present	regular	Physical exercise, hours spent outdoor	Grass, Alternaria, Mites	SABA as needed. Intermittent use of ICS	Any
KS	NR	NR	NR	NR	NR	NR
EA	NR	NR	NR	NR	NR	NR
KK	NR	NR	NR	NR°	NR	NR
RT	Present	2	Food allergy	Grass, parietaria, mites	SABA as needed, short courses of ICS	Any
MA	present	2	NR	Mites, Alternaria°	SABA as needed	Any
OZ	present	4	Drug abuse, heavy smoker	Referred mites	SABA as needed	Many admissions to ER
AB	present	Infrequent	NR	Mites	SABA as needed	Any

NR not reported

Mortality in mild/moderate and severe asthma: evidence from RCTs

	Subjects (n)	Treatment group	Mortality
Rabe et al. Lancet 2006	3394	SMART	(N=4) 0%
Papi et al. Lancet Resp Med 2014	866	As needed in moderate asma	0%
Bateman et al. AJRCCM 2004	3421	GOLD ICS/LABA	0%
Papi et al. Lancet Resp Med 2013	1714	MART	(N=3) 0%
Pauwels RA Lancet 2003	7241	Mild	(N=11 1 in placebo related to asthma) 0%
Greening et al. Lancet 1994	429	Mild/Moderate	0%

Study [ref.]	Subjects n	Duration weeks	Asthma severity[#]	Treatment group	Change from baseline in pre-bronchodilator FEV_1 mL	Exacerbations[¶]		Mortality %[+]
						Overall	ED and hospitalisation	
Busse *et al.* [79]	36 010	26	Moderate	ICS	Not reported	11.7%	0.60%	0
				ICS/LABA	Not reported	9.8%	0.66%	0
DREAM [80]	616	52	Severe	Placebo	60	2.40	0.43	0
				Mepolizumab	115–140	1.15–1.46	0.17–0.25	1
MENSA [81]	576	32	Severe	Placebo	86	1.74	0.20	1
				Mepolizumab	183–186	0.83–0.93	0.08–0.14	0
MUSCA [82]	551	24	Severe	Placebo	56	1.21	0.10	0
				Mepolizumab	176	0.51	0.03	0
CALIMA [83]	1306	56	Severe	Placebo	215[§]	0.93[§]	0.04[§]	0
				Benralizumab	330–340[§]	0.60–0.66[§]	0.04–0.05[§]	0
SCIROCCO [84]	1205	48	Severe	Placebo	239[§]	1.33[§]	0.18[§]	0
				Benralizumab	345–398[§]	0.65–0.73[§]	0.06–0.11[§]	0
Castro *et al.* [85]	953	52	Severe	Placebo	120	1.81	0.12	0
				Reslizumab	220	0.84	0.077	0
QUEST [86]	1902	52	Moderate-to-severe	Placebo	180–210[f]	0.87–0.97	0.065	0
				Dupilumab	320–340[f]	0.46–0.52	0.035	0

(from O'Byrne ERJ 2019)

Limitations

- Rare events/underpowered sample size
- Short duration of follow up
- Comorbidites
- RCT biased/placebo effect

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Key

decision, filters

intervention, treatment

Original Article

The Severe Asthma Network in Italy: Findings and Perspectives

Enrico Heffler, MD, PhD[a,b], Francesco Blasi, MD, PhD[c,d], Manuela Latorre, MD[e], Francesco Menzella, MD[f], Pierluigi Paggiaro, MD[e], Girolamo Pelaia, MD[g], Gianenrico Senna, MD[h], and Giorgio Walter Canonica, MD[a,b]; on behalf of the SANI Network[*] *Milan, Pisa, Reggio Emilia, Catanzaro, Verona, Italy*

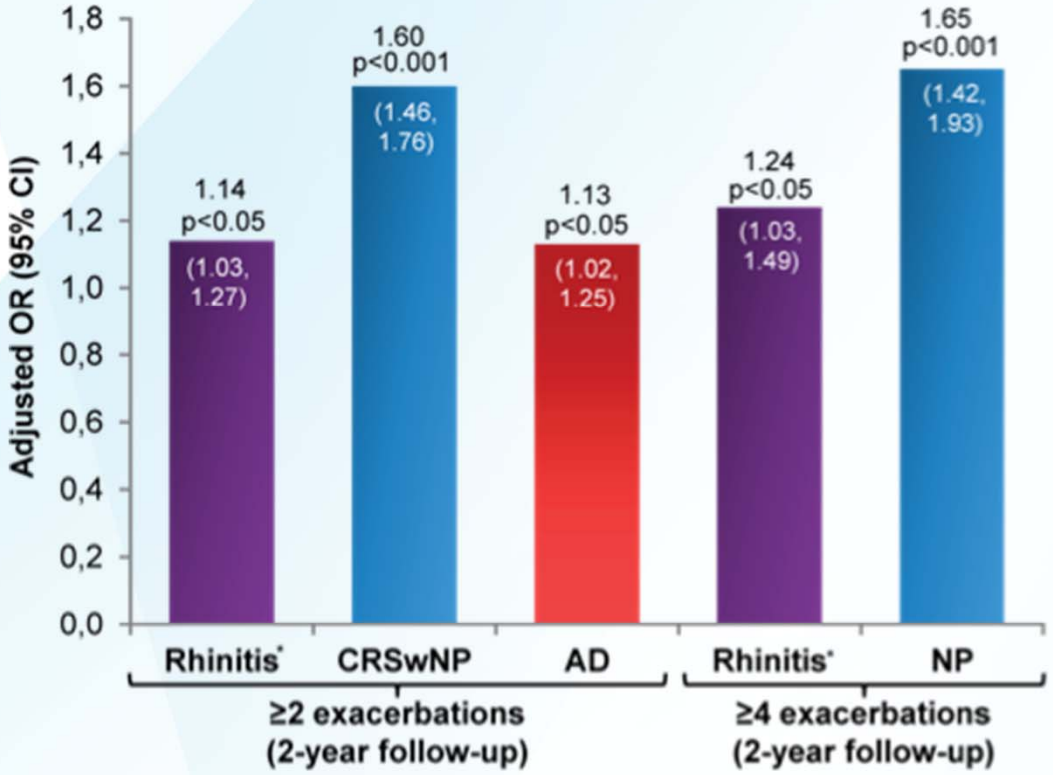
TABLE II. Comorbidities of 437 patients with SA

