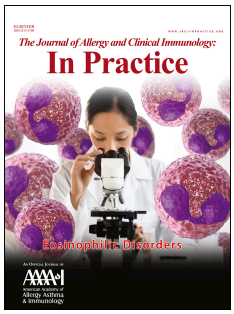

SANI definition of Clinical Remission in Severe Asthma: a Delphi consensus

G.W. Canonica, MD, F. Blasi, MD, PhD, G.E. Carpagnano, MD, PhD, G. Guida, MD, E. Heffler, MD, PhD, P. Paggiaro, MD, on behalf of SANI

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SANI definition of Clinical Remission in Severe Asthma: a Delphi consensus

Canonica GW MD[1,2], Blasi F MD, PhD[3,4], Carpagnano GE MD, PhD[5,6], Guida G, MD[7,8], Heffler E MD, PhD[1,2], Paggiaro P MD[9] on behalf of SANI: Allegrini C MD[10], Antonelli A MD[11], Aruanno A MD, PhD[12], Bacci E MD[13], Bagnasco D MD, PhD[14], Beghè B MD, PhD[15], Bonavia M MD[16], Bonini M MD, PhD[17], Brussino L MD[18], Caiaffa MF MD, PhD[19], Calabrese C MD[20], Camiciottoli G MD[10], Caminati M MD[21], Caruso C MD, PhD[12], Cavallini M MD[22], Chiecobianchi F MD[23], Conte ME MD[24], Corsico AG MD, PhD[25], Cosmi L MD[26], Costantino MT MD[27], Costanzo G MD[28], Crivellaro M MD[23], D'Alò S MD[29], D'Amato M MD[30], Detoraki A MD,PhD[31], Di Proietto MC MD[32], Facciolongo NC MD[33], Ferri S MD[1], Fierro V MD[34], Foschino MP MD[35], Latorre M MD[36], Lombardi C MD[37], Macchia L MD, PhD[38], Milanese M MD, PhD[39], Montagni M MD[40], Parazzini EM MD[41], Parente R MD, PhD[42], Passalacqua G MD[43], Patella V MD[44], Pelaia G MD[45], Pini L MD[46], Puggioni F MD[1], Ricciardi L MD[47], Ridolo E MD, PhD[48], Rolo J MD[32], Scichilone N MD[49], Scioscia G MD, PhD[19], Senna G MD[21], Solidoro P MD[50], Varricchi G MD, PhD[51], Vianello A MD[23], Yacoub MR MD[52], Yang B MD[53].

Affiliations

1. Personalized Medicine, Asthma and Allergy - IRCCS Humanitas Research Hospital -, via Manzoni 56, 20089 Rozzano (Mi) – Italy
2. Department of Biomedical Sciences, Humanitas University, Department of Biomedical Sciences, Via Rita Levi Montalcini 4, 20090 Pieve Emanuele – Milan, Italy
3. Respiratory Unit and Cystic Fibrosis Center, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico di Milano, Milan, Italy
4. Department of Pathophysiology and Transplantation, University of Milan, Italy
5. Department of Translational Biomedicine and Neuroscience “DiBraiN”, University of Bari Aldo Moro
6. Section of Respiratory Diseases, Policlinico Hospital of Bari, Italy
7. Department of Clinical and Biological Sciences, University of Turin, Italy

8. Severe Asthma and Rare Lung Disease Unit, San Luigi Gonzaga University Hospital - Orbassano (TO) (Italy)
9. Department of Surgery, Medicine, Molecular Biology and Critical Care, University of Pisa
10. UNIT ASMA GRAVE - Ambulatorio Asma Grave Pneumologia e Fisiopatologia ToracoPolmonare, Azienda Ospedaliera Universitaria Careggi (FI)
11. Responsabile SS Allergologia e Fisiopatologia Respiratoria, Ospedale S. Croce e Carle, Cuneo
12. Allergologia dell'Istituto di Clinica Medica del Policlinico Gemelli - Università Cattolica di Roma
13. Fisiopatologia Respiratoria e Riabilitazione, P.O. Cisanello, Azienda Ospedaliero Universitaria Pisana, Pisa
14. U.O. Clinica Malattie Respiratorie e Allergologia, IRCCS- AOU San Martino
15. Section of Respiratory Diseases, Department of Medical and Surgical Sciences, Maternal - Infant and Adult, University of Modena and Reggio Emilia, Italy
16. S.S. Pneumologia Riabilitativa - S.C. Pneumologia, Dipartimento Specialità Mediche - ASL3 Genovese, Ospedale la Colletta, Arenzano (GE)
17. U.O.C. Pneumologia, Fondazione Policlinico Universitario A. Gemelli, IRCCS, Roma
18. S.S.D.D.U. Immunologia Clinica ed Allergologia, A.O. Mauriziano, Torino
19. Malattie Apparato Respiratorio, Dipartimenti delle funzioni Mediche e Sanitarie, Azienda Ospedaliero Universitaria - Ospedali Riuniti, Foggia
20. UO Clinica Pneumologica SUN, Dipartimento Pneumologia ed Oncologia, Azienda Ospedaliera Specialistica dei Colli, Napoli
21. USD Allergologia, Azienda Ospedaliera Universitaria Integrata Verona
22. Broncopneumologia, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milano
23. UOC Fisiopaologia Respiratoria - Azienda Ospedaliera di Padova
24. Struttura complessa di Pneumologia - Azienda per l'assistenza sanitaria n.5 “Friuli Occidentale, Pordenone
25. U.O.C. Pneumologia, Fondazione IRCCS Policlinico San Matteo, Pavia
26. SOD Immunologia e Terapie Cellulari, AOUC Azienda Ospedaliero Universitaria Careggi, Firenze
27. Centro Day Hospital, Allergologia e Immunologia Clinica, Dipartimento Medico, Ospedale Carlo Poma, ASST-Azienda Socio Sanitaria Territoriale di Mantova

