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ERS/EAACI Statement on severe exacerbations in asthma in adult: facts, priorities and key research questions

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Abstract:	Despite the use of effective medications to control asthma, severe exacerbations in asthma are still a major health risk and require urgent action on the part of the patient and physician to prevent a serious outcome such as hospitalization or death. Moreover, severe exacerbations are associated with substantial huge healthcare costs, and psychological burden including anxiety and fear for patients and their families. The European Academy of Allergy and Clinical Immunology (EAACI) and the European Respiratory Society (ERS) set up a Task Force (TF) to search for a clear definition of severe exacerbations and to also define research questions and priorities. The statement includes comments from patients who were members of the TF.

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TASK-FORCE Sections and Members

Section no	Section title	Participants
1	**Definitions**	M. Gaga (leader), K. Samitas
2	**Triggers and risk factors**	A. Bourdin (leader)
2A	*Assessment of risk, What is cause and what is effect*	A. Bourdin
2B	*Modifiable vs non-modifiable factors & Mathematical models*	F. Chung
2C	*Risk Factors and epidemiology, pheno/geno/endotypes*	I. Horvath
2D	*Personality type – Gender, Psychosocial factors. Perception, Compliance/adherence*	L. Bjermer, F. Kanniess
2E	*Virus / Allergens*	Z. Diamant, S. Johnston, R. Djukanovic
2F	*Environmental air pollution indoor/outdoor pollution & occupational factors*	G. Brusselle, A. Papi
2G	*Drugs & irritants / Overdose of ~~B2~~ β_2- agonists*	P. Chanez
2H	*Interaction between different trigger factors*	N. Papadopoulos
3	**Acute Management**	E. Zervas (leader)
4	**Prevention**	C. Brightling (leader), Dermot Ryan, Richard Russell and Sarah Diver
5	**ELF Patient perspective**	D. Hamerlijnck, ELP Patient Advisory Group
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Summary

Despite the use of effective medications to control asthma, severe exacerbations in asthma are still a major health risk and require urgent action on the part of the patient and physician to prevent a serious outcome such as hospitalization or death. Moreover, severe exacerbations are associated with substantial huge healthcare costs, and psychological burden including anxiety and fear for patients and their families. The European Academy of Allergy and Clinical Immunology (EAACI) and the European Respiratory Society (ERS) set up a Task Force (TF) to search for a clear definition of severe exacerbations and to also define research questions and priorities. The statement includes comments from patients who were members of the TF.

1. INTRODUCTION

Asthma is one of the most common chronic diseases and its worldwide prevalence has risen around 3-fold in recent decades [1]. With the recognition of the inflammatory nature of the disease and the introduction of inhaled corticosteroidinhaled corticosteroids, asthma control and the quality of life of asthma patients have substantially improved and many deaths have been prevented. Nevertheless, patients still face exacerbations of varying severity ranging from increased symptoms to life-threatening episodes. And any asthmatic patient may suffer severe exacerbation and even die from one. In fact, most exacerbations present in mild asthmatics, who are the majority of asthma sufferers [2, 3]. The causes leading to exacerbations may be exposure to a triggering agent, lack of or adherence to treatment, the inherent severity and hyperresponsiveness of the disease and may be affected by comorbidities. Severe exacerbations of asthma likely carry most of the burden of the disease through their immediate and delayed-associated risks. Severe exacerbations are exposing patients to immediate and delayed side effects of high doses of bronchodilators and systemic corticosteroids, and quite often to antibiotics. Absenteeism, presenteeism, care-associated risks if admitted (nosocomial infection for example), anxiety and many other issues are insufficiently describing the burden of severe exacerbations. Epidemiological data remain heterogenous as very different definitions are used in cohorts and in clinical trials. For example, in TENOR II, 25.8% of the population reported a severe exacerbation [4]. In the MENSA study, among enrolled patients who reported 3.5 ± 2.2 exacerbations before entering the study, 17 to 21% were admitted. During the trial, the mean rate of clinically significant exacerbation and exacerbation requiring admission fell to 1.74 and 0.10 respectively [5]. Unfortunately, asthma deaths still exist. Their rates are low and most of them are seen as preventable [6, 7] in westernized countries. This also implies that

some are not preventable, suggesting a place for new drugs to treat refractory episodes of near fatal asthma.

Accordingly, both the ERS and the EAACI elicited a task force in 2016 that aims to review the most relevant research evidence and the current practice on definition, clinical identification of severe exacerbations, triggers and risk factors, management and prevention. Subsequently, this document does not contain recommendations for clinical practice but offers recommendations for future research.

Methodology

After the initial meetings the Task Force members decided to address four main research questions related to serious exacerbations: 1) what are the available definitions for severe exacerbations in asthmatics and what would be an accurate definition, 2) which are the trigger factors related to the initiation and severity of exacerbations, 3) what is the best way to manage severe exacerbations 4) and finally what is the best strategy to prevent them. Specific keywords and MeSH-terms were identified based on several key-references provided by the Task Force members, and the corresponding literature search was initiated for all sections using the MEDLINE and CENTRAL (Cochrane Library) Databases. Search results were extracted in .txt file formats and imported in a specially designed reference management software (Reference Manager Version 12) in order to screen for duplicates. Further processing of the search results was made in a step-wise approach (as shown in the supplementary file flow-charts) based on the title, the abstract, and finally after reading the whole text, filtering for date (2000 and onwards), age (adults only), language (only English), and type (included: randomized and observational studies and systematic reviews/meta-analyses, excluded: case reports and letters to the editor). All articles remaining after final processing for each section were sent back to the corresponding TF members for final evaluation (corresponding flow charts are available as

a supplementary file). From this sorting of the relevant literature, leaders of the four sections drafted a first version and each statement was kept or removed if any concern was expressed and no consensus could be found. During the subsequent dedicated meetings, research needs were identified and tables and figures were reviewed.

2. Definition of severe exacerbations of asthma

Asthma severity and control have more or less been defined and graded over the years so that the definitions are equally understood by all stakeholders [3, 8–10]. This is not yet the case for asthma exacerbations where exacerbations are defined as episodes characterized by more or less rapid increase in symptoms, sufficient to require a change in treatment [3, 11]. Severe exacerbations are usually defined based on use of systemic, usually oral corticosteroids (OCS), emergency care visits and/or hospitalizations [1], while in some clinical studies reductions in lung function (peak expiratory flow [~~PEFR~~PEF] or forced expiratory volume in one second [FEV1]) of more than 20 or 30% have also been included in the definition. (Table 1) It must be noted that patient perception and easy access to rescue corticosteroids and emergency care facilities may confound the definition and so may the retrospective collection of data. The ERS/ATS statement on exacerbations released in 2009 [12] defines severe exacerbations as events that require urgent action on the part of the patient and physician to prevent a serious outcome, i.e. hospitalization or death. .However, there is subjectivity in the perception of severity and moreover, many studies have shown that the risk of severe exacerbation is associated with a multitude of factors. These factors include (1) the level of asthma control, (2) asthma severity based on ERS/ATS definition [3], (3) lung function, (4) the presence of comorbidities, (5) the psychosocial status (to assess the ability to seek help in case of clinical worsening), (6) previous history of near fatal attacks and (7) response to treatment. Such factors seem important to guide treatment decisions and, importantly, decisions regarding hospitalizations. Moreover, prediction models assessing future risk of exacerbations in adult asthma patients have been proposed, such as the one published by Miller et al, based on the TENOR cohort [13]. However, the applicability of such models has not been examined in large studies and needs to be assessed prospectively. Composite scores have been developed for use in other acute

respiratory conditions, for example the CURB-65 or PSI score for pneumonia or GENEVA score for pulmonary embolism, and they greatly help clinicians in treatment decisions and are important for the safety of the patients. All TF members in their practice consider severe exacerbations of asthma as a significant worsening of the disease that require OCS treatment for at least 5 days. In the ERS/ATS task force in 2009, a three-day course of OCS was the recommended definition for clinical trials. This small difference was supported by all TF members as it may differentiate from patients with episodes of loss of control requiring short courses (e.g. 1-2 days) of OCS and from temporary increase of maintenance treatment to improve the control of their disease. These patients may have an accumulated use of OCS over time equivalent to someone with repeated exacerbations but will not be reported as such. Whether 3 or 5 days of OCS is more accurate for discriminating a mild from a severe exacerbation will probably not be addressable in terms of evidence. 1) Herein we report an expert-based opinion that definitely not intends to change the definition used in trials in order to keep them comparable and 2) as the harmfulness of cumulative doses of corticosteroids is obvious above 0.5 g per year [14], a five-days based definition would make better fit this OCS-associated risk with the threshold of two exacerbations. Although variable among countries and systems, emergency visit or hospitalization, the TF members base hospitalization or initiation of treatment with OCS on the GINA or BTS recommendations to improve standardization. It seems that it would be important to develop, test and use a composite score that takes into consideration the patient's previous health status, the presence of comorbidities, history of severe or near fatal exacerbations, adherence to treatment, psychosocial status, level of control and of course, response to treatment-the latter is already factored into asthma exacerbation management guidelines- rather than just clinical severity at presentation and ~~PEFR~~PEF or spirometry values.

TABLE 1: Examples of definitions of severe exacerbation in asthma patients used in the literature.

Author	Definition of severe exacerbation	Comment
GINA 2019 [1]	Exacerbations of asthma are episodes characterized by a progressive increase in symptoms of shortness of breath, cough, wheezing or chest tightness and progressive decrease in lung function, i.e. they represent a change from the patient's usual status that is sufficient to require a change in treatment. Definition based on symptoms ("talks in words, sits hunched forward, agitated"), clinical findings (RR>30/min, BPM>120/min, SAT<90%, use of accessory muscles) and lung function (~~PEFR~~PEF< 50% pref.)	GINA proposes an accurate definition of exacerbations of asthma. Regarding severe exacerbations, GINA ~~refer to the severity of exacerbations but~~ does not define exact criteria by which to distinguish severity levels
Reddel et al (ERS/ATS 2009) [12]	Severe asthma exacerbations are defined as events that require urgent action on the part of the patient and physician to prevent a serious outcome, such as hospitalization or death from asthma. The definition should include at least 1 of the following: a. Use of systemic corticosteroids or an increase from a stable maintenance dose, for at least 3 days. b. A hospitalization or emergency department (ED) visit because of asthma, requiring systemic corticosteroids	~~The definition should include at least 1 of the following:~~ ~~a. Use of systemic corticosteroids or an increase from a stable maintenance dose, for at least 3 days.~~ ~~b. A hospitalization or emergency department (ED) visit because of asthma, requiring systemic corticosteroids~~ Strength: This is the most commonly used definition Weakness: it relies on patient and doctor subjective assessment, there are no hard criteria for deterioration
Custovic et al (EAACI 2013)[9]	No specific definition provided	Strength: The taskforce stresses the need for a consensus definition of asthma exacerbation that could usefully guide treatment. Weakness: It is not really a definition~~The taskforce stresses the need for a consensus definition of asthma exacerbation that could usefully guide treatment.~~

O'Byrne et al 2009 [15]	Defined as events requiring hospitalization or emergency treatment due to worsening of asthma, or death due to asthma. Emergency treatment was defined as treatment of acute airway obstruction with systemic corticosteroids and nebulized or parenteral bronchodilators given at a healthcare institution.	Strengths and weaknesses same as those of Ref [12] (ERS/ATS 2009) ~~Emergency treatment was defined as treatment of acute airway obstruction with systemic corticosteroids and nebulized or parenteral bronchodilators given at a healthcare institution.~~
Green et al [16], Pauwels et al (FACET study) [17]	Decrease in morning PEF >30% on 2 or more consecutive days, or deterioration in symptoms needing OCS	Strengths: Adds an objective limit in addition to the need for OCS or the vague "deterioration" Weakness: 30% decrease is not universally severe, no reference to length of time
Jayaram et al 2006 [18]	Course of OCS as determined by study investigator	Weakness: No objective criteria given ('determined by study investigator')~~No criteria given for 'determined by study investigator'~~
Demoly P 2004 [19]	Hospitalization was unanimously recognized as the first criterion for severe exacerbations. A decrease in peak expiratory flow of more than 30% below the baseline value on two consecutive days and an episode requiring systemic corticosteroids were the next criteria. This survey emphasizes the complexity of the notions of asthma control and exacerbation	~~This survey emphasizes the complexity of the notions of asthma control and exacerbation~~ Strengths: This survey emphasizes the complexity of the notions of asthma control and exacerbation and reflects real life practice. Uses an objective measure and length of time Weakness: No hard criteria
Fuhlbrigge 2013 (NIH workshop) [20]	An exacerbation is a worsening of asthma requiring the use of systemic corticosteroids (or for patients on a stable maintenance dose, an increase in the use of systemic corticosteroids) to prevent a serious outcome (The subcommittee does not endorse severity stratification in the core outcome definition)~~.~~	~~The subcommittee does not endorse severity stratification in the core outcome definition~~ Strengths and weaknesses same as ref [12]. Addition: increase in use of systemic steroid dose in patients already on steroids

Castro et al 2010 [21]	Those requiring systemic corticosteroids or doubling of ICS dose	Weakness: No criteria given for 'requiring'; 'doubling of ICS dose' ~~No criteria given for 'requiring'; 'doubling of ICS dose' precludes higher dose~~
Murphy et al 2010 [22]	Defined as episodes requiring medical intervention [hospital admission, emergency department presentation, unscheduled doctor visit or the use of oral corticosteroids (OCS)]	Strengths and weaknesses same as ref [12]. ~~The use of OCS is not mandatory~~

3. TRIGGERS AND RISK FACTORS

3A. Assessment of risk: what is cause and what is effect?

The prevention of exacerbations is probably the most important aim for patients with asthma and health care professionals. In order to achieve this aim, it is important to plan the re-assessment of asthma patients and treatment adjustments because of the immediate risks (i.e. acute respiratory failure, death) and future risks (recurrence of exacerbations, decline in lung function, and side effects of treatments) [1]. Routine management strategies assess asthma control based on clinical symptoms, history of exacerbations and pulmonary function testing. In addition, in experienced centers, strategies guided by airway hyperresponsiveness (BHR) or sputum eosinophilia may provide benefit for preventing future exacerbations [16, 23]. In contrast, the use of fractional exhaled nitric oxide (FENO) as a surrogate marker in asthma management is still inconclusive [24–26] except during pregnancy [27]. A recent meta-analysis found more supportive results deserving further evaluations [28].

Since a previous exacerbation has been shown to be an important risk factor for future exacerbations (even though this concept has been challenged) [29], the "frequent exacerbator" likely represents an important clinical phenotype; and asthma treatment should aim to modify

what might look like an irreversible cycle [30]. For this purpose, multiple initiatives have investigated and weighed the importance of individual traits in predicting recurrent exacerbations. Many other characteristics and conditions have also been reported such as amount of asthma medication, comorbidities including obesity, occupational stress [31], sensitization, indoor and outdoor pollution, small airway dysfunction [32], loss of lung elastic recoil [33], and psychological factors [29, 34–44]. Retrospective studies have shown that repeated assessment of composite scores of control such as the Asthma Control Test (ACT) or Asthma Control Questionnaire (ACQ) and other tools, such as eHealth and mHealth[45], may predict severe exacerbations [46]. However, whether self-monitoring of asthma control score questionnaires at home can be useful to predict (and consequently, help to prevent) exacerbations in a real life setting needs to be further investigated [47–49]. An index of fluctuation of Peak Expiratory Flow (~~PEFR~~PEF) measurements at home was able to predict exacerbations [50]. Lastly, although a hospital admission provides proof of a severe exacerbation (see definition), the decision to hospitalize a patient with asthma also depends on the clinical course during management at the emergency department [2, 51, 52], and on additional factors such as age, inflammatory phenotype, presence of comorbidities [53, 54], and familial and social conditions [2, 51, 52].

3B. Modifiable vs non-modifiable factors and mathematical models

Until recently, modifiable risk factors for exacerbations were mostly seen as behavioral issues or environmental triggers [55–58]. This included patients' beliefs (or parents' beliefs in the case of children) and expectations, poor inhalation technique and/or treatment adherence, (active or passive) smoking and allergen exposure (such as in-house pets, for example). More recently, the key role of viruses has been acknowledged, and viral triggers are now perceived as potentially modifiable factors. However, no therapeutic strategies have yet been able to

successfully interfere with rhinovirus carriage and bouts of infections in children and adults; this is an important area of ongoing research. Accordingly, viral infection and impaired host responses to rhinovirus can be modelled to predict the potential of new antiviral drugs [53, 59–61]. The synergistic action of allergen exposure (e.g. seasonal pollens, house dust mite) and viruses may indicate a place for combining strategies targeting each factor alone or in association [38, 55, 62].

High blood eosinophil count, reflecting type 2 (T2) inflammation, is well-recognized as a significant risk factor for asthma exacerbations [63], with a consistent dose-ranging effect reproduced in different large scale studies [64, 65]. The relative weight of elevated blood eosinophilia with any other predictor of future exacerbation is largely unknown, but is influenced by the level of asthma control, asthma severity, asthma phenotype (e.g. age at onset of asthma), lung function and history of exacerbations. Validated biomarkers reflecting non-T2 asthma phenotype(s) remain an urgent unmet need [66]. The recognition of T2-related traits makes a patient with uncontrolled severe asthma eligible for biologic therapies targeting key T2 disease-drivers, such as eosinophils, IL-4, IL-13 and/or IgE [67]. Elevated blood eosinophil count is associated with an increased exacerbation risk and to date this is the most relevant phenotyping marker. The reduction in exacerbation rates provided by anti IgE-, -TSLP, -IL-5- and -IL-4/IL-13 antibody therapy supports the concept that T2-associated asthma is associated with an increased risk of exacerbations [68, 69], even though it is not the only one.