Comorbidity	
Atopics, n (%)	309 (70.7%)
Sensitized to perennial allergens, n (%)	272 (62.2%)
Any kind of rhinitis, n (%)	298 (68.2%)
Allergic rhinitis, n (%)	195 (44.6)
Food allergy, n (%)	38 (8.7%)
CRSwNP, n (%)	186 (42.6%)
Atopic eczema, n (%)	42 (9.6%)
Bronchiectasis, n (%)	70 (16.0%)

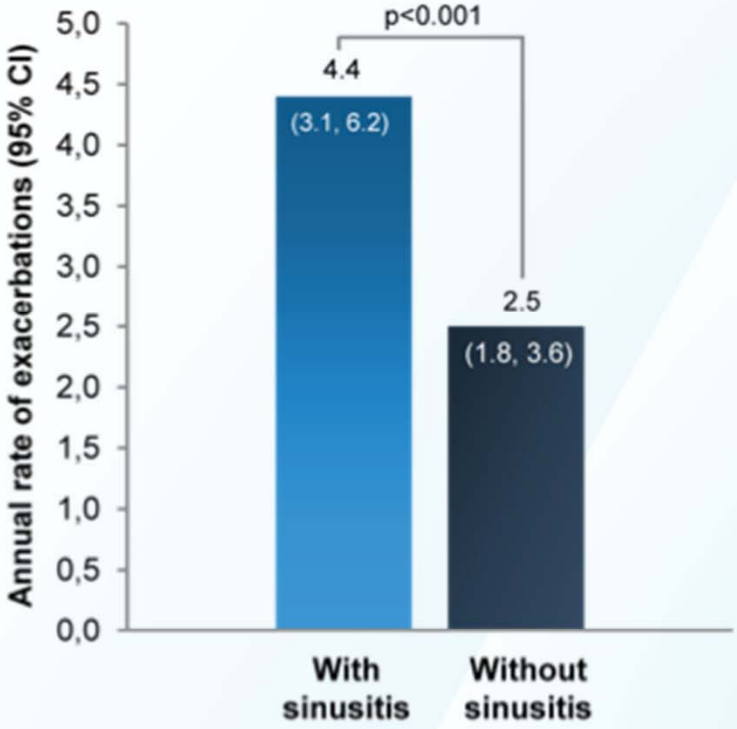
(2018)

Asthma exacerbations increase with the presence of co-morbid Type 2 inflammatory diseases

OPCRD database: Type 2 co-morbidities are independent predictors of asthma exacerbations[12]



SARP-3 database: Sinusitis is associated with increased exacerbation rate in patients with severe asthma (n=709)[13†]



12. Blakey JD, et al. *J Allergy Clin Immunol Pract*. 2017;5:1015–1024.
13. Denlinger LC, et al. *Am J Respir Crit Care Med*. 2017;195:302-313.

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For adolescents and adults with symptoms and/or exacerbations despite GINA Step 4 treatment, or taking maintenance OCS

3 **Optimize management,** including:

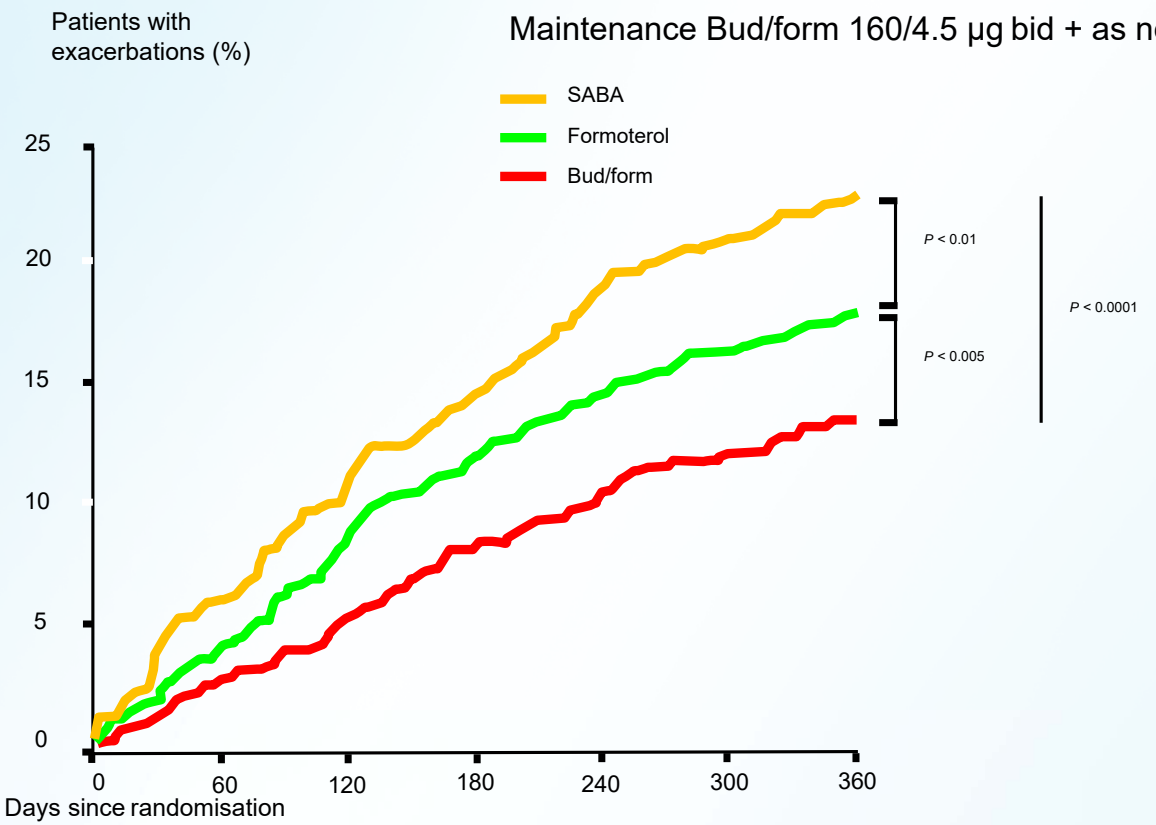
- Asthma education
- Optimize treatment (e.g. check and correct inhaler technique and adherence; switch to ICS-formoterol maintenance and reliever therapy, if available)
- Treat comorbidities and modifiable risk factors
- Consider non-biologic add-on therapy (e.g. LABA, tiotropium, LM/LTRA, if not used)
- Consider non-pharmacological interventions (e.g. smoking cessation, exercise, weight loss, mucus clearance, influenza vaccination)
- Consider trial of high dose ICS, if not used