28. Allergologia e Immunologia Clinica - Policlinico Universitario di Cagliari
29. U.O. Allergologia, P.O. Civitanova Marche, Area Vasta 3, Azienda Sanitaria Unica Regionale (ASUR) Marche, Civitanova Marche (MC)
30. U.O.C. Pneumofisiologia Università Federico II, Azienda Ospedaliera "Dei Colli", Napoli
31. UODS Allergologia ed Immunodeficienze, Azienda Ospedaliera Universitaria Federico II, Napoli
32. S.C. Pneumologia, ASST Grande Ospedale Metropolitano Niguarda, Milano
33. UOC di Pneumologia, Arcispedale S. Maria Nuova Azienda USL di Reggio Emilia
34. UOC Allergologia, Ospedale Pediatrico Bambino Gesù, Roma
35. Malattie Apparato Respiratorio, Azienda Ospedaliera Universitaria, Foggia
36. UO Pneumologia - Ospedale Nuovo Apuano di Massa
37. Unità di Allergologia, Immunologia e Malattie Respiratorie, Fondazione Poliambulanza Istituto Ospedaliero, Brescia
38. Unità Dipartimentale di Allergologia ed Immunologia Clinica, AO Universitaria Policlinico di Bari
39. S.C. Pneumologia - Dipartimento Specialità Mediche, Ospedale S. Corona, Pietra Ligure - ASL2 Savonese, Pietra Ligure (SV)
40. Unità Dipartimentale di Allergologia, Ospedale Guglielmo da Saliceto AUSL Piacenza
41. U.O. di Pneumologia, ASST Santi Paolo e Carlo, Milano
42. U.O. di Diagnosi e terapia delle malattie allergiche e del sistema immunitario, A.O.U. San Giovanni di Dio e Ruggi d'Aragona, Salerno
43. Clinica di Malattie Respiratorie e Allergologia, Dip. Medicina Interna, Univ. degli Studi di Genova, IRCCS- AOU San Martino
44. U.O. di Allergologia e Immunologia Clinica, P.O. Santa Maria della Speranza, Battipaglia (SA)
45. U.O. Malattie dell'Apparato Respiratorio, A.O.U. Mater Domini, Catanzaro
46. Ambulatorio Asma Grave, UOC Medicina Generale 2, Spedali civili di Brescia
47. Allergologia e Immunologia Clinica, AOU Policlinico G. Martino - Università di Messina
48. Ambulatorio di Allergologia ed Immunologia Clinica, UO Lungodegenza, Azienda Ospedaliero- Universitaria di Parma
49. U.O.C. Pneumologia, Azienda Ospedaliera Universitaria Policlinico P. Giaccone di Palermo

50. Azienda Ospedaliero Universitaria Città della Salute e della Scienza di Torino
51. Dipartimento di Scienze Mediche Translazionali - Centro per la Ricerca di Base ed Immunologia Clinica, Università Federico II, Napoli
52. Unità di Immunologia, Reumatologia, Allergologia e Malattie Rare, IRCCS Ospedale San Raffaele, Milano
53. Centro Day Hospital, Allergologia e Immunologia Clinica, Dipartimento Medico, Ospedale Carlo Poma, ASST-Azienda Socio Sanitaria Territoriale di Mantova

Corresponding author:
Giorgio Walter Canonica
Personalized Medicine, Asthma and Allergy - IRCCS Humanitas Research Hospital -, via Manzoni 56, 20089 Rozzano (Mi) – Italy
Department of Biomedical Sciences, Humanitas University, Department of Biomedical Sciences, Via Rita Levi Montalcini 4, 20090 Pieve Emanuele – Milan, Italy
giorgio_walter.canonica@hunimed.eu

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Conflict of interests:

GWC reports having received research grants as well as being lecturer or having received advisory board fees from: A.Menarini , Allergy Therapeutics, AstraZeneca , Chiesi Farmaceutici, Faes, Firma, Guidotti-Malesci, Glaxo Smith Kline, Hal Allergy, Innovacaremd, Novartis, OmPharma, RedMaple, Sanofi-Aventis, Sanofi-Genzyme, Stallergenes-Greer, Uriach Pharma, ThermoFisher, Valeas.
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GEC declared no conflicts of interests.
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Abstract

Severe Asthma affects about 10% of the asthmatic population, and it is characterized by a low lung function and a higher count of blood leucocytes, mainly eosinophils.