Asthma patients may follow many different trajectories [56]. These trajectories can be described under three main categories and sustain the concept of asthma severity (persistently severe, intermittently severe, never severe). Presently, exacerbations represent one of the key outcomes in asthma with the greatest asthma-related risks as defined by GINA [1] and hence, the development of innovative drugs and effective treatment modalities remains a priority.

Exacerbations are episodes of acute respiratory distress; a situation that causes major stress for the patient themselves, their relatives and even for the health care providers. They represent an important economic burden both in terms of health care use and professional absenteeism. They are also associated with long term risks (relapses, side effects of treatments dominated by systemic steroids, lung function decline) [1, 9, 70]. Some single nucleotide polymorphisms (SNPs) and other gene modifiers summarized in **Figure 1** could be associated with such long term risks [62, 71–82]. It appears worthwhile exploring the epigenetic modifications in well-characterized asthma populations, particularly in late onset disease.

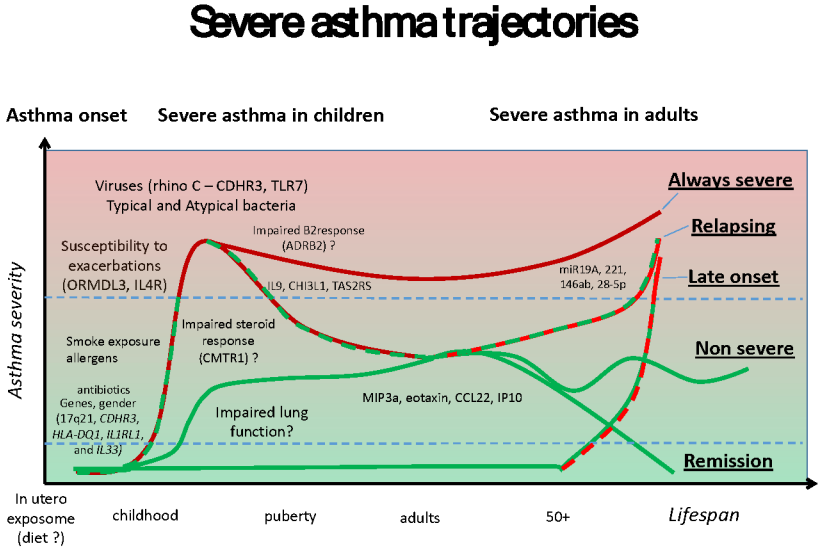


Figure 1 Potential severe asthma trajectories and the importance of risk factors and genetic variants (such as single nucleotide polymorphisms [SNPs]). this figure presents a summary of the literature and is not intended to be exhaustive

3C. Risk factors and epidemiology, pheno/geno/endotypes.

Since severity of asthma is presently defined by treatment requirement, which partly relies on previous exacerbation rates [3], the frequency of exacerbations is associated with severity. However, exacerbations are not restricted to patients with the severe form of asthma.

Near-fatal asthma episodes can occur in patients even with so called "mild asthma", implicating that "mild asthma (GINA step 1 and 2) "does not necessarily mean "low risk asthma". Most of the time, these patients are not receiving any anti-inflammatory treatment at the time of the event and their asthma can be well-controlled when it is correctly managed and treated [2, 35]. Near-fatal episodes represent a minority of exacerbations seen in the emergency department [2]. Interestingly, a hyperbolic curve relating inhaled corticosteroid (ICS) prescription refilling and asthma mortality is highly suggestive of a strong death-preventing effect of ICS use [83]. Actually, asthma deaths due to exacerbations have decreased over time in westernized countries. However, their incidence was still estimated to be more than 900 in the UK in the latest National Review of Asthma Deaths, and at least half of these dramatic cases were considered preventable [6, 84].

Risk factors and clinical characteristics could be identified and robustly confirmed in different countries. These criteria should be known to all health care providers involved in the management of asthma and are shown in **Table 2**.

Better characterization of disease mechanisms is required in those patients with an incomplete response to ICS (across GINA steps) [70]. Defining clinical phenotypes and mechanistic endotypes is a useful concept which has been developed to better manage these patients [85]. In the SARP-3 cohorts, five factors were positively associated with exacerbation frequency: chronic sinusitis, gastro-esophageal reflux, blood eosinophils, body mass index, and bronchodilator responsiveness. Clusters in primary care identified early onset and obesity as risk factors for exacerbations. A cluster of obese female asthmatics with recurrent exacerbations has been described in both SARP and UBIOPRED cohorts [86, 87]. Furthermore, a large scale study on children confirmed that obesity is linked with a shorter period of time between exacerbations [88]. Symptoms such as cough and wheeze are correlated with uncontrolled asthma, but are poorly associated with exacerbations [89]. Interestingly, new

inflammatory patterns of exacerbations are currently described with the integration of the microbiome and T1-related cytokines [90]. A gene signature derived from sputum gene transcriptomics containing Charcot-Leyden crystal galectin [CLC]; carboxypeptidase 3 [CPA3]; deoxyribonuclease 1-like 3 [DNASE1L3]; alkaline phosphatase, liver/bone/kidney [ALPL]; CXCR2; and IL1β (a mixture of eosinophil and mast cell product with neutrophil-associated cytokines) can predict future exacerbation phenotypes of asthma, with the greatest biomarker performance compared to fractional exhaled nitric oxide values and sputum eosinophil counts in identifying those who would experience frequent severe exacerbations [91].

It should be kept in mind that very high blood eosinophil counts (e.g. more than a thousand per mm3) are sometimes associated with other conditions such as eosinophilic granulomatous with polyangiitis (EGPA) or allergic bronchopulmonary aspergillosis (ABPA) which overlap with severe asthma. These specific conditions are prone to very frequent exacerbations. They are sometimes difficult to discriminate from severe asthma when all the diagnostic criteria are not fulfilled [92].

Table 2. Risk factors for various outcomes in asthma exacerbations

	Likely	Possible	Ref
RF for dying	• B2 agonist overuse • No ICS treatment • Age • Virus infection • Gender • Drug and venom allergy • Allergen exposure (including thunderstorm asthma)	• Intubation outside PICU • High number of ED visit • Sports • Alternaria and penicillium spores • Nitrogen dioxide, ozone • Severe asthma	[35, 93–97]
RF for ICU admission – near fatal asthma	• No ICS treatment • Severe asthma • Virus infection • Loss of elastic recoil • Permanent airflow limitation • Hyperinflation • Menstruation • Steroid dependence • History of intubation • Delayed systemic corticosteroid use	• Heroin, cocaine	[33, 39, 41, 98, 99]
RF for severe exacerbation – ED – admission	• No ICS treatment • Comorbidities • Psychological issues • Age • Absence of ICS • Virus infection		
RF for frequent severe exacerbations (≥ 2 - 3 OCS bursts/y)	• No ICS treatment • Virus infection • High blood eosinophil count • Smoking • Genetic • Atopy • BMI • BD responsiveness • Chronic sinusitis	• Low socioeconomic status • GERD • Aspirin sensitive • Climate- Thunderstorms during pollen season	[54, 100, 101]

RF = risk factor; BD = bronchodilator; BMI = body mass index; ED= emergency department; ICS = inhaled corticosteroids; ICU= intensive care unit; GERD = gastro-esophageal reflux disease; NFA= near-fatal asthma attack; OCS = oral corticosteroids

3D. Typology– gender, psychosocial factors. Perception, Compliance/Adherence

Poor treatment adherence is a major trigger for loss of control at the population level, and this is a common finding also for onset of exacerbations [102]. Although ICS treatment is able to decrease the exacerbation rate at all dose ranges [103], it seems that an adherence of at least 75% of the prescribed dose (hazard ratio [HR] 0.61; 95% confidence interval [CI] 0.41–0.90) is required to achieve this goal [103]. Of note, 24% of exacerbations can be attributed to poor adherence, which is often unintentional due to poor inhalation technique. Moreover, running out of inhaler was frequently reported in ED-attending asthmatics [104]. The use of multiple devices, especially when different principles are mixed, such as dry powder inhalers and metered dose inhalers (MDI), is also a risk [105]. Non-consented switching of inhalers has also been shown to be a significant risk factor for exacerbation; these apparent cost-sparing measures in the short-term are thus subsequently countered by increased health care utilization [106]. Alexithymia [107] , specific personality traits [108], and poor perception of symptoms may lead to a delayed request for help [95–100]. Female gender [109, 110], ethnicity [111, 112] and patient beliefs [113]could also be identified as risk factors for exacerbation. The prevalence of psychological dysfunction, including anxiety and depression, is increased in patients with asthma and has been shown to be related to severity of the disease [114]. Anxiety and depression are also strong predictors for poor asthma control [115].

Poor adherence is well documented for ICS; but new injectable biologics also appear susceptible to this, particularly when self-administered [116]. On the other hand, self-administration is likely to improve access to treatment and to reduce the burden of the disease [117].

Several drawbacks could be raised against therapeutic educational programs, but at present many simple and efficient solutions extensively reviewed elsewhere can work [70, 102]. The benefits of written or web-based action plans are worth investigations [118]. Furthermore,

e-Health solutions such as electronic reminder messages and, more recently, connected (to a computer or a smartphone) inhaler devices can be implemented and have been shown to be effective [119, 120], but as they are usually only geared towards the use of one single inhaler per patient and no other medication it is likely of limited value for patients requiring multiple medications. However, these interventions should be prospectively evaluated for their ability to decrease exacerbation rates over time and whether they are really easing patients' lives. Stronger partnerships between patients and health care professionals are likely to improve adherence and new self-adherence programs should be developed and tested for their effect on preventing (severe) exacerbations.

Although there is no perfect tool for associating a severe asthma exacerbation with poor adherence, a minimal adherence checklist is proposed in GINA and the task force decided to echo it presently (**Table 3**). Dose-counter displaying devices are preferred options according to a European Lung Foundation (ELF) open discussion organized for the present task force.

Factors contributing to poor adherence
Medication/Regimen factors
- Difficulties using inhaler device
- Burdensome regimen (e.g. multiple times per day)
- Multiple different inhalers
Unintentional poor adherence
- Misunderstanding about instructions
- Forgetfulness
- Absence of a daily routine
- Cost
Intentional poor adherence
- Perception that treatment is not necessary
- Denial or anger about asthma or its treatment
- Inappropriate expectations
- Concerns about side-effects (real or perceived)
- Dissatisfaction with health care providers
- Stigmatization
- Cultural or religious issues
- Cost
How to identify poor adherence in clinical practice
Ask an empathic question
- Acknowledge the likelihood of incomplete adherence and encourage an open non-judgmental discussion
Check medication usage
- Check the date of the last controller prescription
- Check the date and dose counter on the inhaler
- In some health systems, prescribing and dispensing frequency can be monitored electronically by clinicians and/or pharmacists
Examples of successful adherence interventions
- Shared decision-making for medication/dose choice
- Inhaler reminders for missed doses
- Prescribing ICS once-daily versus twice-daily
- Home visits for a comprehensive asthma program by an asthma nurse

Table 3. Factors affecting adherence in clinical practice, according to GINA [1].

3E. Virus/allergens

A synergy exists between respiratory viral infections and allergen exposure inducing asthma and causing exacerbations in susceptible, sensitized asthmatics [38, 55, 62]. Additionally, interaction between lower respiratory tract viral infections (LRTI) and atopic sensitization has been recognized as a major risk factor contributing to asthma development and exacerbations [62, 121]. Birth cohort studies provide strong evidence for a synergistic effect of viral LRTIs and atopic sensitization on risk of asthma inception, particularly in predisposed children [122, 123]. Several studies in both sensitized children [55, 124] and adults [16, 38] found a strong association between the levels of specific IgE to inhaled allergens and viral LRTIs in increasing the risk of severe asthma exacerbations requiring hospital admission.

The synergism between allergen sensitization and viral LRTIs has been indirectly confirmed in a study in asthmatic children, showing that pretreatment with omalizumab decreases asthma exacerbations in fall, which are likely (rhino-)virus-induced [125]. Recent evidence demonstrates that omalizumab restores deficient anti-viral immunity in children with asthma, and that exacerbation reduction with omalizumab was greatest in those with greatest restoration of anti-viral immunity [125]. Rhinoviruses (RV), especially RV-A and RV-C groups, are the most frequent viruses detected during an asthma exacerbation including severe asthma exacerbations with near-fatal and fatal asthma, and allergic asthmatics usually experience more severe and prolonged LRTI symptoms with RV infection compared to non-atopic healthy controls [38, 55, 126]. Interestingly, CDHR3 polymorphism is a risk factor for RV induced severe asthma exacerbations in children [71], possibly because it has recently been shown to be an RV-C receptor [127]. Another study showed that documenting a viral infection in the ED was a strong predictor for ED re-attendance in children [128]. Impaired interferon responses to RV infection are associated with asthma in both adults and children [105, 106], and are

associated with increased RV-induced asthma exacerbation severity [131] Although appealing, the development of a RV vaccine appears highly challenging [132]However, a proof of concept study on inhaled IFN-β as a therapeutic intervention in virus-induced asthma exacerbations only showed benefit in a subgroup of people with moderate/severe asthma [133], implicating that further research is needed to investigate the concept of interferon supplementation in asthmatics at exacerbation onset.

3F. Environmental factors: indoor/outdoor air pollution & occupational factors

Outdoor air pollution is an established risk factor for asthma exacerbations, although the magnitude of effect remains difficult to assess precisely [101]. Diesel exhaust particles and peaks of ambient air pollution, (reflected by, amongst others, high levels of nitrogen dioxide and ozone) were shown as concomitant factors to emergency department attendance in asthmatics but also could be epidemiologically related to asthma exacerbations and deaths [97]. Work-related exacerbations are probably underestimated whereas many different non-specific irritants could be identified such as mineral dusts, gas and fumes etc. [134].

Indoor air pollution comprises second-hand tobacco smoke exposure, which is of special interest in children, but also other less well-known contributors such as volatile organic compounds (VOC) [135]. Open fire place, sick building syndrome, cleaning supplies and household products, and inadequate ventilation are also to be integrated into potential sources of indoor air pollution. We propose to test whether facilitating access to air quality data records may prevent asthma exacerbations. The European Lung Foundation (ELF), while reviewing the present manuscript, supports the use of portable air quality sensors, but more research is needed to know what and how to measure the right substances.

Occupational sensitizers and triggers have been cause for concern for many years and efforts have been taken to limit their impact. All TF members in their practice consider it worthwhile

facilitating access to free and independent experts in occupational medicine, as well as using FENO, spirometry, and potentially other relevant diagnostic tests (e.g. induced sputum) at work, especially considering their relatively low direct and indirect costs. More research is needed on occupational triggers and their effect on severe asthma exacerbations. Patients also raised the need to support asthma patients when choosing careers to avoid known and dangerous sensitizers and triggers.

3G. Drugs & irritants / Excessive use of β_2-agonists~~beta2 agonists~~

Whether drugs known to affect airway smooth muscle tone (such as ~~beta~~ β-blockers) are able to trigger an asthma exacerbation is unclear. Non-steroidal anti-inflammatory drugs (NSAID) and aspirin intake in susceptible patients induces asthma exacerbations, and low dose induction of tolerance must be investigated to assess their benefit in preventing exacerbations.

Excessive use of short-acting β_2-agonists ~~beta2 agonists~~ (SABA) in the absence of ICS use has long been linked to hospitalizations and asthma deaths, best exemplified by asthma deaths epidemics related to high doses of fenoterol reported in New Zealand and other countries [136]. Also regular use of long-acting β_2-agonists ~~beta2 agonists~~ (LABA) in the absence of ICS has been shown to increase significantly the risk of asthma exacerbations and asthma deaths potentially through a "masking" effect [137–139]. Not only overuse, but also regular use of SABA – without ICS [140] – has also been associated with paradoxical asthma worsening [52, 141]. Mechanisms involved are not fully understood, but may relate to induction of inflammatory mediators in bronchial epithelial cells by β_2-agonists ~~beta2 agonists~~ (both SABA and LABA), when administered in the absence of ICS [142] , and/or by a tachyphylaxis phenomenon but this is still to be demonstrated in vivo [143]. Because several short and long acting β_2-agonists ~~beta2 agonists~~ are now available, their potential side effects should be assessed in detail and reported, especially as paradoxical triggers for loss of control and

exacerbations. The TF members limit these issues by systematic concomitant ICS use and reassess the patients repeatedly. Most TF members avoid frequent and inappropriate use of repeated or regular high doses of SABA irrespective of the manner of administration (inhaled: pMDI, DPI, or nebulisation) without medical supervision.