Key

decision, filters

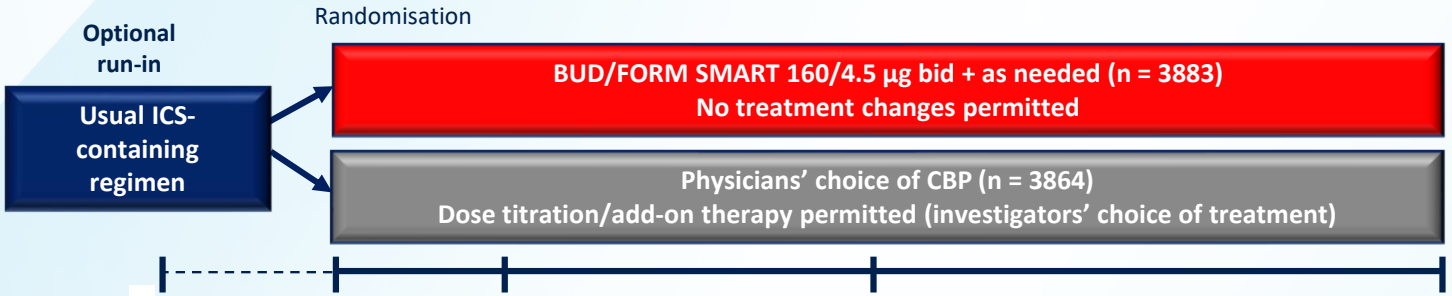
intervention, treatment

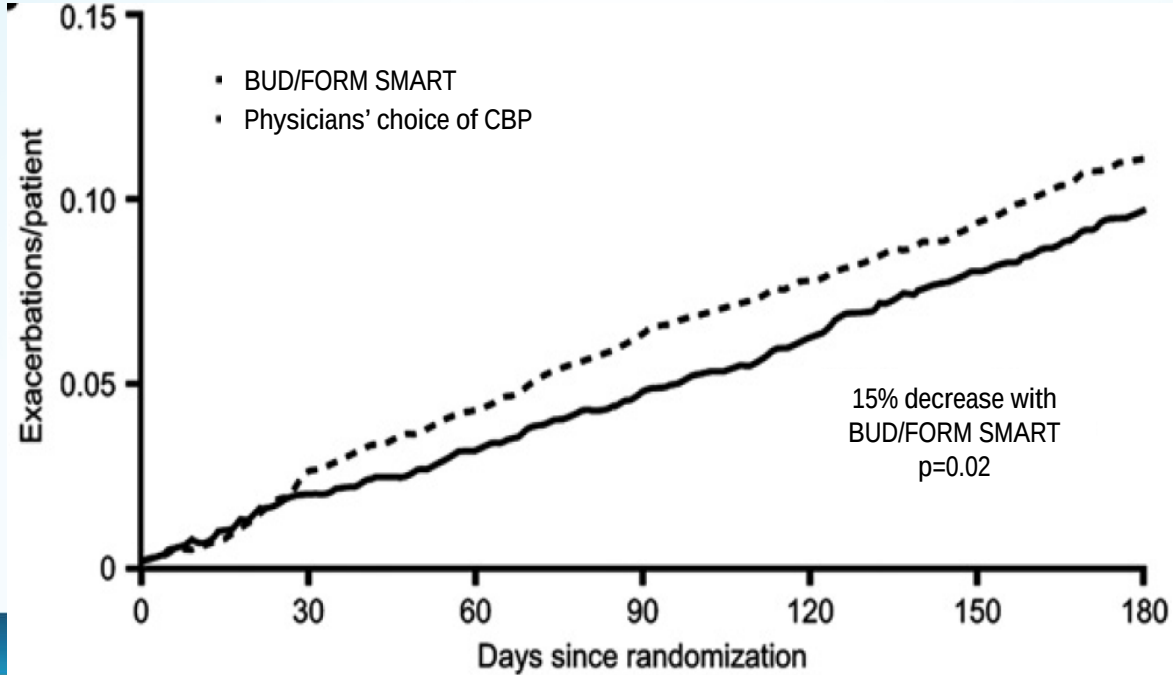
SMART & MART



Rabe KF, et al. Lancet 2006

CHAMPION: SMART vs. physicians free choice of conventional best practice (a pooled analysis)





Demoly P et al. *Respir Med* 2009; 103: 1623–32.