To date, various definitions are used in clinical practice and in the literature to identify asthma remission: clinical remission, inflammatory remission, and complete remission. The aim of this work is to highlight a *consensus for asthma remission* using a Delphi method.

In the context of SANI (Severe Asthma Network Italy), accounting for 57 Severe Asthma Centers and more then 2200 patients, a Board of six expert drafted a list of candidate statements in a questionnaire, which has been revised to minimize redundancies and ensure clear and consistent wording for the first round (R1) of the analysis.

32 statements have been included in the R1 questionnaire, and then submitted to a panel of 80 experts, which used a 5-points Likert scale to measure their agreement to each statement. Then, an Interim Analysis of R1 data have been performed, items were discussed and considered to produce a consistent questionnaire for the round 2 (R2) of the analysis. After this, the Board set the R2 questionnaire, which included only the important key topics. Panelists have been asked to vote the statements in the R2 questionnaire afterwards. During R2, the criteria of **complete clinical remission** (the absence of need for OCS, symptoms, exacerbations/attacks, and a pulmonary function stability) and those of **partial clinical remission** (the absence of need for OCS, and 2 out of 3 criteria: the absence of symptoms, exacerbations/attacks, and a pulmonary stability) were confirmed.

This SANI Delphi Analysis defined a valuable, independent and easy to use tool to test the efficacy of different treatments in patients with severe asthma enrolled into the SANI registry.

Keywords: asthma, asthma remission, allergy, inflammation, Delphi analysis.

Introduction

Asthma is a long-term respiratory inflammatory disease, characterized by a chronic lung inflammation and affecting up to 18% of people worldwide)[1,2].

According to the European Respiratory Society/American Thoracic Society, in severe asthma a high-dosage inhaled corticosteroid (ICS) plus a second controller (such as a β2-agonists -LABA-) required to maintain the disease controlled. Most of the time, disease remains uncontrolled, leading different asthma exacerbations, hospitalizations, and low quality of life [3,4]. Severe asthma can be characterized by various and unspecific symptoms (such as cough, wheeze, and breathlessness), numerous comorbidities and increased bronchial hyper-responsiveness with frequent exacerbations [5,6].

To date, epidemiological data describing severe asthma are limited. According to the European Network For Understanding Mechanisms Of Severe Asthma[7], about 10% of the asthmatic population develop severe asthma[7]. Patients with severe asthma are usually older and they received a late diagnosis of asthma. Also, severe asthma is characterized by a low lung function and a higher count of blood leucocytes, mainly eosinophils and neutrophils. Moreover, patients with severe asthma experience a high impact on their quality of life[8].

A chronic inflammatory response, characterized by leucocytes recruitment and cytokine production, can be related to the development of severe asthma. Indeed, this immune dysregulation in severe asthma is high heterogeneous [9].

Differential diagnosis should be mandatory when severe asthma needs to be assessed, and a multidisciplinary approach (which includes patient communication, education and follow up) should be applied. Diagnosis begins with the assessment of medication adherence and inhaler technique. Also, other comorbidities (such as rhinosinusitis, nasal polyps, gastrointestinal reflux obstructive sleep dyspnea, obesity, or some psychiatric conditions) need to be evaluated [10]. Moreover, asthma management should be continuously personalized and adjusted to prevent exacerbations [11]. In this context, high dose of ICS and long-acting β-agonist (LABA) and, often, a maintenance dose of oral corticosteroids are currently used for the treatment of severe asthma [12]. Asthma is a variable disease, which may deteriorate or improve over time, depending on patient growth, the inducer/trigger avoidance, comorbidities and pharmacologic treatment, potentially leading in some cases to a spontaneous remission (on treatment) of the disease.

Indeed, various definitions are currently used in clinical practice: clinical remission, inflammatory remission, and complete remission. While in the previous years remission was used to describe the lack of symptoms without any regular treatment, for severe asthma this outcome was considered too optimistic, and the the concept of "on-treatment remission" was used in the current study.

A recent independent definition of Clinical Disease Remission in asthma, linked to the concept of Disease Modifyng Anti Asthmatic Drugs was proposed according to four main criteria: sustained absence of asthma symptoms, sustained absence of asthma exacerbations, stable lung function and no need for systemic corticosteroids for the treatment of asthma for at least 12 months[13]. This has been the basis to develop our Delphi consensus.