4. ACUTE MANAGEMENT

TREATMENT OF SEVERE ASTHMA EXACERBATIONS

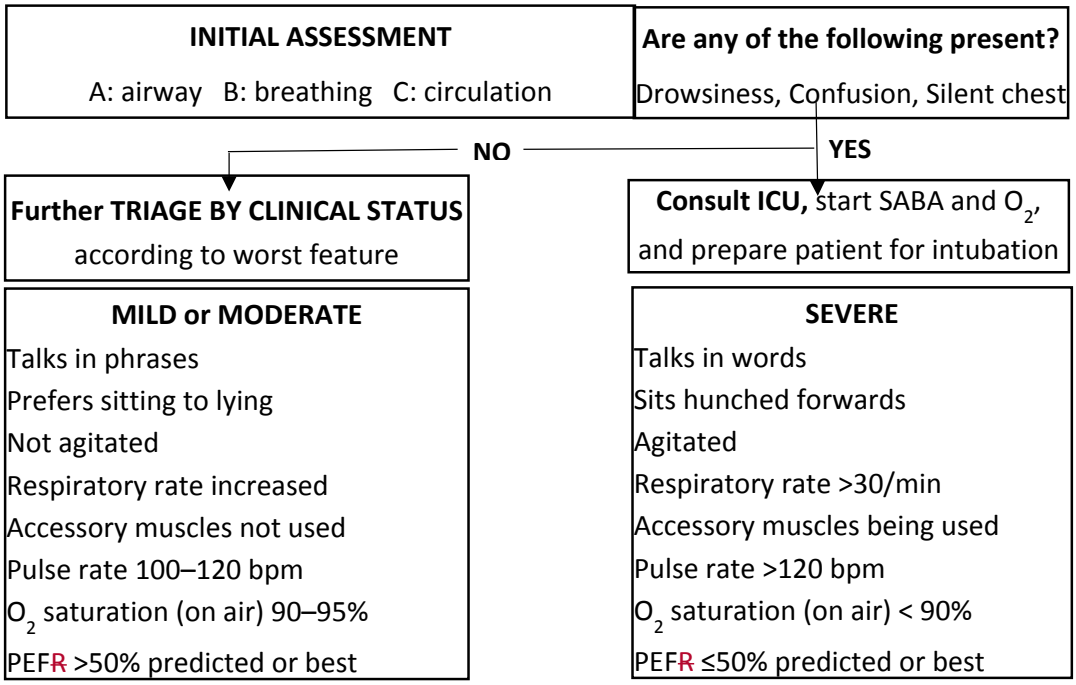
Despite optimum maintenance therapy and appropriate prevention strategies, severe exacerbations occur, even in patients with mild disease or well-controlled asthma [1, 144]. Therefore, proper assessment and adequate intervention are crucial to stabilize asthma and alleviate symptoms. Although in recent years there has been ample research into the treatment of stable asthma and several new drugs and formulations have been marketed, so far a limited number of treatments are available for asthma exacerbations while limited evidence exists in support of their use [145].

For patients presenting with acute asthma to primary care or emergency department (ED), the TF members consider that a proper assessment of exacerbation severity is determined based on history, physical examination and objective measurements of lung function and oxygen saturation [146] (**Figure 2**). Arterial blood gas measurements and chest X-ray are not included in the guidelines dedicated to the initial assessment, nevertheless they are performed by all the TF members for patients with severe exacerbations and for those who do not respond to initial treatment or are deteriorating [147–149].

Information from patients' history can identify those who are at increased risk of worst outcome and asthma-related death and prompt arrangements to be made for more frequent evaluation and aggressive treatment (**Table 2**).

Treatment is usually started immediately and simultaneously with the initial evaluation of the patient. The following treatments are usually administered concurrently to achieve the most rapid resolution of the exacerbation and prevent patient deterioration.

Figure 2: Assessment of exacerbation severity based physical signs and objective measurements (adapted from GINA [1])



Oxygen

Oxygen is usually delivered by nasal cannula or Venturi mask in order to achieve arterial oxygen saturation of 93–98%. In severe exacerbations, high concentration oxygen increases the risk of hypercapnia while controlled low flow oxygen therapy is associated with better outcomes [150–152].

Short-acting β_2-agonists ~~b2-agonists~~ (SABA)

SABAs intend to resolve bronchospasm and to relieve acute symptoms of asthma, and are usually initially administered every 15 to 20 minutes for the first hour during an acute asthma exacerbation. Comparison of pMDI-spacer and nebulizer has shown increased efficiency of SABA delivery via pMDI-spacer and equivalent clinical outcomes [153, 154]. Data are conflicting whether continuous nebulization with a SABA is superior to intermittent

nebulization [155, 156]. In severe asthma exacerbations, continuous nebulization may be preferred, based on evidence of reduced admissions and improved pulmonary function [155, 157]. There is no evidence to support the routine use of intravenous β_2-agonists ~~beta2-agonists~~ in patients with severe asthma exacerbations [158].

Ipratropium bromide

Adding ipratropium bromide to SABA decreases rates of hospitalizations and shortens ED stays for patients with severe asthma exacerbations [159–161]. Some evidence shows that the use of combination ipratropium/β~~eta~~-agonist therapy in acute asthmatic exacerbations provides benefit without increased risk of adverse events [161].

Corticosteroids

Early administration of systemic corticosteroids for the treatment of asthma exacerbations is considered a standard of care and is recommended worldwide to be given to the patient within 1 hour of presentation [162, 163]. A systematic review showed that the use of systemic corticosteroids reduces the rate of hospital admission in ED settings, especially in patients with severe asthma and those not currently receiving corticosteroids [164].

The optimal dose for systemic corticosteroids in asthma exacerbations remains to be established. Doses above 2 mg/kg or 60-80 mg/day do not add benefit to improving lung function, rates of hospital admission or length of hospital stay [162, 165]. Furthermore, no differences are found between oral and intravenous administration of comparable corticosteroid doses [166, 167]. Thus, daily doses of OCS equivalent to 50 mg prednisolone as a single morning dose, or 200 mg hydrocortisone in divided doses, are adequate for most patients [1]. A short course of 5 days OCS after ED treatment of acute asthma exacerbations

has been shown to reduce the rate of relapse [1, 164]. Courses longer than 5 days or a dose tapering did not provide additional benefit while increased side effects [168, 169].

The role of ICS in the management of asthma in the emergency department remain unclear and their use in severe asthma exacerbations is not evenly adopted [170].

Other treatments

None of the TF members use intravenous aminophylline and theophylline in the management of asthma exacerbations, in view of their poor efficacy and safety profile [1]. Intravenous magnesium sulphate (given as a single 2g infusion over 20 minutes) has been shown to reduce hospital admissions in severe exacerbations and in patients who fail to respond to initial treatment [171, 172]. Evidence does not support a role of antibiotics in asthma exacerbations unless there is strong presumption of lung infection [1, 173]. Other associated advices of management (hydration, physiotherapy, avoid exercise, etc.) are poorly evidenced [174]. Noteworthy, exercise outside an episode of exacerbation should be largely supported as it was shown to prevent exacerbations and to improve control [175].

5. PREVENTION

Here we describe the evidence for current therapies available across the severity spectrum of asthma, licensed biologics and those in phase 3 clinical development.

Current small molecule asthma therapies

Corticosteroids

Extensive data support the role of inhaled corticosteroids in asthma with increasing dose reducing exacerbation frequency [1, 176, 177]. Increasing the ICS dose four-fold at the onset of exacerbation symptoms reduced the need for systemic corticosteroids by 19% [178]. No randomized controlled trials exist of prednisolone versus placebo as add-on therapy in severe asthma [179]. Registry data suggested that maintenance oral corticosteroid use was associated with reduced exacerbations among a cohort of severe asthmatics [180]. In a small study, high-dose intramuscular triamcinolone reduced hospital admissions and emergency department attendances; however, the long-term side effect profiles of systemic steroids have to be taken in mind. TF members use maintenance OCS as a therapeutic strategy for reducing exacerbations as a less preferred option and suggest this practice be supervised in expert referral centers familiar with the management and prevention of OCS side effects [181].

Presence of eosinophilic inflammation predicts a good response to corticosteroids in airways disease [182–184]. Tailoring corticosteroid dose to control sputum eosinophilia in asthma has achieved marked reductions in exacerbation rates [16, 18, 185] and the ERS/ATS guideline advocates measurement of eosinophilic inflammation in severe asthma [3].

Given the superiority of an on-demand ICS-containing regimen in two separate trials performed in patients with mild asthma in reducing the risk of exacerbation [186, 187], later confirmed in a real-life setting [188], the last GINA update promotes this strategy as early as

step 1, acknowledging the obvious inflammatory nature of the disease and in particular during episodes of poor control that precedes exacerbation.

The management of asthma using a sputum-guided adjustment of the daily dose of ICS was shown efficient to prevent exacerbations in expert centers where induced sputum cytology can be assessed routinely, in patients able to provide an adequate sample within the safety margins of induction [16, 18].

Long Acting Beta-Agonists (LABA) added to ICS

ICS-LABA combination therapy is standard in severe asthma and the addition of a LABA to ICS reduces exacerbation frequency in asthma [1, 176, 177]. The TF echoed recurrent warnings regarding monotherapy with LABA in asthma [189].

Long Acting Muscarinic Antagonists (LAMA) added to ICS

Tiotropium, as add-on therapy for asthmatics uncontrolled while treated with ICS and LABA, increased time to first exacerbation by 56 days versus placebo (P=0.03) [190]. A Cochrane review of LAMA added to ICS vs ICS alone across all severities of asthma showed a reduction in exacerbations requiring oral corticosteroids, and a trend towards reduction in hospital admissions [191].

Leukotriene Receptor Antagonists (LTRA)

A systematic review of LTRAs identified a significant reduction in exacerbations when used as monotherapy compared to placebo, but no effect on exacerbation rates when used in patients already taking inhaled corticosteroids [192]. Whether LTRAs reduce severe exacerbations in severe asthmatics is unknown.

Theophylline

A study comparing ICS/LABA and theophylline vs ICS/LABA and placebo found a significant reduction in severe exacerbations in the theophylline group in asthmatics who were treatment naïve [193]. Whether theophylline affects exacerbation frequency in severe asthma is unknown. Most TF members do not use theophylline as an add-on therapy for preventing exacerbations.

Antimicrobials

In a large clinical trial thrice-weekly azithromycin in moderate-to-severe asthma resulted in a 41% reduction in severe exacerbations with benefits independent of inflammatory phenotype [194], in contrast to a previous sub-analysis in severe asthmatic patients where the benefits were limited to the non-eosinophilic subgroup [195]. Of note, worldwide, azithromycin is not approved to the best of knowledge in this indication. Anti-fungal agents in fungal-sensitized severe asthma not meeting criteria for allergic bronchopulmonary aspergillosis demonstrated no impact on severe exacerbations [196].

Immunosuppressants

Data reporting exacerbations was limited in a Cochrane review examining the corticosteroid sparing effect of cyclosporin in severe oral corticosteroid dependent asthma [197]. A similar review examining the corticosteroid sparing effects of methotrexate in severe asthma did not demonstrate a beneficial effect on exacerbation rates [198].

Allergen avoidance and immunotherapy

Allergen avoidance advice is standard clinical practice in severe asthma [1, 176, 177], but allergen avoidance has shown controversial benefit [199] possibly due to difficulty in achieving this effectively. Allergen immunotherapy (AIT) strategies in asthma report some benefit for

reducing symptoms and corticosteroid usage but have not been tested in severe asthma [200]. It is unknown whether measures such as nocturnal temperature controlled laminar flow will be effective. Reductions in airway inflammation are reported in atopic asthma [201] and studies in severe asthma are ongoing [202].

Current biologics for asthma (Table 4)

The phase 3 RCTs for currently available biological therapy in asthma, except for anti-IgE as more established, are summarized in Table 4, including phase 2b studies that were considered pivotal for registration. Studies in less severe asthma with a very low event rate, open-label extensions that confirmed earlier findings and studies that did not report exacerbations were not included.

Anti-IgE: Omalizumab

A Cochrane review of omalizumab as add-on therapy in moderate-to-severe asthma reported a reduction (odds ratio (OR) 0.55, 95% confidence interval (CI) 0.42 to 0.60; ten studies, 3261 participants) in severe exacerbations [203], however subgroup analysis of severe asthma alone did not demonstrate a clear benefit. Further clinical trials remain ongoing [201].

Anti-IL5: Mepolizumab and Reslizumab

Mepolizumab reduces exacerbation frequency by ~50% [5, 65, 204–206] and reduces the requirement for maintenance oral corticosteroid [206]. Benefits were observed in severe asthmatics with blood eosinophils >150cells/μL [207], with greatest exacerbation frequency reductions seen with increasing eosinophilic inflammation. These beneficial effects were not sustained over the 12 months following treatment withdrawal [208] while it was the case when treatment was maintained [209]. This exacerbation rate reduction was also achieved while

tapering OCS in long term OCS users[210]. Reslizumab demonstrated a reduction in severe exacerbations in severe asthmatics with a baseline blood eosinophil count >400 cells/μL [211]. Improvements were greatest in those with GINA step 5 disease [212].

Anti-IL5R: Benralizumab

Benralizumab reduces severe exacerbations [64, 213, 214] in those with a blood eosinophil count >300 cells/μL. A priori sub-analyses using an eosinophil cut off of 150 cells/μL also demonstrated significant reductions in exacerbation rates [215], although higher blood eosinophils and more frequent exacerbations predicted greater benefits [216]. This exacerbation rate reduction was also achieved while tapering OCS in long term OCS users [214]. A study of benralizumab administered in the setting of acute asthma exacerbation [66] reported a positive impact on recovery rates, however further work would be required to define the use of biologics in this setting.

Bronchial Thermoplasty

In 190 subjects who received bronchial thermoplasty (BT) versus 98 who underwent sham procedures severe exacerbations were reduced by 32% in the 3-12 months post therapy with an increase in exacerbation events in the peri-procedure period [21]. This reduction in exacerbations was maintained over a 5 year follow up period [217]. BT is currently performed only in trained centers for both managing severe asthma and handling BT.

Emerging biologics

Anti-IL4R: Dupilumab

Dupilumab reduced severe exacerbations in all-comers irrespectively of the atopic status, with the greatest reduction in those with elevated FeNO and/or eosinophilic inflammation, and

reduced oral corticosteroid requirement for severe asthmatics receiving maintenance oral corticosteroids [68, 218, 219]. Studies of IL4 inhibition alone and more recently of the anti-IL13 biologics lebrikizumab [220] and tralokinumab [221] have failed to meet their primary endpoints of exacerbation reduction, suggesting that inhibition of both IL-4 and 13, as with anti-IL4R, is necessary to observe sufficient clinical efficacy for this aspect of the disease.

Anti-TSLP: Tezepelumab

A recent phase II trial investigated the impact of tezepelumab on exacerbation rates in 584 moderate-to-severe asthmatics, showing a 60-70% reduction in exacerbations in all-comers across dosing regimens [222]. Effects were observed irrespective of markers of T2 inflammation, although substantial reductions in these measures were noted, suggesting that targeting upstream cytokine pathways may reduce exacerbations across inflammatory profiles.

CRTH2 antagonists, anti IL17 and others

ILC2 are now seen as the pivotal cells ofT2 airway inflammation. Because they specifically express the PGD2 receptor DP2 or CRTH2, a proof of concept study showed that anti-DP2 treatment could significantly reduce the blood eosinophil count [223]. Whether this will be sufficient for preventing exacerbations is the aim of a larger ongoing phase III trial.

The IL33-ST2 axis is also specifically targeting ILC2 [224] and pivotal studies are ongoing. In non T2 asthma, the relevance of blocking IL17 for preventing exacerbations is also currently being tested [225].

Conclusion

Reduction and ultimately elimination of severe exacerbations in severe asthma remains an important therapeutic target. In addition to corticosteroids and allergen avoidance/immunotherapy, the biologics targeting T2-immunity and eosinophilic inflammation (anti-IgE, IL-5, IL-4R and TSLP) reduce exacerbations. Whether other therapies that reduce eosinophilic inflammation such as anti-DP2, will demonstrate a similar efficacy remains to be determined. Beyond T2 inflammation, macrolide antibiotics and bronchial thermoplasty may have a role, but reducing severe exacerbations in non-T2 severe asthma remains an unmet need, although the scale of its importance once T2-mediated disease is adequately treated is uncertain.

5. CONCLUSION AND BULLET POINTS FROM THE ELF

Preventing severe exacerbations in asthma is very important from the perspective of people with asthma. Too many patients still die, whereas these deaths are likely preventable, from a severe exacerbation. In some countries asthma and respiratory deaths are still increasing, especially in non-severe and moderate asthma [84]. Why this is happening still needs to be explored but facilitating access to care and medications would probably be efficient.

- In all types of asthma: It is important to remain aware that severe exacerbations don't just happen in patients with the more severe types of asthma.
- Exacerbations and especially recurrent exacerbations are very debilitating for patients. More research is needed to avoid exacerbations and to break the cycle of recurrent exacerbations. The medications and treatments plans that are available at this time do not seem to be working well enough for all patients.
- Adherence: patients and physicians need to work together on improving adherence. Good communication between physician and patient is key. There are many factors that impede adherence for patients. Some straight-forward ways to support patients can be

implemented easily like having dose-counters on all inhalators. It can be more challenging to address patients developing additional behavior. All aspects require continuous positive attention from physicians.

- Indoor and outdoor environmental factors: the advice to avoid environmental factors is an additional burden moreover because it is extremely complex to put into practice for patients. More and better advice needs to be given to patients on living conditions, occupational choices etc.
- Working together with patients in improving their asthma care is key. Many patients have good knowledge on their asthma and their reaction to medications. Not all patients have this insight and not all patients are able to manage their asthma on a daily basis. We all need personalized help. E-health can support some patients, but only if these solutions are developed with patients and are sufficiently flexible and personalized.