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Add-on long-acting muscarinic antagonists (LAMA)

- Step 5 recommendations for add-on LAMA have been expanded to include combination ICS-LABA-LAMA, if asthma is persistently uncontrolled despite ICS-LABA
  - Add-on tiotropium in separate inhaler (ages ≥6 years)
  - Triple combinations (ages ≥ 18 years): beclometasone-formoterol-glycopyrronium; fluticasone furoate-vilanterol-umeclidinium; mometasone-indacaterol-glycopyrronium
- Lung function:
  - Adding LAMA to medium or high dose ICS-LABA modestly improves lung function (Evidence A) but not symptoms
- Severe exacerbations
  - In some studies, add-on LAMA modestly increased the time to severe exacerbation requiring OCS (Evidence B)
  - For patients with exacerbations, it is important to ensure that the patient receives sufficient ICS, i.e. at least medium dose ICS-LABA, before considering adding a LAMA

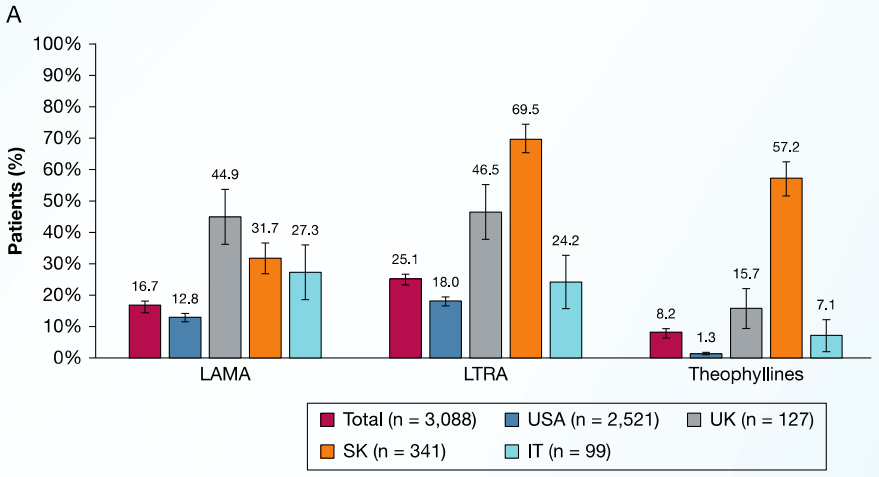
ICS: inhaled corticosteroids; LABA: long-acting beta$_2$-agonist; LAMA: long-acting muscarinic antagonist; OCS: oral corticosteroids

CHEST

Characterization of Severe Asthma Worldwide

Data From the International Severe Asthma Registry

Eileen Wang, MD, MPH; Michael E. Wechsler, MD; Trung N. Tran, MD, PhD; Liam G. Heaney, MD; Rupert C. Jones, MD; Andrew N. Menzies-Gow, MD; John Busby, PhD; David J. Jackson, MD, PhD; Paul E. Pfeffer, MD, PhD; Chin Kook Rhee, MD, PhD; You Sook Cho, MD, PhD; G. Walter Canonica, MD; Enrico Heffler, MD, PhD; Peter G. Gibson, D Med; Mark Hew, PhD; Matthew Peters, MD, PhD; Erin S. Harvey, PhD; Marianna Alacqua, MD, PhD; James Zangrilli, MD; Lakmini Bulathsinhala, MPH; Victoria A. Carter, BSc; Isha Chaudhry, MSc; Neva Eleangovan, BSc; Naeimeh Hosseini, MD; Ruth B. Murray, PhD; and David B. Price, MD



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- Consider trial of high dose ICS, if not used

4 Review **response after ~3-6 months**

Is asthma still uncontrolled? — *yes* → DIAGNOSIS: *"Severe asthma"* → If not done by now, refer to a specialist, if possible.

Is asthma still uncontrolled? — *no* → Consider stepping down treatment, OCS first (if used.)

Does asthma become uncontrolled when treatment is stepped down? — *yes* → Restore previous dose

Does asthma become uncontrolled when treatment is stepped down? — *no* → Continue optimizing management

Key

decision, filters

intervention, treatment

SPECIALIST CARE; SEVERE ASTHMA CLINIC IF AVAILABLE

Assess and treat severe asthma phenotypes

Continue to optimize management as in section **3** (including inhaler technique, adherence, comorbidities)

5 Assess the **severe asthma phenotype** and factors contributing to symptoms, quality of life and exacerbations → **6a** Consider ***non-biologic*** treatments

- ***Assess the severe asthma phenotype during high dose ICS treatment*** *(or lowest possible dose of OCS)*

Type 2 inflammation	
Could patient have Type 2 airway inflammation?	• Blood eosinophils ≥150/µl and/or • FeNO ≥20 ppb and/or • Sputum eosinophils ≥2%, and/or • Asthma is clinically allergen-driven and/or • Need for maintenance OCS
Note: these are not the criteria for add-on biologic therapy (see **6b***)*	(Repeat blood eosinophils and FeNO up to 3x, on lowest possible OCS dose)