Inflammatory remission is characterized by very low concentration or absence of any inflammatory marker, such as eosinophils, allergen specific IgE, periostin, FENO (Fractional Exhaled Nitric Oxide), and eventually airway obstruction.

Lastly, *complete remission* is defined as complete absence of symptoms without any medication. In this case, the lung function is completely restored and no bronchial hyperresponsiveness can be detected [14].

The aim of this work is to highlight a *consensus for asthma remission* using a Delphi method with the contribution of a panel of experts belonging to SANI (Severe Asthma Network Italy), a network of 57 Centers of Excellence (Heffler JACIP 2018) in treating currently more than 2200 Severe Asthma patients in Italy.

Methods

This study was conducted using a Delphi method to reach expert consensus on definition of asthma remission as previously described [15,16].

Delphi methods is defined as a structured technique aimed to guide a group of experts dealing with complex problems[17]. To date, Delphi method is applied to a wide range of application and topics. Specifically, in healthcare, this method is used to gain consensus in topics where accurate tested data are not available, where guidelines are insufficient or where knowledge is uncertain or incomplete[18,19], providing qualitative and quantitative elaboration data[20]. To do this, Delphi method must include three crucial stages: panel selection, development of the surveys and iterative processes to gain consensus[19].

The goal of the multiple iterations in the Delphi method is to gradually reduce responses and gain consensus[19], through three pivotal points: anonymity, controlled feedback, and statistical group response[21].

Briefly, a Board of six expert (four pneumologists and 2 allergists) was appointed as a scientific committee. During the first meeting, experts discussed and clearly defined the scope of the survey. Afterwards, according to the state-of-art of the literature and their clinical expertise, they drafted a list of candidate statements in a questionnaire, which has been revised to minimize redundancies and ensure clear and consistent wording for the first round (R1) of the analysis.

Thirty-two statements, divided in four main categories (1. General questions about remission; 2. Clinical remission criteria; 3. Complete or partial clinical remission and its duration; 4. Cut-off values of different scores regarding disease control, lung function and inflammation) have been included in the R1 questionnaire, and then submitted to a panel of 80 experts (both pneumologists and allergists), selected from the SEVERE ASTHMA NETWORK ITALY -SANI network-.

Panelists used a 5-points Likert scale to measure their agreement to each statement (1: strongly disagree; 2: disagree; 3: neither agree nor disagree; 4: agree; 5: strongly agree). The cut-off value for a high consensus has been defined from grade 4 and needed to be reached for at least 2/3 of the experts (66.6%). Then, the Board of experts proceeded with an Interim Analysis of R1 data and selected bibliographic references. During this phase, panelists had the opportunity to write comments for each item, which were also discussed and considered to produce a consistent questionnaire for the round 2 (R2) of the analysis. After this, the Board set the R2 questionnaire,

which included only the important key topics. Panelists have been asked to vote the statements in the R2 questionnaire afterwards. Lastly, the final Data Analysis and generation of the final Delphi report was performed, with the support of a methodology expert.

Results

The Board elaborated a total of 32 statements. A group of 80 experts were included in the Expert panel and invited to anonymously vote the statements. During the R1, 53 experts voted the statements (66.25%) (Table 1). Consensus has been reached for 13 statements out of 23. In fact, 9-out-of 32 items included in R1 were exploratory items, in which panelists were not asked to express a consensus but a choice regarding multiple options (the mode was always single-choice question except in the case of item 4, in which multiple options could be selected). These were called “exploratory items” because they were useful for better drafting R2 items. The exploratory items of R1 were as follows: 2, 3, 4, 18, 22, 24, 28, 29, 30.

During R1, a wide consensus was obtained among the statements related to the composite nature of clinical remission, absence of symptoms, absence of exacerbations/acute attacks, stability of lung function, and no need for OCS. Similarly, consensus was obtained in the statement regarding whether complete remission is achieved when there is no need for OCS and all the following criteria are present: absence of asthmatic symptoms, absence of exacerbations/attacks, and stability of lung function. Moreover, consensus was also obtained in the statement addressing the partial clinical remission, which is defined when there is no need for OCS and two of the three criteria are met: absence of symptoms, absence of exacerbations/attacks, and stability of lung function (table 3). As for duration, most experts agreed that remission is defined as the absence of exacerbations for at least one year, and that persistent remission is defined as lasting three years (52.8% consensus) and one year (37% consensus). The absence of corticosteroids has been reaffirmed. On the matter of patients with severe asthma on biologic therapy, consensus was not reached on either discontinuation of biologic treatment or its maintenance. Similarly, there has been no consensus on whether asthma can be completely controlled with biological treatments.