Research needs and knowledge caps identified throughout this task force are summarized table 5.

Table 4: Pivotal Phase 3 randomised clinical trials of licensed biologics (excluding anti-IgE)

Intervention	Reference	Population	Description of intervention/ duration	Effect on exacerbations
Mepolizumab Anti-IL5	MUSCA [205]	Adults and children (>12 years), n = 556 ≥2 exacerbations in last year Blood eosinophils ≥300/µl in last 12 months or ≥150/µl at screening	100mg SC Q4W 24 weeks	↓ exacerbation rate 42% ↓ exacerbations requiring emergency department (ED) visit or hospitalization 32% No significant change in hospitalizations alone
	SIRIUS [226]	Adults (16 – 74 years), n = 135 Background therapy 5 to 35 mg/day of prednisone or its equivalent for > 6 months Blood eosinophil count ≥150 cells/µL at screening or ≥300 cells/µL in the last year	100mg SC Q4W 20 weeks	↓ exacerbation rate 32% OR for glucocorticoid reduction 2.39 in mepolizumab group (0.008) Median glucocorticoid reduction 50% (vs 0% in controls)
	MENSA [5]	Adults and children (aged ≥12 years), n = 576 ≥2 exacerbations in last year Blood eosinophil count ≥150 cells/µL at screening or ≥300 cells/µL in the last year	75mg IV Q4W or 100mg SC Q4W 32 weeks	↓ exacerbation rate 47 - 53% SC mepolizumab ↓ exacerbations requiring ED/hospitalization (61%) and exacerbations requiring hospitalization (69%) ↓ systemic glucocorticoid exposure 41%
	Pavord Lancet 2012 [53] (Phase 2b/3)	Adults and children (12 – 74 years), n = 621 ≥2 exacerbations in last year Sputum eosinophils ≥ 3%, FeNO ≥ 50 ppb, blood eosinophil count ≥ 300 cells/µL or deterioration in asthma control with ≤ 25% reduction in corticosteroid treatment (in the last year)	75mg IV Q4W or 250mg IV Q4W or 750mg IV Q4W 52 weeks	↓ exacerbations 39 - 52% Exacerbations requiring ED/hospitalization reduced across all groups Greatest reduction in exacerbations with baseline eosinophils > 500 cells/µL
Reslizumab Anti-IL-5	Castro [211]	Adults and children (12 – 75 years), n = 953 (study 1 n=489, study 2 n=464) ≥1 exacerbation in last year Blood eosinophil count ≥400 cells/µL	3mg/kg IV Q4W 52 weeks	↓ exacerbation rate 54% ↓ exacerbations requiring OCS 57% ↓ exacerbations in those on OCS at baseline by 68% Exacerbations ↓ 64% if ≥4 exacerbations in last 12 months at baseline (vs. ↓ 32% if 1 exacerbation last 12 months)
Benralizumab Anti-IL-5R	ZONDA [214]	Adults (18 – 75 years), n = 220 Background therapy (7.5 – 40mg/day prednisolone or its equivalent for > 6 months) Blood eosinophils ≥150 cells/µL at screening	30mg SC Q4W or Q8W 28 weeks	↓ exacerbation rate 55 - 70% Q8W Q8W dosing reduced exacerbations associated with ED visit or hospitalization by 93% OR for glucocorticoid reduction 4.1 Median glucocorticoid reduction 75% (vs 25% in controls)
	SIROCCO [64]	Adults and children (12 – 75 years), n = 1205 ≥2 exacerbations in last year	30mg SC Q4W or Q8W 48 weeks	Eosinophil High (≥300 cells per µL): ↓ exacerbations 45 - 51% Q8W dosing reduced exacerbations associated with ED visit or hospitalization by 68%

	CALIMA [213]	As per SIROCCO, n = 306	30mg SC Q4W or Q8W 56 weeks	Eosinophil High ↓ exacerbations 28 - 36% No effect on hospitalizations/ED visits
Dupilumab Anti-IL4Rα	Castro NEJM 2018 QUEST [68]	Adults and children (≥12 years), n = 1902 ≥ 1 exacerbation in last year	200mg SC Q2W or 300mg SC Q2W 52 weeks	↓ severe exacerbations 46% across treatment population ≥150 eosinophils/μL: ↓ exacerbations 60% ≥300 eosinophils/μL: ↓ exacerbations 67%
	VENTURE [69]	Adults and children (≥12 years), n = 210 Background therapy (5 – 35mg/day prednisolone or equivalent for > 6 months)	300mg SC Q2W 24 weeks	↓ severe exacerbations 59% across treatment populations ≥150 eosinophils/μL: ↓ exacerbations 58% ≥300 eosinophils/μL: ↓ exacerbations 71% Median glucocorticoid reduction 100% (vs 50% in controls)

Table 5. Research needs and knowledge gaps

Item	Research needs	Type of study design	Type of outcomes that need to be assessed
Definition of severe exacerbation ~~of asthma~~	To assess in routine practice~~,~~ what is the most sensitive and specific definition (duration of OCS requirement, daily dose and cumulative dose)	Re-analysis of RCT and real-life trials where diaries and home monitoring were used Registries and cohorts	Rates of OCS bursts ≥ 5d, ED, admissions, need for ICU
Definition of severe exacerbation	To assess prediction models in real life cohorts~~Whether prediction model would work in real life~~	Re-analysis of RCT and real-life trials where diaries and home monitoring were used Registries and cohorts	Rates of OCS bursts ≥ 5d, ED, admissions, need for ICU
Definition of severe exacerbation	To ~~E~~establish composite scores to assess immediate risk	Retrospective analysis of databases of exacerbations	Short term outcomes: admission, ICU, intubation, deaths, treatment related adverse events
Strategy	To assess the impact of self-monitoring on asthma control and prevention of exacerbations~~Self monitoring of asthma control can prevent exacerbation ?~~	Randomised controlled trials comparing conventional vs self-monitoring strategy	Rates of OCS bursts ≥ 5d, ED, admissions, need for ICU
Strategy	To assess the effectiveness of interventions to prevent human rhinovirus carriage~~Prevent human rhinovirus carriage ?~~	Randomised controlled trials comparing strategies	Rates of OCS bursts ≥ 5d, ED, admissions, need for ICU
Risk factor/trigger	~~What~~ To assess~~is~~ the weight of blood eosinophilia ~~when~~ compared to other risk factors at the individual level	Prospective cohort studies integrating all risk factors	Rates of OCS bursts ≥ 5d, ED, admissions, need for ICU
Risk factor/trigger	~~Is there a place for~~To assess the benefits and risks of genetic analysis awareness at the individual level to predict severe exacerbation and asthma trajectory	Test acceptability RCT comparing strategies of management in patients with known at-risk allele carriage vs routine	Severe exacerbation rates in patients and relatives, in particular in children with high risk scores (familial risk, patients already admitted in ICU)

Risk factor/trigger	~~What~~ To more accurately know~~s~~ the mechanisms, rate and risk factors of ~~non-preventable~~ death~~s~~ attributable to severe exacerbations that occurred despite an optimal preventive strategy and acute management	Multiple exhaustive reviews of asthma deaths. Worldwide collection of cases where death occurred despite optimal management	Biology, pathology
Risk factor/trigger	To ~~l~~identify and weight all risk factors associated with death, ICU, ED and frequent exacerbations	Cohorts and registries of compelling cases	Rates of OCS bursts ≥ 5d, ED, admissions, need for ICU
Risk factor/trigger	To ~~l~~identify tools for assessing/improving adherence	RCT comparing strategies	Rates of OCS bursts ≥ 5d, ED, admissions, need for ICU
Risk factor/trigger	To a~~A~~ssess the benefits of eHealth-connected devices to prevent severe exacerbation	RCT comparing strategies	Rates of OCS bursts ≥ 5d, ED, admissions, need for ICU
Risk factor/trigger	to assess tools / resources / methods (e.g. shared decision making, systematic multidisciplinary approaches, referral to asthma centres) to improve patient-HCP partnership~~Improve patient-HCP partnership~~	Studies assessing changes in patient-HCP partnership through training, education programs, etc.	Parallel studies associating changes in patient-HCP partnership with changes in severe exacerbation rates
Risk factor/trigger	To A~~a~~ssess the benefits of using air quality sensors	RCT in selected populations	Rates of OCS bursts ≥ 5d, ED, admissions, need for ICU
Risk factor/trigger	To assess the benefits of more accurately evidence the ~~R~~role of occupational triggers	Basic science, models, psycho and sociology	Rooms of exposition with inflammatory / lung function monitoring HRQOL
Risk factor/trigger	To assess the preventive benefits of convincingly ~~S~~support patient when choosing careers	Prospective cohorts with randomized strategies	In teenagers/young adults and in people changing of occupation

Risk factor/trigger	To assess the exact role of drugs in severe ~~E~~exacerbations.(incidence, dose, diagnosis, prevention) ~~induced by drugs (BB, NSAID)~~	Prospective cohorts with randomized strategies. Models of exposition in animals and cell models	Prospective recording of severe exacerbation. Maximal documentation of each event.
Treatment of severe exacerbation	To define the ~~V~~value of CXR and arterial blood gases in acute management	Randomized controlled trials	Dedicated populations such as ED attending
Treatment of severe exacerbation	To establish an ~~O~~optimal scheme for SABA administration	Randomized controlled trials comparing different strategies of SABA administration (dose, route, frequency, duration, associated treatment)	Rates of OCS bursts ≥ 5d, ED discharge vs admissions, need for ICU, adverse events
Treatment of severe exacerbation	To assess the ~~R~~role of ICS during the exacerbation and at discharge	Randomized controlled trials	Rates of relapses, spred of recovery, adverse events
Treatment of severe exacerbation	To assess ~~What are~~ the benefits of hydration, physiotherapy, exercise avoidance during exacerbation; optimal time to go back to exercise	Randomized controlled trials, comparative studies	Rates of relapses, speed of recovery, adverse events, quality of life
Prevention	~~Whether~~ To assess whether LTRAs add-on reduce severe exacerbations in severe asthmatics ~~is unknown~~	Randomized controlled trials	Rates of OCS bursts ≥ 5d, ED discharge vs admissions, need for ICU, adverse events
Prevention	~~whether~~ To assess the benefits of measures such as nocturnal temperature controlled laminar flow ~~will be effective~~	Randomized controlled trials	Rates of OCS bursts ≥ 5d, ED discharge vs admissions, need for ICU, adverse events
Prevention	~~further work would be required~~ to ~~define~~ assess the use of biologics in the setting of acute exacerbation	Randomized controlled trials	Rates of relapses, speed of recovery, disease associated and hospital acquired-adverse events, quality of life

From the patients' perspective	Overall, to find treatments for patients not responding well to currently available medications and treatments plans ~~that are available at this time do not seem to be working well enough for all patients~~	Randomized controlled trials in non eligible patients to existing drugs (low T2, failure of currently available biologics for example)	Rates of OCS bursts ≥ 5d, ED discharge vs admissions, need for ICU, adverse events

Table 6.

Section no	Section title	Keypoints
1	**Definitions**	A definition based on five days of OCS is preferred to three to better fit with the recognized harmfulness of cumulative doses of OCS; a composite score assessing risk factors (age, comorbidities, history) would be helpful.
2	**Triggers and risk factors**	Within trajectories of asthma, the frequent exacerbator phenotype is a reality, and is more frequently associated with a T2 pattern
2A	*Assessment of risk, What is cause and what is effect*	T2 inflammation and lack of adequate treatment more likely exposes to exacerbation rather than the opposite.
2B	*Modifiable vs non-modifiable factors & Mathematical models*	Viral infections are now considered modifiable, associated with prevention of noxious environmental exposures.
2C	*Risk Factors and epidemiology, pheno/geno/endotypes*	Susceptibility to severe exacerbations is not always shared with susceptibility to asthma severity. Low T2 asthma and other newly identified endotypes are currently orphans of targeted drugs.
2D	*Personality type – Gender, Psychosocial factors. Perception, Compliance/adherence*	Multidisciplinary approaches may help in identifying and managing better patients at risk of death, ICU admission and severe exacerbations
2E	*Virus / Allergens*	Rhinoviruses are ideal culprit fostering severity of exacerbations amplifyable by allergens. No dedicated treatment or preventive strategy currently exist.
2F	*Environmental air pollution indoor/outdoor pollution & occupational factors*	Although obvious, the environmental impact is under-recognized and occupational factors insufficiently assessed and evidenced in practice.
2G	*Drugs & irritants / Overdose of β_2-agonists*	Dangers of high SABA use includes worsening of asthma itself.
3	**Acute Management**	Systemic corticosteroids and bronchodilators are still the cornerstones of the acute management. Because some asthma deaths are not preventable, there is a place to develop new drugs on top of standard of care
4	**Prevention**	Inhaled corticosteroids +/- bronchodilators and in eligible patients with more severe disease biologics prevent severe exacerbations.

5	**ELF Patient perspective**	The currently available treatments and supports are not working well enough for all. More research and partnership are needed.

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ERS/EAACI Statement on severe exacerbations in asthma in adult: facts, priorities and key research questions

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TASK-FORCE Sections and Members

Section no	Section title	Participants
1	**Definitions**	M. Gaga (leader), K. Samitas
2	**Triggers and risk factors**	A. Bourdin (leader)
2A	*Assessment of risk, What is cause and what is effect*	A. Bourdin
2B	*Modifiable vs non-modifiable factors & Mathematical models*	F. Chung
2C	*Risk Factors and epidemiology, pheno/geno/endotypes*	I. Horvath
2D	*Personality type – Gender, Psychosocial factors. Perception, Compliance/adherence*	L. Bjermer, F. Kanniess
2E	*Virus / Allergens*	Z. Diamant, S. Johnston, R. Djukanovic
2F	*Environmental air pollution indoor/outdoor pollution & occupational factors*	G. Brusselle, A. Papi
2G	*Drugs & irritants / Overdose of β_2-agonists*	P. Chanez
2H	*Interaction between different trigger factors*	N. Papadopoulos
3	**Acute Management**	E. Zervas (leader)
4	**Prevention**	C. Brightling (leader), Dermot Ryan, Richard Russell and Sarah Diver
5	**ELF Patient perspective**	D. Hamerlijnck, ELP Patient Advisory Group
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Summary

Despite the use of effective medications to control asthma, severe exacerbations in asthma are still a major health risk and require urgent action on the part of the patient and physician to prevent a serious outcome such as hospitalization or death. Moreover, severe exacerbations are associated with substantial huge healthcare costs, and psychological burden including anxiety and fear for patients and their families. The European Academy of Allergy and Clinical Immunology (EAACI) and the European Respiratory Society (ERS) set up a Task Force (TF) to search for a clear definition of severe exacerbations and to also define research questions and priorities. The statement includes comments from patients who were members of the TF.

1. INTRODUCTION

Asthma is one of the most common chronic diseases and its worldwide prevalence has risen around 3-fold in recent decades [1]. With the recognition of the inflammatory nature of the disease and the introduction of inhaled corticosteroidinhaled corticosteroids, asthma control and the quality of life of asthma patients have substantially improved and many deaths have been prevented. Nevertheless, patients still face exacerbations of varying severity ranging from increased symptoms to life-threatening episodes. And any asthmatic patient may suffer severe exacerbation and even die from one. In fact, most exacerbations present in mild asthmatics, who are the majority of asthma sufferers [2, 3]. The causes leading to exacerbations may be exposure to a triggering agent, lack of or adherence to treatment, the inherent severity and hyperresponsiveness of the disease and may be affected by comorbidities. Severe exacerbations of asthma likely carry most of the burden of the disease through their immediate and delayed-associated risks. Severe exacerbations are exposing patients to immediate and delayed side effects of high doses of bronchodilators and systemic corticosteroids, and quite often to antibiotics. Absenteeism, presenteeism, care-associated risks if admitted (nosocomial infection for example), anxiety and many other issues are insufficiently describing the burden of severe exacerbations. Epidemiological data remain heterogenous as very different definitions are used in cohorts and in clinical trials. For example, in TENOR II, 25.8% of the population reported a severe exacerbation [4]. In the MENSA study, among enrolled patients who reported 3.5 ± 2.2 exacerbations before entering the study, 17 to 21% were admitted. During the trial, the mean rate of clinically significant exacerbation and exacerbation requiring admission fell to 1.74 and 0.10 respectively [5]. Unfortunately, asthma deaths still exist. Their rates are low and most of them are seen as preventable [6, 7] in westernized countries. This also implies that

some are not preventable, suggesting a place for new drugs to treat refractory episodes of near fatal asthma.

Accordingly, both the ERS and the EAACI elicited a task force in 2016 that aims to review the most relevant research evidence and the current practice on definition, clinical identification of severe exacerbations, triggers and risk factors, management and prevention. Subsequently, this document does not contain recommendations for clinical practice but offers recommendations for future research.