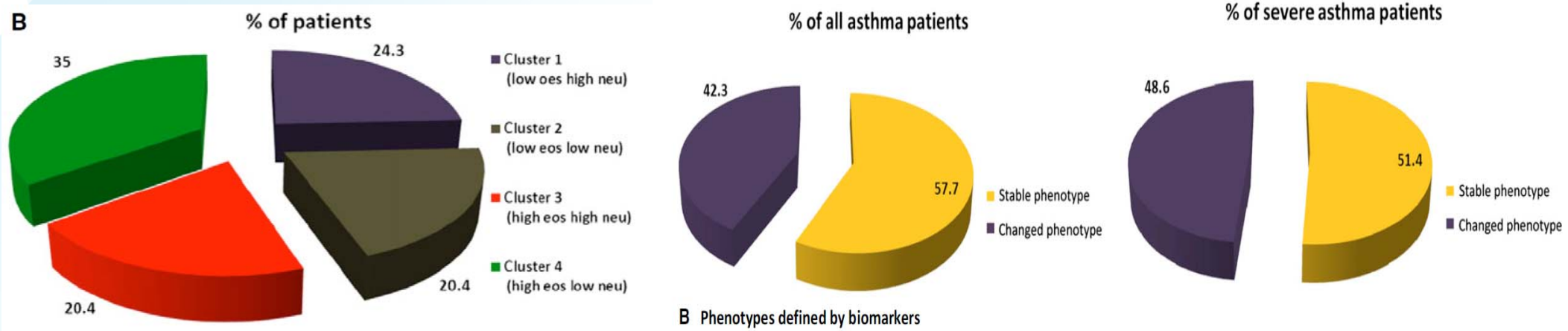
- ***Investigate for comorbidities/differential diagnoses*** *and treat/refer as appropriate*
  - Consider: CBC, CRP, IgG, IgA, IgM, IgE, fungal precipitins; CXR and/or HRCT chest; DLCO
  - Skin prick testing or specific IgE for relevant allergens, if not already done
  - Other directed testing (e.g. ANCA, CT sinuses, BNP, echocardiogram) based on clinical suspicion
- ***Consider need for social/psychological support***
- ***Involve multidisciplinary team care (if available)***
- ***Invite patient to enroll in registry (if available) or clinical trial (if appropriate)***

Allergy
EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY
EAACI
Allergy

ORIGINAL ARTICLE AIRWAY DISEASES

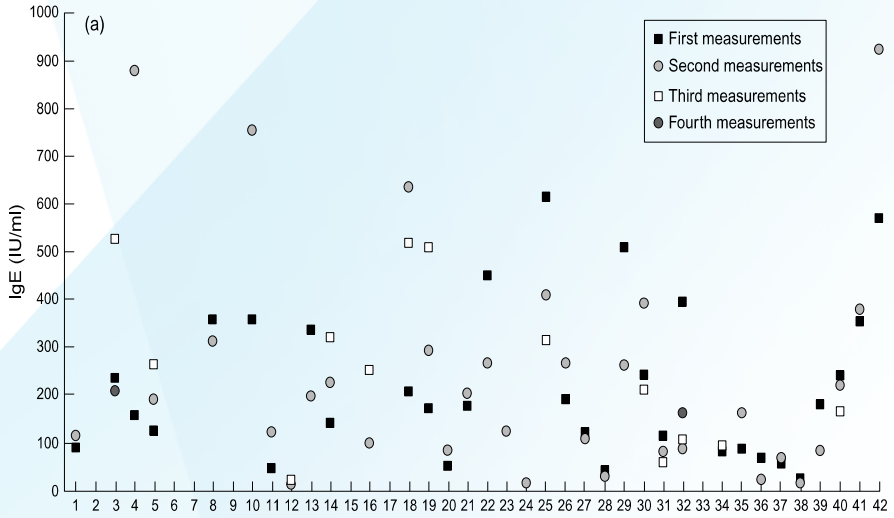
Stability of phenotypes defined by physiological variables and biomarkers in adults with asthma

M. Kupczyk[1,2], B. Dahlén[1], P. J. Sterk[3], E. Nizankowska-Mogilnicka[4], A. Papi[5], E. H. Bel[3], P. Chanez[6], P. H. Howarth[7], S. T. Holgate[7], G. Brusselle[8], N. M. Siafakas[9], M. Gjomarkaj[10] & S.-E. Dahlén[1] on behalf of the BIOAIR investigators*

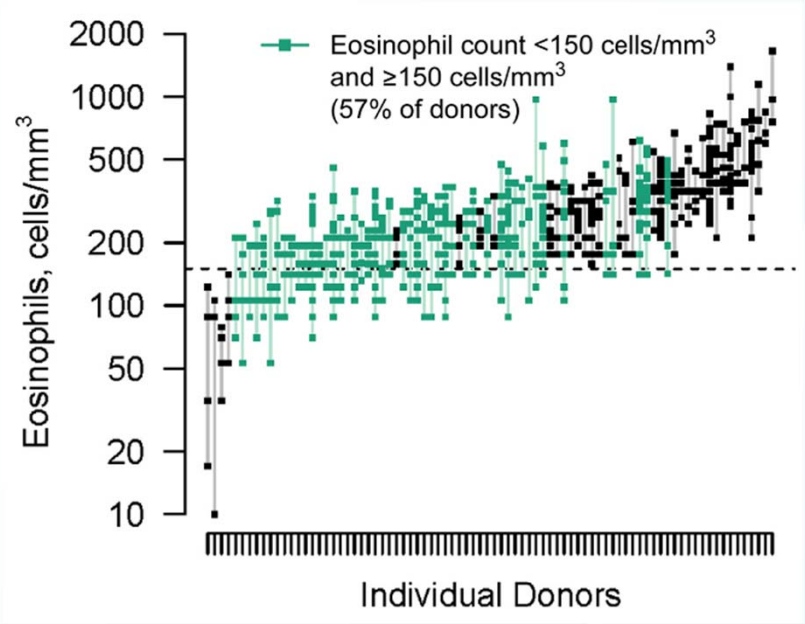


(2014)

Biomarkers & Variability



(Srinivas J Asthma 2012)



Mathur SK Ann Allergy Asthma Immunol 2016

SPECIALIST CARE; SEVERE ASTHMA CLINIC IF AVAILABLE

Assess and treat severe asthma phenotypes

Continue to optimize management as in section **3** (including inhaler technique, adherence, comorbidities)

5 Assess the **severe asthma phenotype** and factors contributing to symptoms, quality of life and exacerbations → **6a** Consider ***non-biologic*** treatments

- ***Assess the severe asthma phenotype during high dose ICS treatment*** *(or lowest possible dose of OCS)*

Type 2 inflammation

Could patient have Type 2 airway inflammation?