During the R2, the number of statements was reduced to 24. For this round, responses were provided by 43 panel members (53.75%). Consensus has been reached for 18 statements out of 24 (Table 1). During R2, the composite definition of remission, the criteria of **complete clinical remission** (the absence of need for OCS, the absence of symptoms, the absence of exacerbations/attacks, and pulmonary stability) and those of **partial clinical remission** (the absence of need for OCS, and 2 out of 3 criteria: the absence of symptoms, the absence of exacerbations/attacks, and pulmonary stability) were confirmed.

Regarding the duration required to define a patient in remission, in this round, the item reporting a duration of 1 year obtains greater consensus (in contrast to R1, in which the greatest consensus was obtained for a duration of 3 years).

Regarding the *role of therapy*, the chance to reduce inhaled therapy while on biologic therapy or maintain it, were excluded as advisable criteria for remission since R1.

The last section of the questionnaire focused on quantitative parameters about clinical and functional response and inflammatory *parameters*. During R1, experts reached a broad consensus to say that achieving an ACT score between 20-25 is indicative of clinical remission (73.8%), as is an ACQ score of less than 0.5 (56.6%). Although, in this case, a value of 1.5 also achieved a fair amount of consensus (43.4%).

Regarding *improvement in lung function* as a criterion for remission, there is no consensus on the value to be used as a reference (neither 100 mL, 200 mL, or function greater than or equal to 80 percent over the uncontrolled phase).

Regarding *markers of inflammation* involved in the inflammatory remission, and their cut offs consensus has been achieved with an eosinophil value of less than 300 cells/L and a FENO level of less than 25 ppb.

Regarding the *quality of life*, full consensus has not been reached about a SAQ (severe asthma questionnaire) cut-off value greater than 96 (58.5%), nor about the need for clinician-patient agreement in jointly defining remission, in the absence of validated tools (64.2%).

During R2, the consensus regarding having an ACT score between 20/25 and 25/25 was strengthened, and an ACQ less than 1.5 was reiterated as being enough to indicate clinical remission, and statements regarding improvement in lung function were removed, as they had not reached consensus.

Although a cut off for eosinophils less than 300 cells/L has been confirmed as a criterion to define inflammatory remission, this statement did not reach consensus. Similarly, although a FENO value lower than 25ppm is defined as a good marker when defining a reduction in inflammation, there was no consensus when considering it a criterion for inflammatory remission. Moreover, the need for a *clinician-patient agreement* about remission, in the absence of validated tools, has achieved wide agreement.

In table 2 the definition of clinical remission according to the main results obtained from the Delphi Analysis has been shown. The first four criteria (absence of asthma symptoms, absence of asthma

exacerbations/attacks, stability of lung function and no further need of OCS treatment) reached the consensus and have been used as criteria to define the remission (partial or complete). The last three criteria included the time range and the ACT and ACQ scores which need to be considered for clinical remission: these parameters did not reach the consensus to be used in the priority definition of remission (partial or complete).

Discussion

Firstly mentioned in 1951, Barach asthma remission is, today, a very important concept[22]. For this reason, it is crucial to define disease remission to identify the best strategies for modifying therapy. Aim of this work was to obtain a definition of severe asthma remission shared by all clinical stakeholders, especially in consideration of the different biological treatments currently available. A Delphi methodology has been applied to achieve the aim of the work.

In 2020**,** Menzies-Gow classified the concept of remission into Clinical Remission and Complete remission[23]. To date, remission is classified into Complete Clinical Remission and Partial Clinical Remission, also considering inflammatory remission or biological remission.

Clinical disease remission in asthma is currently defined according to three main criteria: absence of exacerbations, no oral steroid treatment and improvement of lung function for at least 12 months[23]. Lommatzsch et al, more recently reported Clinical disease remission in asthma as defined according to four main criteria: sustained absence of asthma symptoms, sustained absence of asthma exacerbations, stable lung function, no need for systemic corticosteroids for the treatment of asthma, and it was assumed as the basis of our Delphi procedure.[13]

During the first round of our analysis, clinical remission was chosen as the appropriate outcome to verify the effectiveness of therapy. However, inflammatory remission, as indicated by 37% of experts, is also an important parameter to evaluate. During the R2, the definition of remission as a composite set of several criteria has been confirmed. Regarding the debate on whether clinical remission should be considered an outcome of severe asthma, the consensus obtained in R1 was confirmed.

According to Carpaij and colleagues, asthma remission is defined by various criteria, such as the absence of symptoms, its period, the absence of treatment, the absence of lung function impairment and bronchial hyperresponsiveness[24]. On this matter, the criteria suggested by Delphi should be applied to patients with severe asthma on treatment with biologics drugs. Regarding the criteria defining a remission, during R1 the experts stated that the absence of systemic corticosteroids, the absence of symptoms, and the absence of exacerbations should be the criteria to define a clinical remission in severe asthma. As for the lung function, a consensus has been reached regarding both the stability of lung function and its improvement over time.