Methodology

After the initial meetings the Task Force members decided to address four main research questions related to serious exacerbations: 1) what are the available definitions for severe exacerbations in asthmatics and what would be an accurate definition, 2) which are the trigger factors related to the initiation and severity of exacerbations, 3) what is the best way to manage severe exacerbations 4) and finally what is the best strategy to prevent them. Specific keywords and MeSH-terms were identified based on several key-references provided by the Task Force members, and the corresponding literature search was initiated for all sections using the MEDLINE and CENTRAL (Cochrane Library) Databases. Search results were extracted in .txt file formats and imported in a specially designed reference management software (Reference Manager Version 12) in order to screen for duplicates. Further processing of the search results was made in a step-wise approach (as shown in the supplementary file flow-charts) based on the title, the abstract, and finally after reading the whole text, filtering for date (2000 and onwards), age (adults only), language (only English), and type (included: randomized and observational studies and systematic reviews/meta-analyses, excluded: case reports and letters to the editor). All articles remaining after final processing for each section were sent back to the corresponding TF members for final evaluation (corresponding flow charts are available as

a supplementary file). From this sorting of the relevant literature, leaders of the four sections drafted a first version and each statement was kept or removed if any concern was expressed and no consensus could be found. During the subsequent dedicated meetings, research needs were identified and tables and figures were reviewed.

2. Definition of severe exacerbations of asthma

Asthma severity and control have more or less been defined and graded over the years so that the definitions are equally understood by all stakeholders [3, 8–10]. This is not yet the case for asthma exacerbations where exacerbations are defined as episodes characterized by more or less rapid increase in symptoms, sufficient to require a change in treatment [3, 11]. Severe exacerbations are usually defined based on use of systemic, usually oral corticosteroids (OCS), emergency care visits and/or hospitalizations [1], while in some clinical studies reductions in lung function (peak expiratory flow [PEF] or forced expiratory volume in one second [FEV1]) of more than 20 or 30% have also been included in the definition. (Table 1) It must be noted that patient perception and easy access to rescue corticosteroids and emergency care facilities may confound the definition and so may the retrospective collection of data. The ERS/ATS statement on exacerbations released in 2009 [12] defines severe exacerbations as events that require urgent action on the part of the patient and physician to prevent a serious outcome, i.e. hospitalization or death. However, there is subjectivity in the perception of severity and moreover, many studies have shown that the risk of severe exacerbation is associated with a multitude of factors. These factors include (1) the level of asthma control, (2) asthma severity based on ERS/ATS definition [3], (3) lung function, (4) the presence of comorbidities, (5) the psychosocial status (to assess the ability to seek help in case of clinical worsening), (6) previous history of near fatal attacks and (7) response to treatment. Such factors seem important to guide treatment decisions and, importantly, decisions regarding hospitalizations. Moreover, prediction models assessing future risk of exacerbations in adult asthma patients have been proposed, such as the one published by Miller et al, based on the TENOR cohort [13]. However, the applicability of such models has not been examined in large studies and needs to be assessed prospectively. Composite scores have been developed for use in other acute

respiratory conditions, for example the CURB-65 or PSI score for pneumonia or GENEVA score for pulmonary embolism, and they greatly help clinicians in treatment decisions and are important for the safety of the patients. All TF members in their practice consider severe exacerbations of asthma as a significant worsening of the disease that require OCS treatment for at least 5 days. In the ERS/ATS task force in 2009, a three-day course of OCS was the recommended definition for clinical trials. This small difference was supported by all TF members as it may differentiate from patients with episodes of loss of control requiring short courses (e.g. 1-2 days) of OCS and from temporary increase of maintenance treatment to improve the control of their disease. These patients may have an accumulated use of OCS over time equivalent to someone with repeated exacerbations but will not be reported as such. Whether 3 or 5 days of OCS is more accurate for discriminating a mild from a severe exacerbation will probably not be addressable in terms of evidence. 1) Herein we report an expert-based opinion that definitely not intends to change the definition used in trials in order to keep them comparable and 2) as the harmfulness of cumulative doses of corticosteroids is obvious above 0.5 g per year [14], a five-days based definition would make better fit this OCS-associated risk with the threshold of two exacerbations. Although variable among countries and systems, emergency visit or hospitalization, the TF members base hospitalization or initiation of treatment with OCS on the GINA or BTS recommendations to improve standardization. It seems that it would be important to develop, test and use a composite score that takes into consideration the patient's previous health status, the presence of comorbidities, history of severe or near fatal exacerbations, adherence to treatment, psychosocial status, level of control and of course, response to treatment-the latter is already factored into asthma exacerbation management guidelines- rather than just clinical severity at presentation and PEF or spirometry values.

TABLE 1: Examples of definitions of severe exacerbation in asthma patients used in the literature.

Author	Definition of severe exacerbation	Comment
GINA 2019 [1]	Exacerbations of asthma are episodes characterized by a progressive increase in symptoms of shortness of breath, cough, wheezing or chest tightness and progressive decrease in lung function, i.e. they represent a change from the patient's usual status that is sufficient to require a change in treatment. Definition based on symptoms ("talks in words, sits hunched forward, agitated"), clinical findings (RR>30/min, BPM>120/min, SAT<90%, use of accessory muscles) and lung function (PEF< 50% pref.)	GINA proposes an accurate definition of exacerbations of asthma. Regarding severe exacerbations, GINA does not define exact criteria by which to distinguish severity levels
Reddel et al (ERS/ATS 2009) [12]	Severe asthma exacerbations are defined as events that require urgent action on the part of the patient and physician to prevent a serious outcome, such as hospitalization or death from asthma. The definition should include at least 1 of the following: a. Use of systemic corticosteroids or an increase from a stable maintenance dose, for at least 3 days. b. A hospitalization or emergency department (ED) visit because of asthma, requiring systemic corticosteroids	Strength: This is the most commonly used definition Weakness: it relies on patient and doctor subjective assessment, there are no hard criteria for deterioration
Custovic et al (EAACI 2013)[9]	No specific definition provided	Strength: The taskforce stresses the need for a consensus definition of asthma exacerbation that could usefully guide treatment. Weakness: It is not really a definition
O'Byrne et al 2009 [15]	Defined as events requiring hospitalization or emergency treatment due to worsening of asthma, or death due to asthma.	Strengths and weaknesses same as those of Ref [12] (ERS/ATS 2009)

	Emergency treatment was defined as treatment of acute airway obstruction with systemic corticosteroids and nebulized or parenteral bronchodilators given at a healthcare institution.	
Green et al [16], Pauwels et al (FACET study) [17]	Decrease in morning PEF >30% on 2 or more consecutive days, or deterioration in symptoms needing OCS	Strengths: Adds an objective limit in addition to the need for OCS or the vague "deterioration" Weakness: 30% decrease is not universally severe, no reference to length of time
Jayaram et al 2006 [18]	Course of OCS as determined by study investigator	Weakness: No objective criteria given ('determined by study investigator')
Demoly P 2004 [19]	Hospitalization was unanimously recognized as the first criterion for severe exacerbations. A decrease in peak expiratory flow of more than 30% below the baseline value on two consecutive days and an episode requiring systemic corticosteroids were the next criteria. This survey emphasizes the complexity of the notions of asthma control and exacerbation	Strengths: This survey emphasizes the complexity of the notions of asthma control and exacerbation and reflects real life practice. Uses an objective measure and length of time Weakness: No hard criteria
Fuhlbrigge 2013 (NIH workshop) [20]	An exacerbation is a worsening of asthma requiring the use of systemic corticosteroids (or for patients on a stable maintenance dose, an increase in the use of systemic corticosteroids) to prevent a serious outcome (The subcommittee does not endorse severity stratification in the core outcome definition)	Strengths and weaknesses same as ref [12]. Addition: increase in use of systemic steroid dose in patients already on steroids
Castro et al 2010 [21]	Those requiring systemic corticosteroids or doubling of ICS dose	Weakness: No criteria given for 'requiring'; 'doubling of ICS dose'
Murphy et al 2010 [22]	Defined as episodes requiring medical intervention [hospital admission, emergency department	Strengths and weaknesses same as ref [12].

	presentation, unscheduled doctor visit or the use of oral corticosteroids (OCS)]	

3. TRIGGERS AND RISK FACTORS

3A. Assessment of risk: what is cause and what is effect?

The prevention of exacerbations is probably the most important aim for patients with asthma and health care professionals. In order to achieve this aim, it is important to plan the re-assessment of asthma patients and treatment adjustments because of the immediate risks (i.e. acute respiratory failure, death) and future risks (recurrence of exacerbations, decline in lung function, and side effects of treatments) [1]. Routine management strategies assess asthma control based on clinical symptoms, history of exacerbations and pulmonary function testing. In addition, in experienced centers, strategies guided by airway hyperresponsiveness (BHR) or sputum eosinophilia may provide benefit for preventing future exacerbations [16, 23]. In contrast, the use of fractional exhaled nitric oxide (FENO) as a surrogate marker in asthma management is still inconclusive [24–26] except during pregnancy [27]. A recent meta-analysis found more supportive results deserving further evaluations [28].

Since a previous exacerbation has been shown to be an important risk factor for future exacerbations (even though this concept has been challenged) [29], the "frequent exacerbator" likely represents an important clinical phenotype; and asthma treatment should aim to modify what might look like an irreversible cycle [30]. For this purpose, multiple initiatives have investigated and weighed the importance of individual traits in predicting recurrent exacerbations. Many other characteristics and conditions have also been reported such as amount of asthma medication, comorbidities including obesity, occupational stress [31], sensitization, indoor and outdoor pollution, small airway dysfunction [32], loss of lung elastic

recoil [33], and psychological factors [29, 34–44]. Retrospective studies have shown that repeated assessment of composite scores of control such as the Asthma Control Test (ACT) or Asthma Control Questionnaire (ACQ) and other tools, such as eHealth and mHealth[45], may predict severe exacerbations [46]. However, whether self-monitoring of asthma control score questionnaires at home can be useful to predict (and consequently, help to prevent) exacerbations in a real life setting needs to be further investigated [47–49]. An index of fluctuation of Peak Expiratory Flow (PEF) measurements at home was able to predict exacerbations [50]. Lastly, although a hospital admission provides proof of a severe exacerbation (see definition), the decision to hospitalize a patient with asthma also depends on the clinical course during management at the emergency department [2, 51, 52], and on additional factors such as age, inflammatory phenotype, presence of comorbidities [53, 54], and familial and social conditions [2, 51, 52].

3B. Modifiable vs non-modifiable factors and mathematical models

Until recently, modifiable risk factors for exacerbations were mostly seen as behavioral issues or environmental triggers [55–58]. This included patients' beliefs (or parents' beliefs in the case of children) and expectations, poor inhalation technique and/or treatment adherence, (active or passive) smoking and allergen exposure (such as in-house pets, for example). More recently, the key role of viruses has been acknowledged, and viral triggers are now perceived as potentially modifiable factors. However, no therapeutic strategies have yet been able to successfully interfere with rhinovirus carriage and bouts of infections in children and adults; this is an important area of ongoing research. Accordingly, viral infection and impaired host responses to rhinovirus can be modelled to predict the potential of new antiviral drugs [53, 59–61]. The synergistic action of allergen exposure (e.g. seasonal pollens, house dust mite) and

viruses may indicate a place for combining strategies targeting each factor alone or in association [38, 55, 62].

High blood eosinophil count, reflecting type 2 (T2) inflammation, is well-recognized as a significant risk factor for asthma exacerbations [63], with a consistent dose-ranging effect reproduced in different large scale studies [64, 65]. The relative weight of elevated blood eosinophilia with any other predictor of future exacerbation is largely unknown, but is influenced by the level of asthma control, asthma severity, asthma phenotype (e.g. age at onset of asthma), lung function and history of exacerbations. Validated biomarkers reflecting non-T2 asthma phenotype(s) remain an urgent unmet need [66]. The recognition of T2-related traits makes a patient with uncontrolled severe asthma eligible for biologic therapies targeting key T2 disease-drivers, such as eosinophils, IL-4, IL-13 and/or IgE [67]. Elevated blood eosinophil count is associated with an increased exacerbation risk and to date this is the most relevant phenotyping marker. The reduction in exacerbation rates provided by anti IgE-, -TSLP, -IL-5- and -IL-4/IL-13 antibody therapy supports the concept that T2-associated asthma is associated with an increased risk of exacerbations [68, 69], even though it is not the only one.

Asthma patients may follow many different trajectories [56]. These trajectories can be described under three main categories and sustain the concept of asthma severity (persistently severe, intermittently severe, never severe). Presently, exacerbations represent one of the key outcomes in asthma with the greatest asthma-related risks as defined by GINA [1] and hence, the development of innovative drugs and effective treatment modalities remains a priority. Exacerbations are episodes of acute respiratory distress; a situation that causes major stress for the patient themselves, their relatives and even for the health care providers. They represent an important economic burden both in terms of health care use and professional absenteeism. They are also associated with long term risks (relapses, side effects of treatments dominated by

systemic steroids, lung function decline) [1, 9, 70]. Some single nucleotide polymorphisms (SNPs) and other gene modifiers summarized in **Figure 1** could be associated with such long term risks [62, 71–82]. It appears worthwhile exploring the epigenetic modifications in well-characterized asthma populations, particularly in late onset disease.

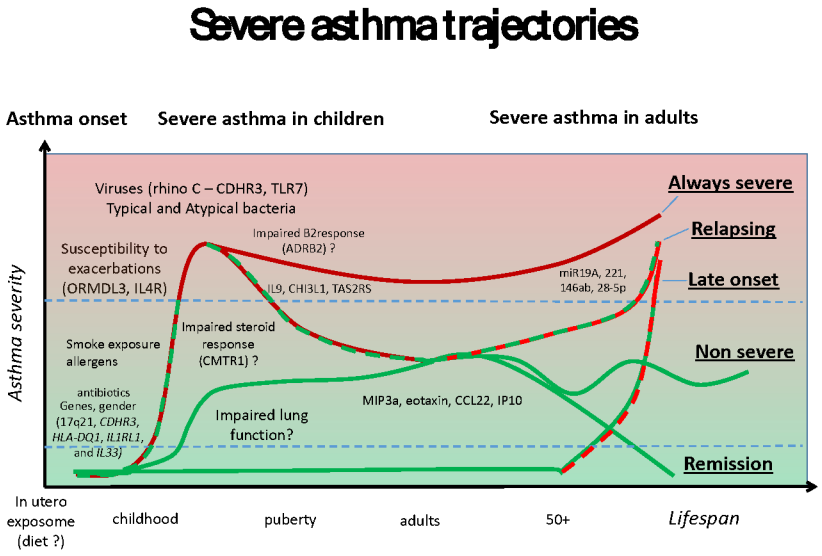


Figure 1 Potential severe asthma trajectories and the importance of risk factors and genetic variants (such as single nucleotide polymorphisms [SNPs]). this figure presents a summary of the literature and is not intended to be exhaustive

3C. Risk factors and epidemiology, pheno/geno/endotypes.

Since severity of asthma is presently defined by treatment requirement, which partly relies on previous exacerbation rates [3], the frequency of exacerbations is associated with severity. However, exacerbations are not restricted to patients with the severe form of asthma.

Near-fatal asthma episodes can occur in patients even with so called "mild asthma", implicating that "mild asthma (GINA step 1 and 2) "does not necessarily mean "low risk asthma". Most of the time, these patients are not receiving any anti-inflammatory treatment at the time of the event and their asthma can be well-controlled when it is correctly managed and treated [2, 35].

Near-fatal episodes represent a minority of exacerbations seen in the emergency department [2]. Interestingly, a hyperbolic curve relating inhaled corticosteroid (ICS) prescription refilling and asthma mortality is highly suggestive of a strong death-preventing effect of ICS use [83]. Actually, asthma deaths due to exacerbations have decreased over time in westernized countries. However, their incidence was still estimated to be more than 900 in the UK in the latest National Review of Asthma Deaths, and at least half of these dramatic cases were considered preventable [6, 84].

Risk factors and clinical characteristics could be identified and robustly confirmed in different countries. These criteria should be known to all health care providers involved in the management of asthma and are shown in **Table 2**.

Better characterization of disease mechanisms is required in those patients with an incomplete response to ICS (across GINA steps) [70]. Defining clinical phenotypes and mechanistic endotypes is a useful concept which has been developed to better manage these patients [85]. In the SARP-3 cohorts, five factors were positively associated with exacerbation frequency: chronic sinusitis, gastro-esophageal reflux, blood eosinophils, body mass index, and bronchodilator responsiveness. Clusters in primary care identified early onset and obesity as risk factors for exacerbations. A cluster of obese female asthmatics with recurrent exacerbations has been described in both SARP and UBIOPRED cohorts [86, 87]. Furthermore, a large scale study on children confirmed that obesity is linked with a shorter period of time between exacerbations [88]. Symptoms such as cough and wheeze are correlated with uncontrolled asthma, but are poorly associated with exacerbations [89]. Interestingly, new inflammatory patterns of exacerbations are currently described with the integration of the microbiome and T1-related cytokines [90]. A gene signature derived from sputum gene transcriptomics containing Charcot-Leyden crystal galectin [CLC]; carboxypeptidase 3 [CPA3]; deoxyribonuclease 1-like 3 [DNASE1L3]; alkaline phosphatase, liver/bone/kidney

[ALPL]; CXCR2; and IL1β (a mixture of eosinophil and mast cell product with neutrophil-associated cytokines) can predict future exacerbation phenotypes of asthma, with the greatest biomarker performance compared to fractional exhaled nitric oxide values and sputum eosinophil counts in identifying those who would experience frequent severe exacerbations [91].

It should be kept in mind that very high blood eosinophil counts (e.g. more than a thousand per mm3) are sometimes associated with other conditions such as eosinophilic granulomatous with polyangiitis (EGPA) or allergic bronchopulmonary aspergillosis (ABPA) which overlap with severe asthma. These specific conditions are prone to very frequent exacerbations. They are sometimes difficult to discriminate from severe asthma when all the diagnostic criteria are not fulfilled [92].