- Blood eosinophils ≥150/µl and/or
- FeNO ≥20 ppb and/or
- Sputum eosinophils ≥2%, and/or
- Asthma is clinically allergen-driven and/or
- Need for maintenance OCS

Note: these are not the criteria for add-on biologic therapy (see **6b***)*

(Repeat blood eosinophils and FeNO up to 3x, on lowest possible OCS dose)

yes

- Consider adherence tests
- Consider increasing the ICS dose for 3-6 months
- Consider AERD, ABPA, chronic rhinosinusitis, nasal polyposis, atopic dermatitis (clinical Type 2 phenotypes with specific add-on treatment)

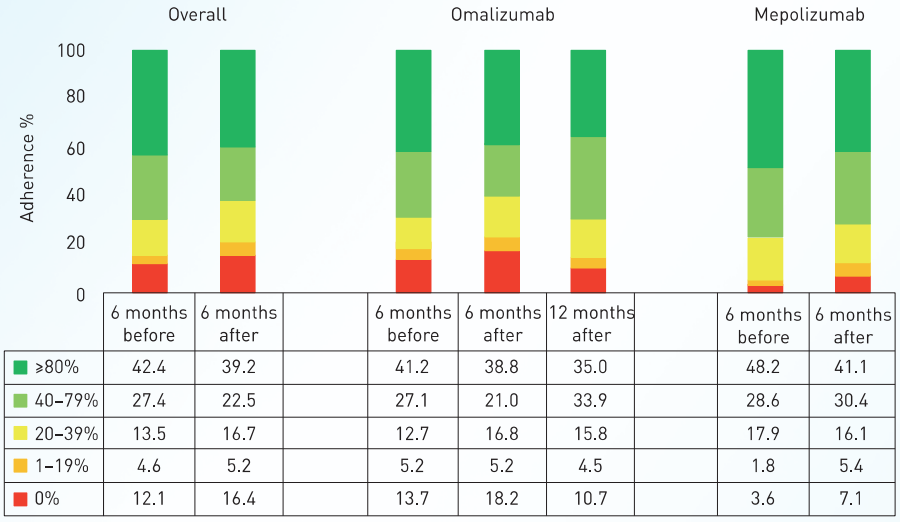
no

- ***Investigate for comorbidities/differential diagnoses*** *and treat/refer as appropriate*
  - Consider: CBC, CRP, IgG, IgA, IgM, IgE, fungal precipitins; CXR and/or HRCT chest; DLCO
  - Skin prick testing or specific IgE for relevant allergens, if not already done
  - Other directed testing (e.g. ANCA, CT sinuses, BNP, echocardiogram) based on clinical suspicion
- ***Consider need for social/psychological support***
- ***Involve multidisciplinary team care (if available)***
- ***Invite patient to enroll in registry (if available) or clinical trial (if appropriate)***

If no evidence of Type 2 inflammation:

- Review the basics: differential diagnosis, inhaler technique, adherence, comorbidities, side-effects
- Avoid exposures (tobacco smoke, allergens, irritants)
- Consider investigations (if available and not done)
  - Sputum induction
  - High resolution chest CT
  - Bronchoscopy for alternative/additional diagnoses
- Consider add-on treatments
  - Trial of tiotropium or macrolide* (if not already tried)
  - Consider add-on low dose OCS, but implement strategies to minimize side-effects
  - Stop ineffective add-on therapies
- Consider bronchial thermoplasty (+ registry)

Low adherence to inhaled corticosteroids/long-acting β2-agonists and biologic treatment in severe asthmatics



Adherence rate class	Overall 6 months before	Overall 6 months after	Omalizumab 6 months before	Omalizumab 6 months after	Omalizumab 12 months after	Mepolizumab 6 months before	Mepolizumab 6 months after
≥80%	42.4	39.2	41.2	38.8	35.0	48.2	41.1
40–79%	27.4	22.5	27.1	21.0	33.9	28.6	30.4
20–39%	13.5	16.7	12.7	16.8	15.8	17.9	16.1
1–19%	4.6	5.2	5.2	5.2	4.5	1.8	5.4
0%	12.1	16.4	13.7	18.2	10.7	3.6	7.1

Cite this article as: Caminati M, Vianello A, Andretta M, *et al.* Low adherence to inhaled corticosteroids/long-acting β_2-agonists and biologic treatment in severe asthmatics. *ERJ Open Res* 2020; 6: 00017-2020 [https://doi.org/10.1183/23120541.00017-2020].

SPECIALIST CARE; SEVERE ASTHMA CLINIC IF AVAILABLE

Assess and treat severe asthma phenotypes

Continue to optimize management as in section **3** (including inhaler technique, adherence, comorbidities)

5 Assess the **severe asthma phenotype** and factors contributing to symptoms, quality of life and exacerbations

- ***Assess the severe asthma phenotype during high dose ICS treatment*** *(or lowest possible dose of OCS)*

Type 2 inflammation

Could patient have Type 2 airway inflammation?	• Blood eosinophils ≥150/µl and/or • FeNO ≥20 ppb and/or • Sputum eosinophils ≥2%, and/or • Asthma is clinically allergen-driven and/or • Need for maintenance OCS (Repeat blood eosinophils and FeNO up to 3x, on lowest possible OCS dose)
Note: these are not the criteria for add-on biologic therapy (see **6b***)*	

- ***Investigate for comorbidities/differential diagnoses*** *and treat/refer as appropriate*
  - Consider: CBC, CRP, IgG, IgA, IgM, IgE, fungal precipitins; CXR and/or HRCT chest; DLCO
  - Skin prick testing or specific IgE for relevant allergens, if not already done
  - Other directed testing (e.g. ANCA, CT sinuses, BNP, echocardiogram) based on clinical suspicion
- ***Consider need for social/psychological support***
- ***Involve multidisciplinary team care (if available)***
- ***Invite patient to enroll in registry (if available) or clinical trial (if appropriate)***

yes

- Consider adherence tests
- Consider increasing the ICS dose for 3-6 months
- Consider AERD, ABPA, chronic rhinosinusitis, nasal polyposis, atopic dermatitis (clinical Type 2 phenotypes with specific add-on treatment)