The statements about the possibility to reduce ICS treatment and normalization of airway hyperresponsiveness did not reach consensus. There was consensus on normalizing quality of life,

achieving a clinically relevant reduction in bronchial inflammation, and on the requirement that the physician and patient must agree that it is remission, instead.

During R2, two items which did not reach consensus were removed, namely those concerning the possibility to reduce current inhaled treatments and the normalization of pulmonary hyperreactivity. In contrast, the statement on improvement of lung function was removed due to lack of consensus due to the lack of agreement about the different criteria to be used for defining a significant improvement in FEV1. The items which had gained consensus during R1, namely the absence of OCS use, the absence of symptoms, and the absence of exacerbations/attacks, were confirmed, as well as the one about the stability of lung function. Finally, the importance to normalize quality of life, to highlight a clinically relevant reduction on lung function, and the agreement about the remission between patient and clinician have been proposed. Nevertheless, they didn't reach the priority level to be included in the criteria of remission.

In 2022, Ribas et al. highlighted the multicomponent nature of clinical remission in severe asthma[25]. In agreement with that, in the current study, during R1, a wide consensus was obtained among the statements related to the composite nature of clinical remission, absence of symptoms, absence of exacerbations and acute attacks, stability of lung function, and no need for OCS. Similarly, consensus was obtained in the statement regarding whether complete remission is achieved when there is no need for OCS and all the following criteria are present: absence of asthmatic symptoms, absence of exacerbations/attacks, and stability of lung function. Moreover, consensus was also obtained in the statement addressing the partial clinical remission, which is defined when there is no need for OCS and two of the three criteria are met: absence of symptoms, absence of exacerbations/attacks, and stability of lung function (table 3). As for duration, most experts agreed that remission is defined as the absence of exacerbations for at least one year, and that persistent remission is defined as lasting three years (52.8% consensus) and one year (37% consensus). The absence of corticosteroids has been reaffirmed. On the matter of patients with severe asthma on biologic therapy, consensus was not reached on either discontinuation of biologic treatment or its maintenance. Similarly, there has been no consensus on whether asthma can be completely controlled with biological treatments. These results found confirmation in the literature. In fact, all available data reported a success rate of 30% in patients using different biologics, even when different definitions for remission have been used[26]. During R2, the composite definition of remission, the criteria of **complete clinical remission** (the absence of need

for OCS, the absence of symptoms, the absence of exacerbations/attacks, and pulmonary stability) and those of **partial clinical remission** (the absence of need for OCS, and 2 out of 3 criteria: the absence of symptoms, the absence of exacerbations/attacks, and pulmonary stability) were confirmed.

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Regarding the *quality of life*, full consensus has not been reached about a SAQ[27] cut-off value greater than 96 (58.5%), nor about the need for clinician-patient agreement in jointly defining remission, in the absence of validated tools (64.2%).

During R2, the consensus regarding having an ACT score between 20/25 and 25/25 was strengthened, and an ACQ less than 1.5 was reiterated as being enough to indicate clinical remission, and statements regarding improvement in lung function were removed, as they had not reached consensus.

Although a cut off for eosinophils less than 300 cells/L has been confirmed as a criterion to define inflammatory remission, this statement did not reach consensus. Similarly, although a FENO value lower than 25ppm is defined as a good marker when defining a reduction in inflammation, there was no consensus when considering it a criterion for inflammatory remission. Moreover, the need

for a *clinician-patient agreement* about remission, in the absence of validated tools, has achieved wide agreement.

Conclusions

To date, asthma is considered the most widespread respiratory disease. 10% of asthma patients have Severe Disease and it is crucial to clearly define criteria to better address their remission. Although wide agreement among scientific community has been reached about the general concept of remission and criteria to define it, there is more variability regarding the concept of duration, the role of therapy during remission, and the concept of inflammatory remission. This is prompting Corbett & Oppenheimer to define remission as "Ultimate Goal" of pediatric asthma management, thus highlighting the need of a Consensus Definition of Remission in Pediatric Asthma too[28].
The results obtained in this study appear to be congruent with the current popular concept among the scientific community of remission. Moreover, the definitions of partial and complete clinical remission obtained from the Delphi Analysis will be the ones used to test the efficacy of different treatments in patients (>2200) enrolled and followed into the SANI registry. This work was designed to create an independent, valuable, easy to use and effective tool, which might help clinicians to identify remission.

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536 **Table 1**. List of Statements with the Respective Level of Consensus Reached During the First and
537 Second Round. A cut-off value for a high and low consensus is defined from grade 4 and at least
538 2/3 of the agreement among the experts (66.6%) (green) and less of 2/3 of the agreement among
539 the experts (66.6%) (red), respectively.