Table 2. Risk factors for various outcomes in asthma exacerbations

	Likely	Possible	Ref
RF for dying	• B2 agonist overuse • No ICS treatment • Age • Virus infection • Gender • Drug and venom allergy • Allergen exposure (including thunderstorm asthma)	• Intubation outside PICU • High number of ED visit • Sports • Alternaria and penicillium spores • Nitrogen dioxide, ozone • Severe asthma	[35, 93–97]
RF for ICU admission – near fatal asthma	• No ICS treatment • Severe asthma • Virus infection • Loss of elastic recoil • Permanent airflow limitation • Hyperinflation • Menstruation • Steroid dependence • History of intubation • Delayed systemic corticosteroid use	• Heroin, cocaine	[33, 39, 41, 98, 99]
RF for severe exacerbation – ED – admission	• No ICS treatment • Comorbidities • Psychological issues • Age • Absence of ICS • Virus infection		
RF for frequent severe exacerbations (≥ 2 - 3 OCS bursts/y)	• No ICS treatment • Virus infection • High blood eosinophil count • Smoking • Genetic • Atopy • BMI • BD responsiveness • Chronic sinusitis	• Low socioeconomic status • GERD • Aspirin sensitive • Climate- Thunderstorms during pollen season	[54, 100, 101]

RF = risk factor; BD = bronchodilator; BMI = body mass index; ED= emergency department; ICS = inhaled corticosteroids; ICU= intensive care unit; GERD = gastro-esophageal reflux disease; NFA= near-fatal asthma attack; OCS = oral corticosteroids

3D. Typology– gender, psychosocial factors. Perception, Compliance/Adherence

Poor treatment adherence is a major trigger for loss of control at the population level, and this is a common finding also for onset of exacerbations [102]. Although ICS treatment is able to decrease the exacerbation rate at all dose ranges [103], it seems that an adherence of at least 75% of the prescribed dose (hazard ratio [HR] 0.61; 95% confidence interval [CI] 0.41–0.90) is required to achieve this goal [103]. Of note, 24% of exacerbations can be attributed to poor adherence, which is often unintentional due to poor inhalation technique. Moreover, running out of inhaler was frequently reported in ED-attending asthmatics [104]. The use of multiple devices, especially when different principles are mixed, such as dry powder inhalers and metered dose inhalers (MDI), is also a risk [105]. Non-consented switching of inhalers has also been shown to be a significant risk factor for exacerbation; these apparent cost-sparing measures in the short-term are thus subsequently countered by increased health care utilization [106]. Alexithymia [107] , specific personality traits [108], and poor perception of symptoms may lead to a delayed request for help [95–100]. Female gender [109, 110], ethnicity [111, 112] and patient beliefs [113]could also be identified as risk factors for exacerbation. The prevalence of psychological dysfunction, including anxiety and depression, is increased in patients with asthma and has been shown to be related to severity of the disease [114]. Anxiety and depression are also strong predictors for poor asthma control [115].

Poor adherence is well documented for ICS; but new injectable biologics also appear susceptible to this, particularly when self-administered [116]. On the other hand, self-administration is likely to improve access to treatment and to reduce the burden of the disease [117].

Several drawbacks could be raised against therapeutic educational programs, but at present many simple and efficient solutions extensively reviewed elsewhere can work [70, 102]. The benefits of written or web-based action plans are worth investigations [118]. Furthermore,

e-Health solutions such as electronic reminder messages and, more recently, connected (to a computer or a smartphone) inhaler devices can be implemented and have been shown to be effective [119, 120], but as they are usually only geared towards the use of one single inhaler per patient and no other medication it is likely of limited value for patients requiring multiple medications. However, these interventions should be prospectively evaluated for their ability to decrease exacerbation rates over time and whether they are really easing patients' lives. Stronger partnerships between patients and health care professionals are likely to improve adherence and new self-adherence programs should be developed and tested for their effect on preventing (severe) exacerbations.

Although there is no perfect tool for associating a severe asthma exacerbation with poor adherence, a minimal adherence checklist is proposed in GINA and the task force decided to echo it presently (**Table 3**). Dose-counter displaying devices are preferred options according to a European Lung Foundation (ELF) open discussion organized for the present task force.

Factors contributing to poor adherence
Medication/Regimen factors
- Difficulties using inhaler device
- Burdensome regimen (e.g. multiple times per day)
- Multiple different inhalers
Unintentional poor adherence
- Misunderstanding about instructions
- Forgetfulness
- Absence of a daily routine
- Cost
Intentional poor adherence
- Perception that treatment is not necessary
- Denial or anger about asthma or its treatment
- Inappropriate expectations
- Concerns about side-effects (real or perceived)
- Dissatisfaction with health care providers
- Stigmatization
- Cultural or religious issues
- Cost
How to identify poor adherence in clinical practice
Ask an empathic question
- Acknowledge the likelihood of incomplete adherence and encourage an open non-judgmental discussion
Check medication usage
- Check the date of the last controller prescription
- Check the date and dose counter on the inhaler
- In some health systems, prescribing and dispensing frequency can be monitored electronically by clinicians and/or pharmacists
Examples of successful adherence interventions
- Shared decision-making for medication/dose choice
- Inhaler reminders for missed doses
- Prescribing ICS once-daily versus twice-daily
- Home visits for a comprehensive asthma program by an asthma nurse

Table 3. Factors affecting adherence in clinical practice, according to GINA [1].

3E. Virus/allergens

A synergy exists between respiratory viral infections and allergen exposure inducing asthma and causing exacerbations in susceptible, sensitized asthmatics [38, 55, 62]. Additionally, interaction between lower respiratory tract viral infections (LRTI) and atopic sensitization has been recognized as a major risk factor contributing to asthma development and exacerbations [62, 121]. Birth cohort studies provide strong evidence for a synergistic effect of viral LRTIs and atopic sensitization on risk of asthma inception, particularly in predisposed children [122, 123]. Several studies in both sensitized children [55, 124] and adults [16, 38] found a strong association between the levels of specific IgE to inhaled allergens and viral LRTIs in increasing the risk of severe asthma exacerbations requiring hospital admission.

The synergism between allergen sensitization and viral LRTIs has been indirectly confirmed in a study in asthmatic children, showing that pretreatment with omalizumab decreases asthma exacerbations in fall, which are likely (rhino-)virus-induced [125]. Recent evidence demonstrates that omalizumab restores deficient anti-viral immunity in children with asthma, and that exacerbation reduction with omalizumab was greatest in those with greatest restoration of anti-viral immunity [125]. Rhinoviruses (RV), especially RV-A and RV-C groups, are the most frequent viruses detected during an asthma exacerbation including severe asthma exacerbations with near-fatal and fatal asthma, and allergic asthmatics usually experience more severe and prolonged LRTI symptoms with RV infection compared to non-atopic healthy controls [38, 55, 126]. Interestingly, CDHR3 polymorphism is a risk factor for RV induced severe asthma exacerbations in children [71], possibly because it has recently been shown to be an RV-C receptor [127]. Another study showed that documenting a viral infection in the ED was a strong predictor for ED re-attendance in children [128]. Impaired interferon responses to RV infection are associated with asthma in both adults and children [105, 106], and are

associated with increased RV-induced asthma exacerbation severity [131] Although appealing, the development of a RV vaccine appears highly challenging [132]However, a proof of concept study on inhaled IFN-β as a therapeutic intervention in virus-induced asthma exacerbations only showed benefit in a subgroup of people with moderate/severe asthma [133], implicating that further research is needed to investigate the concept of interferon supplementation in asthmatics at exacerbation onset.

3F. Environmental factors: indoor/outdoor air pollution & occupational factors

Outdoor air pollution is an established risk factor for asthma exacerbations, although the magnitude of effect remains difficult to assess precisely [101]. Diesel exhaust particles and peaks of ambient air pollution, (reflected by, amongst others, high levels of nitrogen dioxide and ozone) were shown as concomitant factors to emergency department attendance in asthmatics but also could be epidemiologically related to asthma exacerbations and deaths [97]. Work-related exacerbations are probably underestimated whereas many different non-specific irritants could be identified such as mineral dusts, gas and fumes etc. [134].

Indoor air pollution comprises second-hand tobacco smoke exposure, which is of special interest in children, but also other less well-known contributors such as volatile organic compounds (VOC) [135]. Open fire place, sick building syndrome, cleaning supplies and household products, and inadequate ventilation are also to be integrated into potential sources of indoor air pollution. We propose to test whether facilitating access to air quality data records may prevent asthma exacerbations. The European Lung Foundation (ELF), while reviewing the present manuscript, supports the use of portable air quality sensors, but more research is needed to know what and how to measure the right substances.

Occupational sensitizers and triggers have been cause for concern for many years and efforts have been taken to limit their impact. All TF members in their practice consider it worthwhile

facilitating access to free and independent experts in occupational medicine, as well as using FENO, spirometry, and potentially other relevant diagnostic tests (e.g. induced sputum) at work, especially considering their relatively low direct and indirect costs. More research is needed on occupational triggers and their effect on severe asthma exacerbations. Patients also raised the need to support asthma patients when choosing careers to avoid known and dangerous sensitizers and triggers.

3G. Drugs & irritants / Excessive use of β_2-agonists

Whether drugs known to affect airway smooth muscle tone (such as β-blockers) are able to trigger an asthma exacerbation is unclear. Non-steroidal anti-inflammatory drugs (NSAID) and aspirin intake in susceptible patients induces asthma exacerbations, and low dose induction of tolerance must be investigated to assess their benefit in preventing exacerbations.

Excessive use of short-acting β_2-agonists (SABA) in the absence of ICS use has long been linked to hospitalizations and asthma deaths, best exemplified by asthma deaths epidemics related to high doses of fenoterol reported in New Zealand and other countries [136]. Also regular use of long-acting β_2-agonists (LABA) in the absence of ICS has been shown to increase significantly the risk of asthma exacerbations and asthma deaths potentially through a "masking" effect [137–139]. Not only overuse, but also regular use of SABA – without ICS [140] – has also been associated with paradoxical asthma worsening [52, 141]. Mechanisms involved are not fully understood, but may relate to induction of inflammatory mediators in bronchial epithelial cells by β_2-agonists (both SABA and LABA), when administered in the absence of ICS [142] , and/or by a tachyphylaxis phenomenon but this is still to be demonstrated in vivo [143]. Because several short and long acting β_2-agonists are now available, their potential side effects should be assessed in detail and reported, especially as paradoxical triggers for loss of control and exacerbations. The TF members limit these issues by systematic

concomitant ICS use and reassess the patients repeatedly. Most TF members avoid frequent and inappropriate use of repeated or regular high doses of SABA irrespective of the manner of administration (inhaled: pMDI, DPI, or nebulisation) without medical supervision.

4. ACUTE MANAGEMENT

TREATMENT OF SEVERE ASTHMA EXACERBATIONS

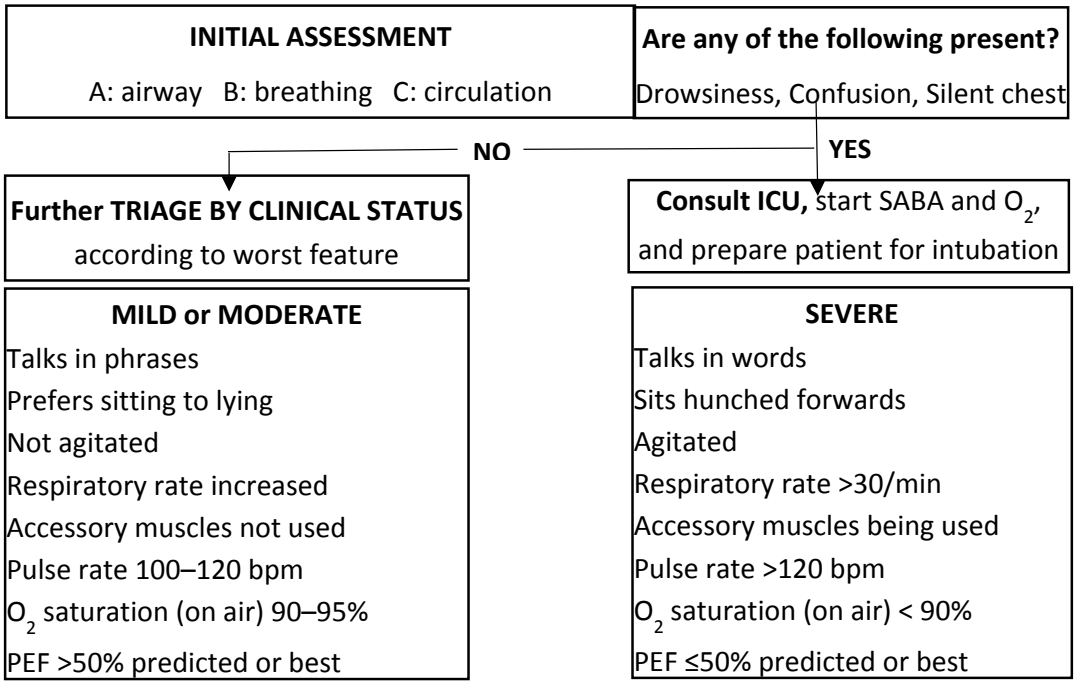
Despite optimum maintenance therapy and appropriate prevention strategies, severe exacerbations occur, even in patients with mild disease or well-controlled asthma [1, 144]. Therefore, proper assessment and adequate intervention are crucial to stabilize asthma and alleviate symptoms. Although in recent years there has been ample research into the treatment of stable asthma and several new drugs and formulations have been marketed, so far a limited number of treatments are available for asthma exacerbations while limited evidence exists in support of their use [145].

For patients presenting with acute asthma to primary care or emergency department (ED), the TF members consider that a proper assessment of exacerbation severity is determined based on history, physical examination and objective measurements of lung function and oxygen saturation [146] (**Figure 2**). Arterial blood gas measurements and chest X-ray are not included in the guidelines dedicated to the initial assessment, nevertheless they are performed by all the TF members for patients with severe exacerbations and for those who do not respond to initial treatment or are deteriorating [147–149].

Information from patients' history can identify those who are at increased risk of worst outcome and asthma-related death and prompt arrangements to be made for more frequent evaluation and aggressive treatment (**Table 2**).

Treatment is usually started immediately and simultaneously with the initial evaluation of the patient. The following treatments are usually administered concurrently to achieve the most rapid resolution of the exacerbation and prevent patient deterioration.

Figure 2: Assessment of exacerbation severity based physical signs and objective measurements (adapted from GINA [1])



Oxygen

Oxygen is usually delivered by nasal cannula or Venturi mask in order to achieve arterial oxygen saturation of 93–98%. In severe exacerbations, high concentration oxygen increases the risk of hypercapnia while controlled low flow oxygen therapy is associated with better outcomes [150–152].

Short-acting β_2-agonists (SABA)

SABAs intend to resolve bronchospasm and to relieve acute symptoms of asthma, and are usually initially administered every 15 to 20 minutes for the first hour during an acute asthma exacerbation. Comparison of pMDI-spacer and nebulizer has shown increased efficiency of SABA delivery via pMDI-spacer and equivalent clinical outcomes [153, 154]. Data are conflicting whether continuous nebulization with a SABA is superior to intermittent

nebulization [155, 156]. In severe asthma exacerbations, continuous nebulization may be preferred, based on evidence of reduced admissions and improved pulmonary function [155, 157]. There is no evidence to support the routine use of intravenous β_2-agonists in patients with severe asthma exacerbations [158].

Ipratropium bromide

Adding ipratropium bromide to SABA decreases rates of hospitalizations and shortens ED stays for patients with severe asthma exacerbations [159–161]. Some evidence shows that the use of combination ipratropium/β-agonist therapy in acute asthmatic exacerbations provides benefit without increased risk of adverse events [161].

Corticosteroids

Early administration of systemic corticosteroids for the treatment of asthma exacerbations is considered a standard of care and is recommended worldwide to be given to the patient within 1 hour of presentation [162, 163]. A systematic review showed that the use of systemic corticosteroids reduces the rate of hospital admission in ED settings, especially in patients with severe asthma and those not currently receiving corticosteroids [164].

The optimal dose for systemic corticosteroids in asthma exacerbations remains to be established. Doses above 2 mg/kg or 60-80 mg/day do not add benefit to improving lung function, rates of hospital admission or length of hospital stay [162, 165]. Furthermore, no differences are found between oral and intravenous administration of comparable corticosteroid doses [166, 167]. Thus, daily doses of OCS equivalent to 50 mg prednisolone as a single morning dose, or 200 mg hydrocortisone in divided doses, are adequate for most patients [1]. A short course of 5 days OCS after ED treatment of acute asthma exacerbations

has been shown to reduce the rate of relapse [1, 164]. Courses longer than 5 days or a dose tapering did not provide additional benefit while increased side effects [168, 169].

The role of ICS in the management of asthma in the emergency department remain unclear and their use in severe asthma exacerbations is not evenly adopted [170].

Other treatments

None of the TF members use intravenous aminophylline and theophylline in the management of asthma exacerbations, in view of their poor efficacy and safety profile [1]. Intravenous magnesium sulphate (given as a single 2g infusion over 20 minutes) has been shown to reduce hospital admissions in severe exacerbations and in patients who fail to respond to initial treatment [171, 172]. Evidence does not support a role of antibiotics in asthma exacerbations unless there is strong presumption of lung infection [1, 173]. Other associated advices of management (hydration, physiotherapy, avoid exercise, etc.) are poorly evidenced [174]. Noteworthy, exercise outside an episode of exacerbation should be largely supported as it was shown to prevent exacerbations and to improve control [175].