Is add-on Type 2 biologic therapy available/ affordable?

no

If add-on Type 2 biologic therapy is NOT available/affordable

- Consider higher dose ICS, if not used
- Consider non-biologic add-on therapy (e.g. LABA, tiotropium, LM/LTRA, macrolide*)
- Consider add-on low dose OCS, but implement strategies to minimize side-effects
- Stop ineffective add-on therapies

no

If no evidence of Type 2 inflammation:

- Review the basics: differential diagnosis, inhaler technique, adherence, comorbidities, side-effects
- Avoid exposures (tobacco smoke, allergens, irritants)
- Consider investigations (if available and not done)
  - Sputum induction
  - High resolution chest CT
  - Bronchoscopy for alternative/additional diagnoses
- Consider add-on treatments
  - Trial of tiotropium or macrolide* (if not already tried)
  - Consider add-on low dose OCS, but implement strategies to minimize side-effects
  - Stop ineffective add-on therapies
- Consider bronchial thermoplasty (+ registry)

Not currently eligible for biologics

6a Consider ***non-biologic*** treatments

*Off-label

SPECIALIST CARE; SEVERE ASTHMA CLINIC IF AVAILABLE

Assess and treat severe asthma phenotypes

Continue to optimize management as in section **3** (including inhaler technique, adherence, comorbidities)

5 Assess the **severe asthma phenotype** and factors contributing to symptoms, quality of life and exacerbations

- ***Assess the severe asthma phenotype during high dose ICS treatment*** *(or lowest possible dose of OCS)*

Type 2 inflammation

Could patient have Type 2 airway inflammation?	• Blood eosinophils ≥150/µl and/or • FeNO ≥20 ppb and/or • Sputum eosinophils ≥2%, and/or • Asthma is clinically allergen-driven and/or • Need for maintenance OCS (Repeat blood eosinophils and FeNO up to 3x, on lowest possible OCS dose)
Note: these are not the criteria for add-on biologic therapy (see **6b***)*	

- ***Investigate for comorbidities/differential diagnoses*** *and treat/refer as appropriate*
  - Consider: CBC, CRP, IgG, IgA, IgM, IgE, fungal precipitins; CXR and/or HRCT chest; DLCO
  - Skin prick testing or specific IgE for relevant allergens, if not already done
  - Other directed testing (e.g. ANCA, CT sinuses, BNP, echocardiogram) based on clinical suspicion
- ***Consider need for social/psychological support***
- ***Involve multidisciplinary team care (if available)***
- ***Invite patient to enroll in registry (if available) or clinical trial (if appropriate)***

yes

- Consider adherence tests
- Consider increasing the ICS dose for 3-6 months
- Consider AERD, ABPA, chronic rhinosinusitis, nasal polyposis, atopic dermatitis (clinical Type 2 phenotypes with specific add-on treatment)

6a Consider ***non-biologic*** treatments

Is add-on Type 2 biologic therapy available/ affordable?

yes

no

If add-on Type 2 biologic therapy is NOT available/affordable

- Consider higher dose ICS, if not used
- Consider non-biologic add-on therapy (e.g. LABA, tiotropium, LM/LTRA, macrolide*)
- Consider add-on low dose OCS, but implement strategies to minimize side-effects
- Stop ineffective add-on therapies

no

If no evidence of Type 2 inflammation:

- Review the basics: differential diagnosis, inhaler technique, adherence, comorbidities, side-effects
- Avoid exposures (tobacco smoke, allergens, irritants)
- Consider investigations (if available and not done)
  - Sputum induction
  - High resolution chest CT
  - Bronchoscopy for alternative/additional diagnoses
- Consider add-on treatments
  - Trial of tiotropium or macrolide* (if not already tried)
  - Consider add-on low dose OCS, but implement strategies to minimize side-effects
  - Stop ineffective add-on therapies
- Consider bronchial thermoplasty (+ registry)

Not currently eligible for biologics

**Off-label*

SPECIALIST CARE; SEVERE ASTHMA CLINIC IF AVAILABLE

Assess and treat severe asthma phenotypes *cont'd*

Continue to optimize management as in section **3** (including inhaler technique, adherence, comorbidities)

6b Consider *add-on biologic Type 2* targeted treatments

- Consider add-on Type 2-targeted biologic for patients with exacerbations or poor symptom control on high dose ICS-LABA, who:
  - have eosinophilic or allergic biomarkers, or
  - need maintenance OCS
- Consider **local payer eligibility criteria** and **predictors of response** when choosing between available therapies
- Also consider cost, dosing frequency, route (SC or IV), patient preference

Which biologic is appropriate to start first?

Anti-IgE

*Is the patient eligible for **anti-IgE** for severe allergic asthma?*

- Sensitization on skin prick testing or specific IgE
- Total serum IgE and weight within dosage range
- Exacerbations in last year

What factors may predict good asthma response to anti-IgE?

- Blood eosinophils ≥260/µl ++
- FeNO ≥20 ppb +
- Allergen-driven symptoms +
- Childhood-onset asthma +

no / *no*

Anti-IL5 / Anti-IL5R

*Is the patient eligible for **anti-IL5 / anti-IL5R** for severe eosinophilic asthma?*

- Exacerbations in last year
- Blood eosinophils ≥300/µl

What factors may predict good asthma response to anti-IL5/5R?

- Higher blood eosinophils +++
- More exacerbations in previous year +++
- Adult-onset of asthma ++
- Nasal polyposis ++

no / *no*

Anti-IL4R

*Is the patient eligible for **anti-IL4R***

… for severe eosinophilic/Type 2 asthma?