	Statements R1		**Statements R2**	**Round 1**		**Round 2**	
				N (%) Agreement R1	**Median R1**	**N (%) Agreement R2**	**Median R2**
1.	Clinical remission of severe asthma should be defined by a composite measure of multiple criteria.	1.	Clinical remission of severe asthma should be defined by a composite measure of multiple criteria.	**49 (92.5%)**	**5.00**	**42 (97.7%)**	**5.00**
2.	A definition of clinical remission of severe asthma can be first made after a period of treatment of at least (please choose one of the following): a) 6 months b) 12 months c) 24 months d) 60 months	2.	A definition of clinical remission of severe asthma can be first made after a period of treatment of at least 12 months			**36 (83.7%)**	**4.00**
3.	When measuring the outcomes of a treatment of severe asthma, which of these would provide the clearest evidence: (only one response allowed) a) Clinical remission b) Inflammatory remission c) Histologic remission d) Evidence based on something other than remission (please use comments to provide more detail)	3.	When measuring the outcomes of a treatment of severe asthma, clinical remission would provide the clearest evidence.			**34 (79.1%)**	**4.00**

4.	When measuring the outcomes of a treatment of severe asthma, which of these would provide an acceptable evidence: (multiple responses allowed) a) Clinical remission b) Inflammatory remission c) Histologic remission d) Evidence based on something other than remission (please use comments to provide more detail)	4.	When measuring the outcomes of a treatment of severe asthma, clinical remission would provide an acceptable evidence.			**29 (67.4%)**	**4.00**
	Please indicate the extent to which you agree on the importance of each item on the following list as a criterion for the definition of clinical remission of severe asthma:		Please indicate the extent to which you agree on the importance of each item on the following list as a criterion for the definition of clinical remission of severe asthma:				
5.	no further need for OCS use			**52 (98.1%)**	**5.00**		
6.	absence of asthma symptoms	5.	absence of asthma symptoms	**40 (94.3%)**	**5.00**	**40 (93.0%)**	**5.00**
7.	absence of asthma exacerbations/attacks	6.	absence of asthma exacerbations/attacks	**53 (100.0%)**	**5.00**	**43 (100.0%)**	**5.00**
8.	stability of lung function	7.	stability of lung function	**44 (83.0%)**	**4.00**	**39 (90.7%)**	**4.00**
9.	clinically relevant improvement of lung function	8.	clinically relevant improvement of lung function	**36 (67.9%)**	**4.00**	**23 (53.5%)**	**4.00**
10.	stepping down of baseline treatment			**35 (66.0%)**	**4.00**		

	(ICS and other controllers)						
11.	normalization of airway hyper-reactivity			**23 (43.4%)**	**3.00**		
12.	normalization of asthma-related QoL	9.	normalization of asthma-related QoL	**48 (90.6%)**	**4.00**	**40 (93.0%)**	**4.00**
13.	clinically relevant reduction of lung inflammation	10.	clinically relevant reduction of lung inflammation	**46 (86.8%)**	**4.00**	**37 (86.0%)**	**4.00**
14.	agreement of both patient and HCP regarding disease remission	11.	agreement of both patient and HCP regarding disease remission	**40 (75.5%)**	**4.00**	**39 (90.7%)**	**4.00**
15.	The degree of clinical remission of severe asthma can be defined by means of a composite measure from a combination of: absence of asthma symptoms, absence of asthma exacerbations/attacks, stability of lung function, no further need for OCS use.	12.	The degree of clinical remission of severe asthma can be defined by means of a composite measure from a combination of: absence of asthma symptoms, absence of asthma exacerbations/attacks, stability of lung function, no further need for OCS use.	**50 (94.3%)**	**5.00**	**42 (97.7%)**	**5.00**
16.	Complete Clinical Remission of severe asthma is obtained when there is no further need for using OCS, and all the 3 following criteria are met: absence of asthma symptoms, absence of asthma exacerbations/attack, stability of lung function.	13.	Complete Clinical Remission of severe asthma is obtained when there is no further need for using OCS, and all the 3 following criteria are met: absence of asthma symptoms, absence of asthma exacerbations/atta	**48 (90.6%)**	**5.00**	**37 (86.0%)**	**5.00**

			cks, stability of lung function.				
17.	Partial Clinical Remission of severe asthma is obtained when there is no further need for using OCS, and 2 out of the 3 following criteria are met: absence of asthma symptoms, absence of asthma exacerbations/attack, stability of lung function.	14.	Partial Clinical Remission of severe asthma is obtained when there is no further need for using OCS, and 2 out of the 3 following criteria are met: absence of asthma symptoms, absence of asthma exacerbations/attacks, stability of lung function.	**39 (73.6%)**	**4.00**	**29 (67.4%)**	**4.00**
18.	Persistence of remission in severe asthma can be defined as a period of at least (please choose one of the following): a) 1 year b) 3 years c) 5 years	15.	Persistence of remission in severe asthma can be defined as a period of at least 1 year.			**34 (79.1%)**	**4.00**
		16	Persistence of remission in severe asthma can be defined as a period of at least 3 years.			**28 (65.1%)**	**4.00**
19.	Remission means asthma is fully controlled under biologic therapy and treatment is stepped down to 2/3 of GINA levels.	.		**24 (45.28%)**	**3.00**		
20.	Remission means asthma is fully controlled under biologic therapy and treatment is			**27 (45.3%)**	**4.00**		