5. PREVENTION

Here we describe the evidence for current therapies available across the severity spectrum of asthma, licensed biologics and those in phase 3 clinical development.

Current small molecule asthma therapies

Corticosteroids

Extensive data support the role of inhaled corticosteroids in asthma with increasing dose reducing exacerbation frequency [1, 176, 177]. Increasing the ICS dose four-fold at the onset of exacerbation symptoms reduced the need for systemic corticosteroids by 19% [178]. No randomized controlled trials exist of prednisolone versus placebo as add-on therapy in severe asthma [179]. Registry data suggested that maintenance oral corticosteroid use was associated with reduced exacerbations among a cohort of severe asthmatics [180]. In a small study, high-dose intramuscular triamcinolone reduced hospital admissions and emergency department attendances; however, the long-term side effect profiles of systemic steroids have to be taken in mind. TF members use maintenance OCS as a therapeutic strategy for reducing exacerbations as a less preferred option and suggest this practice be supervised in expert referral centers familiar with the management and prevention of OCS side effects [181].

Presence of eosinophilic inflammation predicts a good response to corticosteroids in airways disease [182–184]. Tailoring corticosteroid dose to control sputum eosinophilia in asthma has achieved marked reductions in exacerbation rates [16, 18, 185] and the ERS/ATS guideline advocates measurement of eosinophilic inflammation in severe asthma [3].

Given the superiority of an on-demand ICS-containing regimen in two separate trials performed in patients with mild asthma in reducing the risk of exacerbation [186, 187], later confirmed in a real-life setting [188], the last GINA update promotes this strategy as early as

step 1, acknowledging the obvious inflammatory nature of the disease and in particular during episodes of poor control that precedes exacerbation.

The management of asthma using a sputum-guided adjustment of the daily dose of ICS was shown efficient to prevent exacerbations in expert centers where induced sputum cytology can be assessed routinely, in patients able to provide an adequate sample within the safety margins of induction [16, 18].

Long Acting Beta-Agonists (LABA) added to ICS

ICS-LABA combination therapy is standard in severe asthma and the addition of a LABA to ICS reduces exacerbation frequency in asthma [1, 176, 177]. The TF echoed recurrent warnings regarding monotherapy with LABA in asthma [189].

Long Acting Muscarinic Antagonists (LAMA) added to ICS

Tiotropium, as add-on therapy for asthmatics uncontrolled while treated with ICS and LABA, increased time to first exacerbation by 56 days versus placebo (P=0.03) [190]. A Cochrane review of LAMA added to ICS vs ICS alone across all severities of asthma showed a reduction in exacerbations requiring oral corticosteroids, and a trend towards reduction in hospital admissions [191].

Leukotriene Receptor Antagonists (LTRA)

A systematic review of LTRAs identified a significant reduction in exacerbations when used as monotherapy compared to placebo, but no effect on exacerbation rates when used in patients already taking inhaled corticosteroids [192]. Whether LTRAs reduce severe exacerbations in severe asthmatics is unknown.

Theophylline

A study comparing ICS/LABA and theophylline vs ICS/LABA and placebo found a significant reduction in severe exacerbations in the theophylline group in asthmatics who were treatment naïve [193]. Whether theophylline affects exacerbation frequency in severe asthma is unknown. Most TF members do not use theophylline as an add-on therapy for preventing exacerbations.

Antimicrobials

In a large clinical trial thrice-weekly azithromycin in moderate-to-severe asthma resulted in a 41% reduction in severe exacerbations with benefits independent of inflammatory phenotype [194], in contrast to a previous sub-analysis in severe asthmatic patients where the benefits were limited to the non-eosinophilic subgroup [195]. Of note, worldwide, azithromycin is not approved to the best of knowledge in this indication. Anti-fungal agents in fungal-sensitized severe asthma not meeting criteria for allergic bronchopulmonary aspergillosis demonstrated no impact on severe exacerbations [196].

Immunosuppressants

Data reporting exacerbations was limited in a Cochrane review examining the corticosteroid sparing effect of cyclosporin in severe oral corticosteroid dependent asthma [197]. A similar review examining the corticosteroid sparing effects of methotrexate in severe asthma did not demonstrate a beneficial effect on exacerbation rates [198].

Allergen avoidance and immunotherapy

Allergen avoidance advice is standard clinical practice in severe asthma [1, 176, 177], but allergen avoidance has shown controversial benefit [199] possibly due to difficulty in achieving this effectively. Allergen immunotherapy (AIT) strategies in asthma report some benefit for

reducing symptoms and corticosteroid usage but have not been tested in severe asthma [200]. It is unknown whether measures such as nocturnal temperature controlled laminar flow will be effective. Reductions in airway inflammation are reported in atopic asthma [201] and studies in severe asthma are ongoing [202].

Current biologics for asthma (Table 4)

The phase 3 RCTs for currently available biological therapy in asthma, except for anti-IgE as more established, are summarized in Table 4, including phase 2b studies that were considered pivotal for registration. Studies in less severe asthma with a very low event rate, open-label extensions that confirmed earlier findings and studies that did not report exacerbations were not included.

Anti-IgE: Omalizumab

A Cochrane review of omalizumab as add-on therapy in moderate-to-severe asthma reported a reduction (odds ratio (OR) 0.55, 95% confidence interval (CI) 0.42 to 0.60; ten studies, 3261 participants) in severe exacerbations [203], however subgroup analysis of severe asthma alone did not demonstrate a clear benefit. Further clinical trials remain ongoing [201].

Anti-IL5: Mepolizumab and Reslizumab

Mepolizumab reduces exacerbation frequency by ~50% [5, 65, 204–206] and reduces the requirement for maintenance oral corticosteroid [206]. Benefits were observed in severe asthmatics with blood eosinophils >150cells/μL [207], with greatest exacerbation frequency reductions seen with increasing eosinophilic inflammation. These beneficial effects were not sustained over the 12 months following treatment withdrawal [208] while it was the case when treatment was maintained [209]. This exacerbation rate reduction was also achieved while

tapering OCS in long term OCS users[210]. Reslizumab demonstrated a reduction in severe exacerbations in severe asthmatics with a baseline blood eosinophil count >400 cells/μL [211]. Improvements were greatest in those with GINA step 5 disease [212].

Anti-IL5R: Benralizumab

Benralizumab reduces severe exacerbations [64, 213, 214] in those with a blood eosinophil count >300 cells/μL. A priori sub-analyses using an eosinophil cut off of 150 cells/μL also demonstrated significant reductions in exacerbation rates [215], although higher blood eosinophils and more frequent exacerbations predicted greater benefits [216]. This exacerbation rate reduction was also achieved while tapering OCS in long term OCS users [214]. A study of benralizumab administered in the setting of acute asthma exacerbation [66] reported a positive impact on recovery rates, however further work would be required to define the use of biologics in this setting.

Bronchial Thermoplasty

In 190 subjects who received bronchial thermoplasty (BT) versus 98 who underwent sham procedures severe exacerbations were reduced by 32% in the 3-12 months post therapy with an increase in exacerbation events in the peri-procedure period [21]. This reduction in exacerbations was maintained over a 5 year follow up period [217]. BT is currently performed only in trained centers for both managing severe asthma and handling BT.

Emerging biologics

Anti-IL4R: Dupilumab

Dupilumab reduced severe exacerbations in all-comers irrespectively of the atopic status, with the greatest reduction in those with elevated FeNO and/or eosinophilic inflammation, and

reduced oral corticosteroid requirement for severe asthmatics receiving maintenance oral corticosteroids [68, 218, 219]. Studies of IL4 inhibition alone and more recently of the anti-IL13 biologics lebrikizumab [220] and tralokinumab [221] have failed to meet their primary endpoints of exacerbation reduction, suggesting that inhibition of both IL-4 and 13, as with anti-IL4R, is necessary to observe sufficient clinical efficacy for this aspect of the disease.

Anti-TSLP: Tezepelumab

A recent phase II trial investigated the impact of tezepelumab on exacerbation rates in 584 moderate-to-severe asthmatics, showing a 60-70% reduction in exacerbations in all-comers across dosing regimens [222]. Effects were observed irrespective of markers of T2 inflammation, although substantial reductions in these measures were noted, suggesting that targeting upstream cytokine pathways may reduce exacerbations across inflammatory profiles.

CRTH2 antagonists, anti IL17 and others

ILC2 are now seen as the pivotal cells ofT2 airway inflammation. Because they specifically express the PGD2 receptor DP2 or CRTH2, a proof of concept study showed that anti-DP2 treatment could significantly reduce the blood eosinophil count [223]. Whether this will be sufficient for preventing exacerbations is the aim of a larger ongoing phase III trial.

The IL33-ST2 axis is also specifically targeting ILC2 [224] and pivotal studies are ongoing. In non T2 asthma, the relevance of blocking IL17 for preventing exacerbations is also currently being tested [225].

Conclusion

Reduction and ultimately elimination of severe exacerbations in severe asthma remains an important therapeutic target. In addition to corticosteroids and allergen avoidance/immunotherapy, the biologics targeting T2-immunity and eosinophilic inflammation (anti-IgE, IL-5, IL-4R and TSLP) reduce exacerbations. Whether other therapies that reduce eosinophilic inflammation such as anti-DP2, will demonstrate a similar efficacy remains to be determined. Beyond T2 inflammation, macrolide antibiotics and bronchial thermoplasty may have a role, but reducing severe exacerbations in non-T2 severe asthma remains an unmet need, although the scale of its importance once T2-mediated disease is adequately treated is uncertain.

5. CONCLUSION AND BULLET POINTS FROM THE ELF

Preventing severe exacerbations in asthma is very important from the perspective of people with asthma. Too many patients still die, whereas these deaths are likely preventable, from a severe exacerbation. In some countries asthma and respiratory deaths are still increasing, especially in non-severe and moderate asthma [84]. Why this is happening still needs to be explored but facilitating access to care and medications would probably be efficient.

- In all types of asthma: It is important to remain aware that severe exacerbations don't just happen in patients with the more severe types of asthma.
- Exacerbations and especially recurrent exacerbations are very debilitating for patients. More research is needed to avoid exacerbations and to break the cycle of recurrent exacerbations. The medications and treatments plans that are available at this time do not seem to be working well enough for all patients.
- Adherence: patients and physicians need to work together on improving adherence. Good communication between physician and patient is key. There are many factors that impede adherence for patients. Some straight-forward ways to support patients can be

implemented easily like having dose-counters on all inhalators. It can be more challenging to address patients developing additional behavior. All aspects require continuous positive attention from physicians.

- Indoor and outdoor environmental factors: the advice to avoid environmental factors is an additional burden moreover because it is extremely complex to put into practice for patients. More and better advice needs to be given to patients on living conditions, occupational choices etc.
- Working together with patients in improving their asthma care is key. Many patients have good knowledge on their asthma and their reaction to medications. Not all patients have this insight and not all patients are able to manage their asthma on a daily basis. We all need personalized help. E-health can support some patients, but only if these solutions are developed with patients and are sufficiently flexible and personalized.

Research needs and knowledge caps identified throughout this task force are summarized table 5.

Table 4: Pivotal Phase 3 randomised clinical trials of licensed biologics (excluding anti-IgE)

Intervention	Reference	Population	Description of intervention/ duration	Effect on exacerbations
Mepolizumab Anti-IL5	MUSCA [205]	Adults and children (>12 years), n = 556 ≥2 exacerbations in last year Blood eosinophils ≥300/µl in last 12 months or ≥150/µl at screening	100mg SC Q4W 24 weeks	↓ exacerbation rate 42% ↓ exacerbations requiring emergency department (ED) visit or hospitalization 32% No significant change in hospitalizations alone
	SIRIUS [226]	Adults (16 – 74 years), n = 135 Background therapy 5 to 35 mg/day of prednisone or its equivalent for > 6 months Blood eosinophil count ≥150 cells/µL at screening or ≥300 cells/µL in the last year	100mg SC Q4W 20 weeks	↓ exacerbation rate 32% OR for glucocorticoid reduction 2.39 in mepolizumab group (0.008) Median glucocorticoid reduction 50% (vs 0% in controls)
	MENSA [5]	Adults and children (aged ≥12 years), n = 576 ≥2 exacerbations in last year Blood eosinophil count ≥150 cells/µL at screening or ≥300 cells/µL in the last year	75mg IV Q4W or 100mg SC Q4W 32 weeks	↓ exacerbation rate 47 - 53% SC mepolizumab ↓ exacerbations requiring ED/hospitalization (61%) and exacerbations requiring hospitalization (69%) ↓ systemic glucocorticoid exposure 41%
	Pavord Lancet 2012 [53] (Phase 2b/3)	Adults and children (12 – 74 years), n = 621 ≥2 exacerbations in last year Sputum eosinophils ≥ 3%, FeNO ≥ 50 ppb, blood eosinophil count ≥ 300 cells/µL or deterioration in asthma control with ≤ 25% reduction in corticosteroid treatment (in the last year)	75mg IV Q4W or 250mg IV Q4W or 750mg IV Q4W 52 weeks	↓ exacerbations 39 - 52% Exacerbations requiring ED/hospitalization reduced across all groups Greatest reduction in exacerbations with baseline eosinophils > 500 cells/µL
Reslizumab Anti-IL-5	Castro [211]	Adults and children (12 – 75 years), n = 953 (study 1 n=489, study 2 n=464) ≥1 exacerbation in last year Blood eosinophil count ≥400 cells/µL	3mg/kg IV Q4W 52 weeks	↓ exacerbation rate 54% ↓ exacerbations requiring OCS 57% ↓ exacerbations in those on OCS at baseline by 68% Exacerbations ↓ 64% if ≥4 exacerbations in last 12 months at baseline (vs. ↓ 32% if 1 exacerbation last 12 months)
Benralizumab Anti-IL-5R	ZONDA [214]	Adults (18 – 75 years), n = 220 Background therapy (7.5 – 40mg/day prednisolone or its equivalent for > 6 months) Blood eosinophils ≥150 cells/µL at screening	30mg SC Q4W or Q8W 28 weeks	↓ exacerbation rate 55 - 70% Q8W Q8W dosing reduced exacerbations associated with ED visit or hospitalization by 93% OR for glucocorticoid reduction 4.1 Median glucocorticoid reduction 75% (vs 25% in controls)
	SIROCCO [64]	Adults and children (12 – 75 years), n = 1205 ≥2 exacerbations in last year	30mg SC Q4W or Q8W 48 weeks	Eosinophil High (≥300 cells per µL): ↓ exacerbations 45 - 51% Q8W dosing reduced exacerbations associated with ED visit or hospitalization by 68%

	CALIMA [213]	As per SIROCCO, n = 306	30mg SC Q4W or Q8W 56 weeks	Eosinophil High ↓ exacerbations 28 - 36% No effect on hospitalizations/ED visits
Dupilumab Anti-IL4Rα	Castro NEJM 2018 QUEST [68]	Adults and children (≥12 years), n = 1902 ≥ 1 exacerbation in last year	200mg SC Q2W or 300mg SC Q2W 52 weeks	↓ severe exacerbations 46% across treatment population ≥150 eosinophils/μL: ↓ exacerbations 60% ≥300 eosinophils/μL: ↓ exacerbations 67%
	VENTURE [69]	Adults and children (≥12 years), n = 210 Background therapy (5 – 35mg/day prednisolone or equivalent for > 6 months)	300mg SC Q2W 24 weeks	↓ severe exacerbations 59% across treatment populations ≥150 eosinophils/μL: ↓ exacerbations 58% ≥300 eosinophils/μL: ↓ exacerbations 71% Median glucocorticoid reduction 100% (vs 50% in controls)

Table 5. Research needs and knowledge gaps

Item	Research needs	Type of study design	Type of outcomes that need to be assessed
Definition of severe exacerbation	To assess in routine practice what is the most sensitive and specific definition (duration of OCS requirement, daily dose and cumulative dose)	Re-analysis of RCT and real-life trials where diaries and home monitoring were used Registries and cohorts	Rates of OCS bursts ≥ 5d, ED, admissions, need for ICU
Definition of severe exacerbation	To assess prediction models in real life cohorts	Re-analysis of RCT and real-life trials where diaries and home monitoring were used Registries and cohorts	Rates of OCS bursts ≥ 5d, ED, admissions, need for ICU
Definition of severe exacerbation	To establish composite scores to assess immediate risk	Retrospective analysis of databases of exacerbations	Short term outcomes: admission, ICU, intubation, deaths, treatment related adverse events
Strategy	To assess the impact of self-monitoring on asthma control and prevention of exacerbations	Randomised controlled trials comparing conventional vs self-monitoring strategy	Rates of OCS bursts ≥ 5d, ED, admissions, need for ICU
Strategy	To assess the effectiveness of interventions to prevent human rhinovirus carriage	Randomised controlled trials comparing strategies	Rates of OCS bursts ≥ 5d, ED, admissions, need for ICU
Risk factor/trigger	To assess the weight of blood eosinophilia compared to other risk factors at the individual level	Prospective cohort studies integrating all risk factors	Rates of OCS bursts ≥ 5d, ED, admissions, need for ICU
Risk factor/trigger	To assess the benefits and risks of genetic analysis awareness at the individual level to predict severe exacerbation and asthma trajectory	Test acceptability RCT comparing strategies of management in patients with known at-risk allele carriage vs routine	Severe exacerbation rates in patients and relatives, in particular in children with high risk scores (familial risk, patients already admitted in ICU)
Risk factor/trigger	To more accurately know the mechanisms, rate and risk factors of deaths attributable to severe exacerbations that	Multiple exhaustive reviews of asthma deaths.	Biology, pathology

	occurred despite an optimal preventive strategy and acute management	Worldwide collection of cases where death occurred despite optimal management	
Risk factor/trigger	To identify and weight all risk factors associated with death, ICU, ED and frequent exacerbations	Cohorts and registries of compelling cases	Rates of OCS bursts ≥ 5d, ED, admissions, need for ICU
Risk factor/trigger	To identify tools for assessing/improving adherence	RCT comparing strategies	Rates of OCS bursts ≥ 5d, ED, admissions, need for ICU
Risk factor/trigger	To assess the benefits of eHealth-connected devices to prevent severe exacerbation	RCT comparing strategies	Rates of OCS bursts ≥ 5d, ED, admissions, need for ICU
Risk factor/trigger	to assess tools / resources / methods (e.g. shared decision making, systematic multidisciplinary approaches, referral to asthma centres) to improve patient-HCP partnership	Studies assessing changes in patient-HCP partnership through training, education programs, etc.	Parallel studies associating changes in patient-HCP partnership with changes in severe exacerbation rates
Risk factor/trigger	To assess the benefits of using air quality sensors	RCT in selected populations	Rates of OCS bursts ≥ 5d, ED, admissions, need for ICU
Risk factor/trigger	To assess the benefits of more accurately evidence the role of occupational triggers	Basic science, models, psycho and sociology	Rooms of exposition with inflammatory / lung function monitoring HRQOL
Risk factor/trigger	To assess the preventive benefits of convincingly support patient when choosing careers	Prospective cohorts with randomized strategies	In teenagers/young adults and in people changing of occupation
Risk factor/trigger	To assess the exact role of drugs in severe exacerbations.(incidence, dose, diagnosis, prevention)	Prospective cohorts with randomized strategies. Models of exposition in animals and cell models	Prospective recording of severe exacerbation. Maximal documentation of each event.