- Exacerbations in last year
- Blood eosinophils ≥150/µl or FeNO ≥25 ppb

… or because of need for maintenance OCS?

What factors may predict good asthma response to anti-IL4R?

- Higher blood eosinophils +++
- Higher FeNO +++

Anti-IL4R may also be used to treat

- Moderate/severe atopic dermatitis
- Nasal polyposis

Eligible for none?
Return to section **6a**

Check local eligibility criteria for specific biologic therapies as these may vary from those listed

SPECIALIST CARE; SEVERE ASTHMA CLINIC IF AVAILABLE

Assess and treat severe asthma phenotypes *cont'd*

Continue to optimize management as in section **3** (including inhaler technique, adherence, comorbidities)

6b Consider *add-on biologic Type 2* targeted treatments

- Consider add-on Type 2-targeted biologic for patients with exacerbations or poor symptom control on high dose ICS-LABA, who:
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- Consider **local payer eligibility criteria** and **predictors of response** when choosing between available therapies
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Anti-IgE

*Is the patient eligible for **anti-IgE** for severe allergic asthma?*

- Sensitization on skin prick testing or specific IgE
- Total serum IgE and weight within dosage range
- Exacerbations in last year

What factors may predict good asthma response to anti-IgE?

- Blood eosinophils ≥260/µl ++
- FeNO ≥20 ppb +
- Allergen-driven symptoms +
- Childhood-onset asthma +

no / *no*

Anti-IL5 / Anti-IL5R

*Is the patient eligible for **anti-IL5 / anti-IL5R** for severe eosinophilic asthma?*

- Exacerbations in last year
- Blood eosinophils ≥300/µl

What factors may predict good asthma response to anti-IL5/5R?

- Higher blood eosinophils +++
- More exacerbations in previous year +++
- Adult-onset of asthma ++
- Nasal polyposis ++

no / *no*

Anti-IL4R

*Is the patient eligible for **anti-IL4R***

… for severe eosinophilic/Type 2 asthma?

- Exacerbations in last year
- Blood eosinophils ≥150/µl or FeNO ≥25 ppb

… or because of need for maintenance OCS?

What factors may predict good asthma response to anti-IL4R?

- Higher blood eosinophils +++
- Higher FeNO +++

Anti-IL4R may also be used to treat

- Moderate/severe atopic dermatitis
- Nasal polyposis

Eligible for none?
Return to section **6a**

Choose one if eligible; trial for at least 4 months and assess response

Good asthma response?

yes — Good response to T2-targeted therapy

no — Extend trial to 6-12 months

unclear — Extend trial to 6-12 months

Check local eligibility criteria for specific biologic therapies as these may vary from those listed

SPECIALIST CARE; SEVERE ASTHMA CLINIC IF AVAILABLE

Assess and treat severe asthma phenotypes *cont'd*

Continue to optimize management as in section **3** (including inhaler technique, adherence, comorbidities)

6b Consider *add-on biologic Type 2* targeted treatments

- Consider add-on Type 2-targeted biologic for patients with exacerbations or poor symptom control on high dose ICS-LABA, who:
  - have eosinophilic or allergic biomarkers, or
  - need maintenance OCS
- Consider **local payer eligibility criteria** and **predictors of response** when choosing between available therapies
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Which biologic is appropriate to start first?

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- Total serum IgE and weight within dosage range
- Exacerbations in last year

What factors may predict good asthma response to anti-IgE?

- Blood eosinophils ≥260/µl ++
- FeNO ≥20 ppb +
- Allergen-driven symptoms +
- Childhood-onset asthma +

no / *no*

Anti-IL5 / Anti-IL5R

*Is the patient eligible for **anti-IL5 / anti-IL5R** for severe eosinophilic asthma?*

- Exacerbations in last year
- Blood eosinophils ≥300/µl

What factors may predict good asthma response to anti-IL5/5R?

- Higher blood eosinophils +++
- More exacerbations in previous year +++
- Adult-onset of asthma ++
- Nasal polyposis ++

no / *no*

Anti-IL4R

*Is the patient eligible for **anti-IL4R***

… for severe eosinophilic/Type 2 asthma?

- Exacerbations in last year
- Blood eosinophils ≥150/µl or FeNO ≥25 ppb

… or because of need for maintenance OCS?

What factors may predict good asthma response to anti-IL4R?

- Higher blood eosinophils +++
- Higher FeNO +++

Anti-IL4R may also be used to treat

- Moderate/severe atopic dermatitis
- Nasal polyposis

Eligible for none?
Return to section **6a**

Choose one if eligible; trial for at least 4 months and assess response

Good asthma response?

yes — Good response to T2-targeted therapy

unclear — Extend trial to 6-12 months

no

STOP add-on

Consider switching to a different Type 2-targeted therapy, if eligible

no — Little/no response to T2-targeted therapy

Check local eligibility criteria for specific biologic therapies as these may vary from those listed

Add-on biologic therapy for severe Type 2 asthma

- When assessing eligibility, repeat blood eosinophils if low at first assessment
  - One study found that 65% patients on medium or high dose ICS-LABA shifted their eosinophil category during 12 months' follow-up *(Lugogo et al, Ann Allergy Asthma Immunol 2020)*
- Additional indications for these therapies in Europe and/or USA have been listed
  - Omalizumab: chronic idiopathic urticaria, nasal polyposis
  - Mepolizumab: hypereosinophilic syndrome, eosinophilic granulomatosis with polyangiitis (EGPA)
  - Benralizumab: no additional indications at present
  - Dupilumab: chronic rhinosinusitis with nasal polyposis (CRSwNP); atopic dermatitis
- Check local regulatory approvals and eligibility criteria

ICS: inhaled corticosteroids; LABA: long-acting beta$_2$-agonist

Linee guida GINA 2019 sull'asma grave: key points

Definizione asma grave

Aspetti clinici

Ottimizzazione trattamento

Farmaci biologici