	maintained at 4/5 of GINA levels.						
21.	Remission means asthma is fully controlled after suspension of biologic treatment.			**21 (50.9%)**	**3.00**		
22.	Remission means complete absence of exacerbations in the last: a) 1 year b) 3 years c) 5 years						
		17.	Remission means asthma is fully controlled under biologic therapy and the descalation of inhaled treatment.			**25 (58.1%)**	**4.00**
23.	Remission means no use of regular or burst OCS.	18.	Remission means no use of regular or burst OCS.	**46 (86.8%)**	**4.00**	**33 (76.7%)**	**5.00**
24.	Remission means an ACT score of: a) 25/25 b) 20 to 25/25	19.	Clinical remission means an ACT score of 20 to 25/25.			**33 (76.7%)**	**4.00**
25.	Remission means a lung function improvement of at least 100ml of FEV1 compared to the uncontrolled period.			**11 (20.8%)**	**3.00**		
26.	Remission means obtaining a normalized pulmonary function (FEV1 ≥ 80%).			**23 (43.4%)**	**3.00**		
27.	Remission means to obtain an improvement of at	20.	Remission means to obtain an improvement of at	**13 (24.5%)**	**3.00**	**16 (37.2%)**	**3.00**

	least 200ml and a 12% improvement in FEV1 compared to the uncontrolled period.		least 200ml and a 12% improvement in FEV1 compared to the uncontrolled period.				
28.	Remission means reaching an eosinophil count of: a) < 300 cells/µl b) < 150 cells/µl	21.	Inflammatory remission means reaching an eosinophil count of less than 300 cells/µl			**14 (32.6%)**	**3.00**
29.	Remission means reaching a FENO level of: a) < 50 ppb b) < 25 ppb	22.	Inflammatory remission means reaching a FENO less than 25 ppb)			**21 (48.8%)**	**3.00**
30.	Remission means reaching a severe asthma questionnaire (ACQ) score of: a) < 1,5 b) < 0,5	23.	Clinical remission means reaching a severe asthma questionnaire (ACQ) score of less than 1,5.			**34 (79.1%)**	**4.00**
31.	Remission means reaching a severe asthma questionnaire (SAQ) score of > 96 and a SAQ – Global scale score of > 85.			**31 (58.5%)**	**4.00**		
32.	Because there are no validated HCP-reported disease activity instruments in asthma, HCP and patient concurrence regarding asthma remission should be required for a patient to be considered in remission.	24.	Because there are no validated HCP-reported disease activity instruments in asthma, HCP and patient concurrence regarding asthma remission should be required for a patient to be considered in remission.	**34 (64.2%)**	**4.00**	**32 (74.4%)**	**4.00**

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Table 2. Definition of clinical remission according to the main results obtained from the Delphi Analysis. The first four criteria (absence of asthma symptoms, absence of asthma exacerbations/attacks, stability of lung function and no further need of OCS treatment) reached the consensus and have been used as criteria to define the remission (partial or complete). The last three criteria included the time range and the ACT and ACQ scores which need to be considered for clinical remission: these parameters did not reach the consensus to be used in the priority definition of remission (partial or complete).

How should clinical remission be defined	
Definition	Clinical remission is defined by a composite measure of **multiple criteria**
Criteria	absence of asthma symptoms
	absence of asthma exacerbations/attacks
	stability of lung function
	no further need of OCS treatment
	normalization of asthma-related QoL
	stability of lung function
	clinically relevant reduction of lung inflammation
	agreement of both patient and HCP regarding disease remission
	For at least 12 months
Time	
	ACT score of 20/25 to 25/25
Scores	ACQ score of less than 1,5

553 **Table 3**. Definition of partial and complete remission according to the main results obtained from
554 the Delphi Analysis.

	Partial clinical remission	**Complete clinical remission**
Definition	Partial clinical remission is obtained when there is no further need for using OCS, and 2 out of the 3 following criteria are met:	Complete clinical remission is obtained when there is no further need for using OCS, and all the 3 following criteria are met:
Criteria	• absence of asthma symptoms • absence of asthma exacerbations/attacks • stability of lung function	• absence of asthma symptoms • absence of asthma exacerbations/attacks • stability of lung function
Time	For at least 12 months	For at least 12 months
Scores	ACT score of 20/25 to 25/25 ACQ score of less than 1,5	ACT score of 20/25 to 25/25 ACQ score of less than 1,5

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