Treatment of severe exacerbation	To define the value of CXR and arterial blood gases in acute management	Randomized controlled trials	Dedicated populations such as ED attending
Treatment of severe exacerbation	To establish an optimal scheme for SABA administration	Randomized controlled trials comparing different strategies of SABA administration (dose, route, frequency, duration, associated treatment)	Rates of OCS bursts ≥ 5d, ED discharge vs admissions, need for ICU, adverse events
Treatment of severe exacerbation	To assess the role of ICS during the exacerbation and at discharge	Randomized controlled trials	Rates of relapses, spred of recovery, adverse events
Treatment of severe exacerbation	To assess the benefits of hydration, physiotherapy, exercise avoidance during exacerbation; optimal time to go back to exercise	Randomized controlled trials, comparative studies	Rates of relapses, speed of recovery, adverse events, quality of life
Prevention	To assess whether LTRAs add-on reduce severe exacerbations in severe asthmatics	Randomized controlled trials	Rates of OCS bursts ≥ 5d, ED discharge vs admissions, need for ICU, adverse events
Prevention	To assess the benefits of measures such as nocturnal temperature controlled laminar flow	Randomized controlled trials	Rates of OCS bursts ≥ 5d, ED discharge vs admissions, need for ICU, adverse events
Prevention	to assess the use of biologics in the setting of acute exacerbation	Randomized controlled trials	Rates of relapses, speed of recovery, disease associated and hospital acquired-adverse events, quality of life
From the patients' perspective	Overall, to find treatments for patients not responding well to currently available medications and treatments plans	Randomized controlled trials in non eligible patients to existing drugs (low T2, failure of currently available biologics for example)	Rates of OCS bursts ≥ 5d, ED discharge vs admissions, need for ICU, adverse events

Table 6.

Section no	Section title	Keypoints
1	**Definitions**	A definition based on five days of OCS is preferred to three to better fit with the recognized harmfulness of cumulative doses of OCS; a composite score assessing risk factors (age, comorbidities, history) would be helpful.
2	**Triggers and risk factors**	Within trajectories of asthma, the frequent exacerbator phenotype is a reality, and is more frequently associated with a T2 pattern
2A	*Assessment of risk, What is cause and what is effect*	T2 inflammation and lack of adequate treatment more likely exposes to exacerbation rather than the opposite.
2B	*Modifiable vs non-modifiable factors & Mathematical models*	Viral infections are now considered modifiable, associated with prevention of noxious environmental exposures.
2C	*Risk Factors and epidemiology, pheno/geno/endotypes*	Susceptibility to severe exacerbations is not always shared with susceptibility to asthma severity. Low T2 asthma and other newly identified endotypes are currently orphans of targeted drugs.
2D	*Personality type – Gender, Psychosocial factors. Perception, Compliance/adherence*	Multidisciplinary approaches may help in identifying and managing better patients at risk of death, ICU admission and severe exacerbations
2E	*Virus / Allergens*	Rhinoviruses are ideal culprit fostering severity of exacerbations amplifyable by allergens. No dedicated treatment or preventive strategy currently exist.
2F	*Environmental air pollution indoor/outdoor pollution & occupational factors*	Although obvious, the environmental impact is under-recognized and occupational factors insufficiently assessed and evidenced in practice.
2G	*Drugs & irritants / Overdose of β_2-agonists*	Dangers of high SABA use includes worsening of asthma itself.
3	**Acute Management**	Systemic corticosteroids and bronchodilators are still the cornerstones of the acute management. Because some asthma deaths are not preventable, there is a place to develop new drugs on top of standard of care
4	**Prevention**	Inhaled corticosteroids +/- bronchodilators and in eligible patients with more severe disease biologics prevent severe exacerbations.

5	**ELF Patient perspective**	The currently available treatments and supports are not working well enough for all. More research and partnership are needed.

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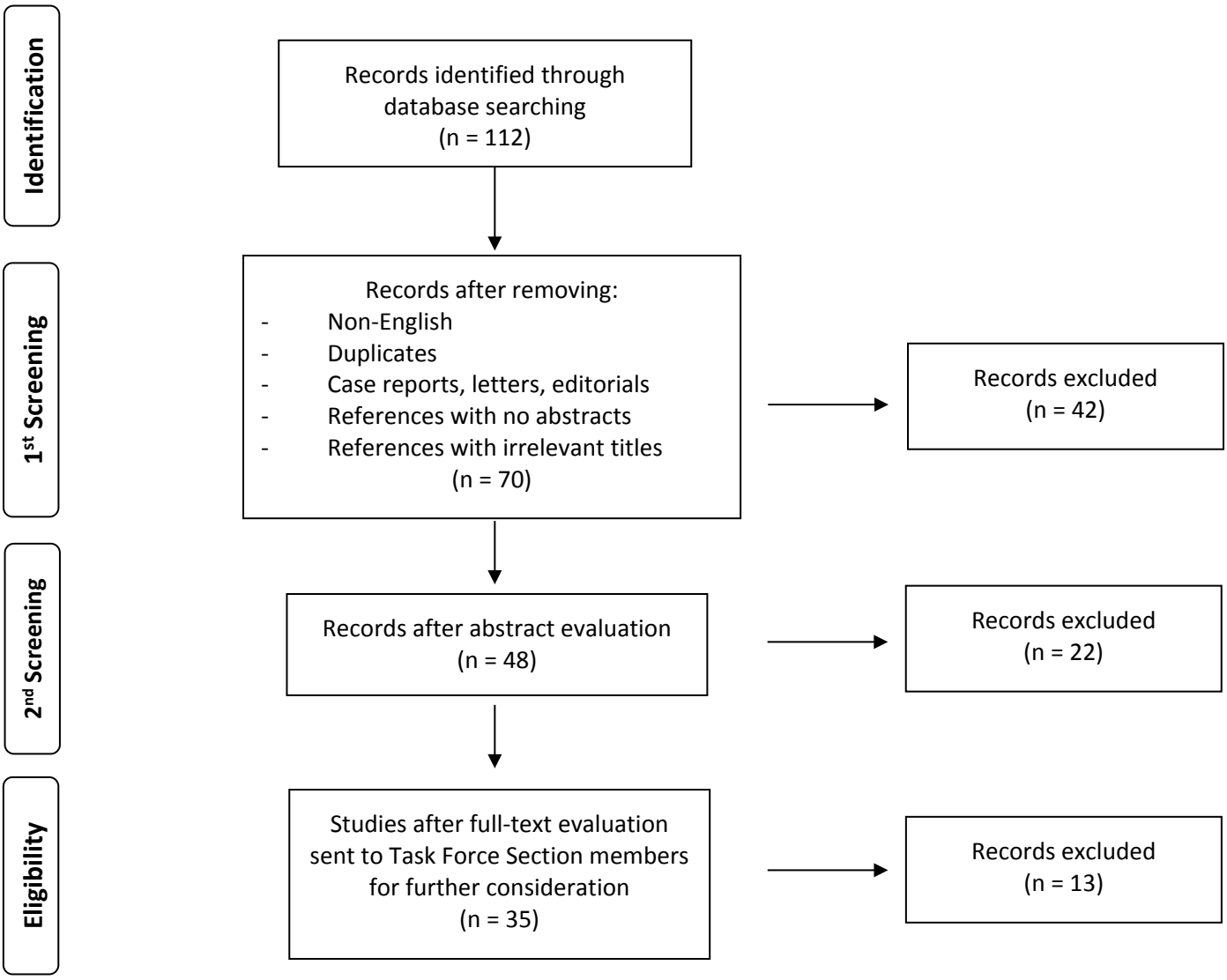
FLOW CHART: SECTION 1



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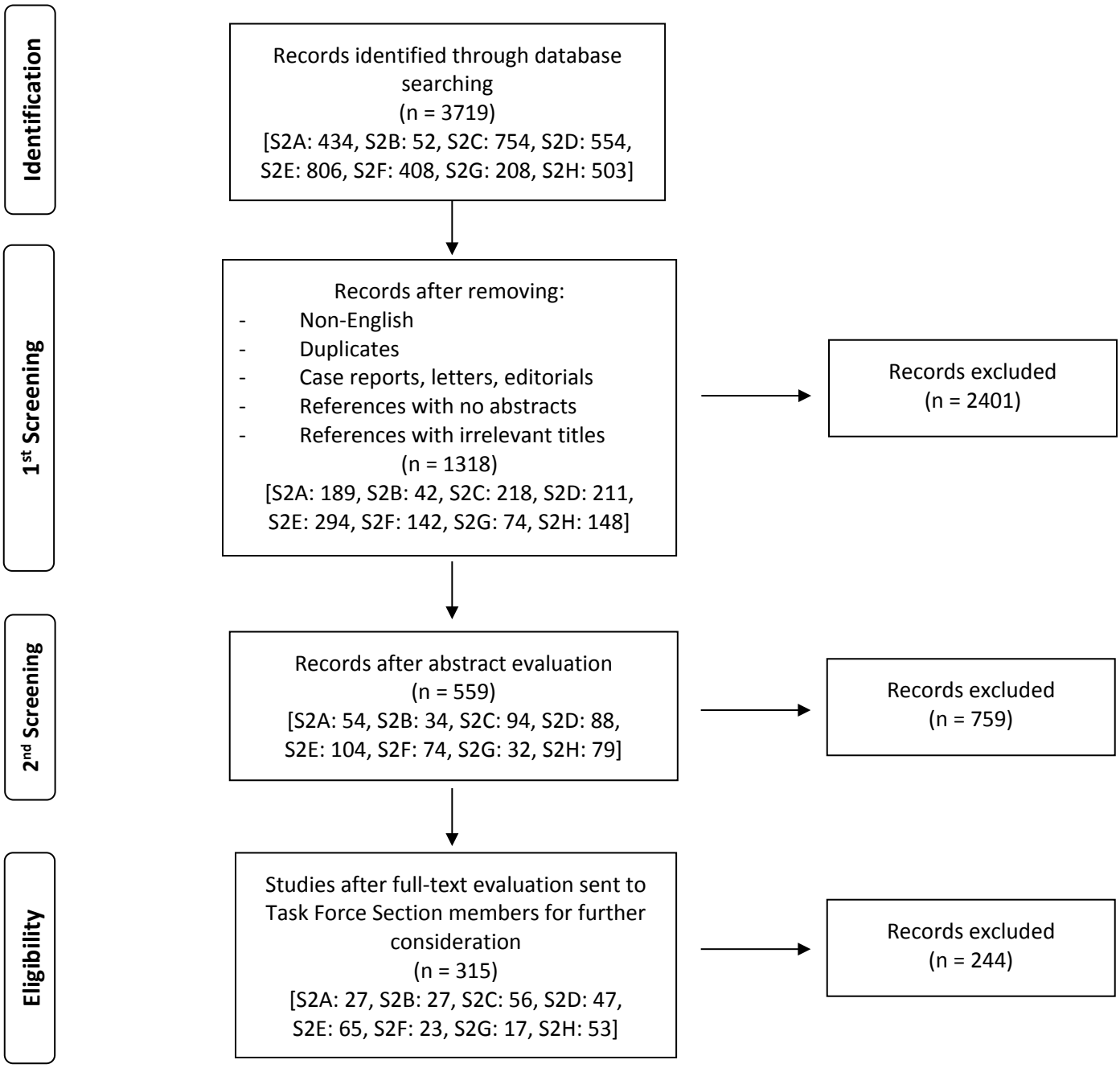

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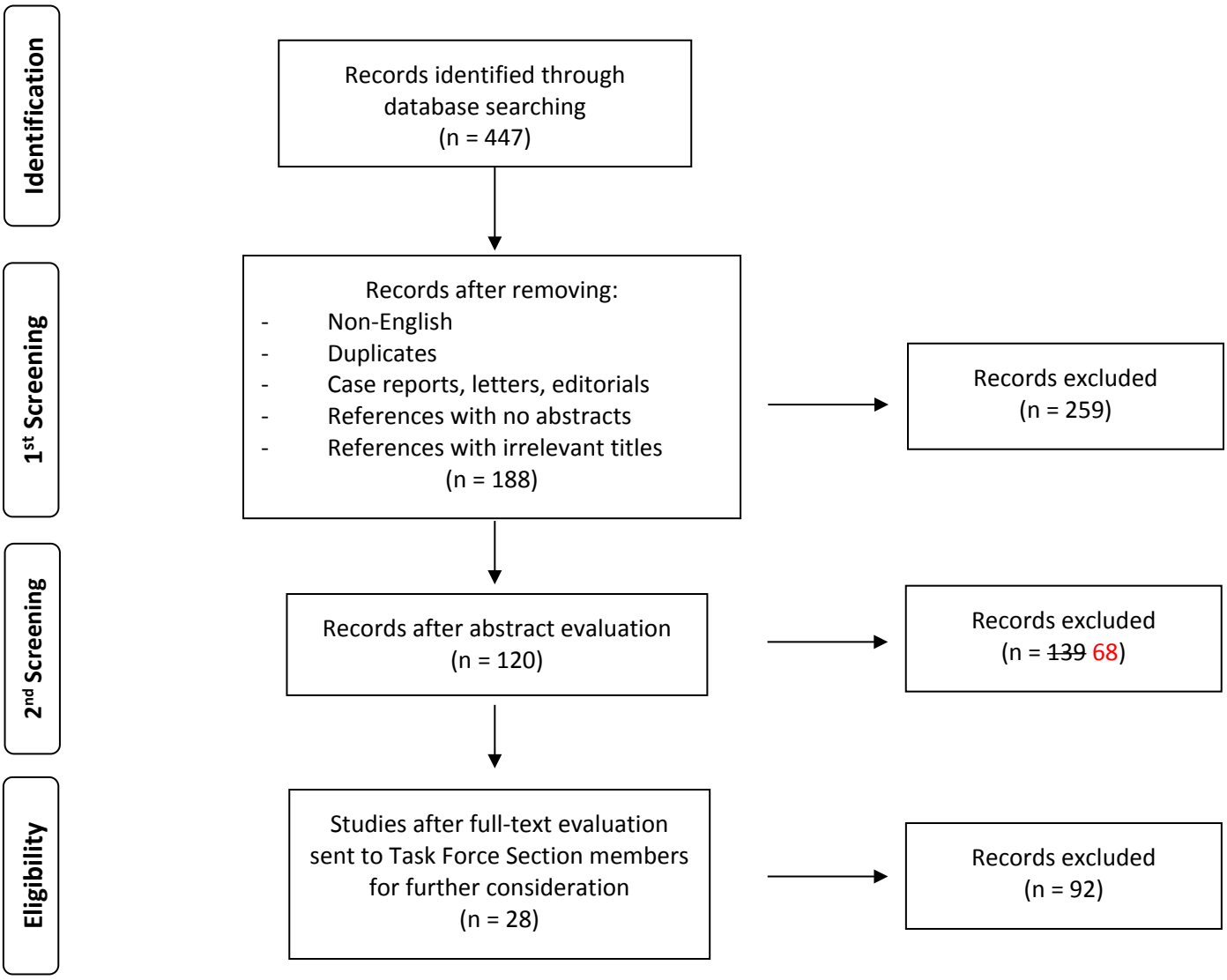
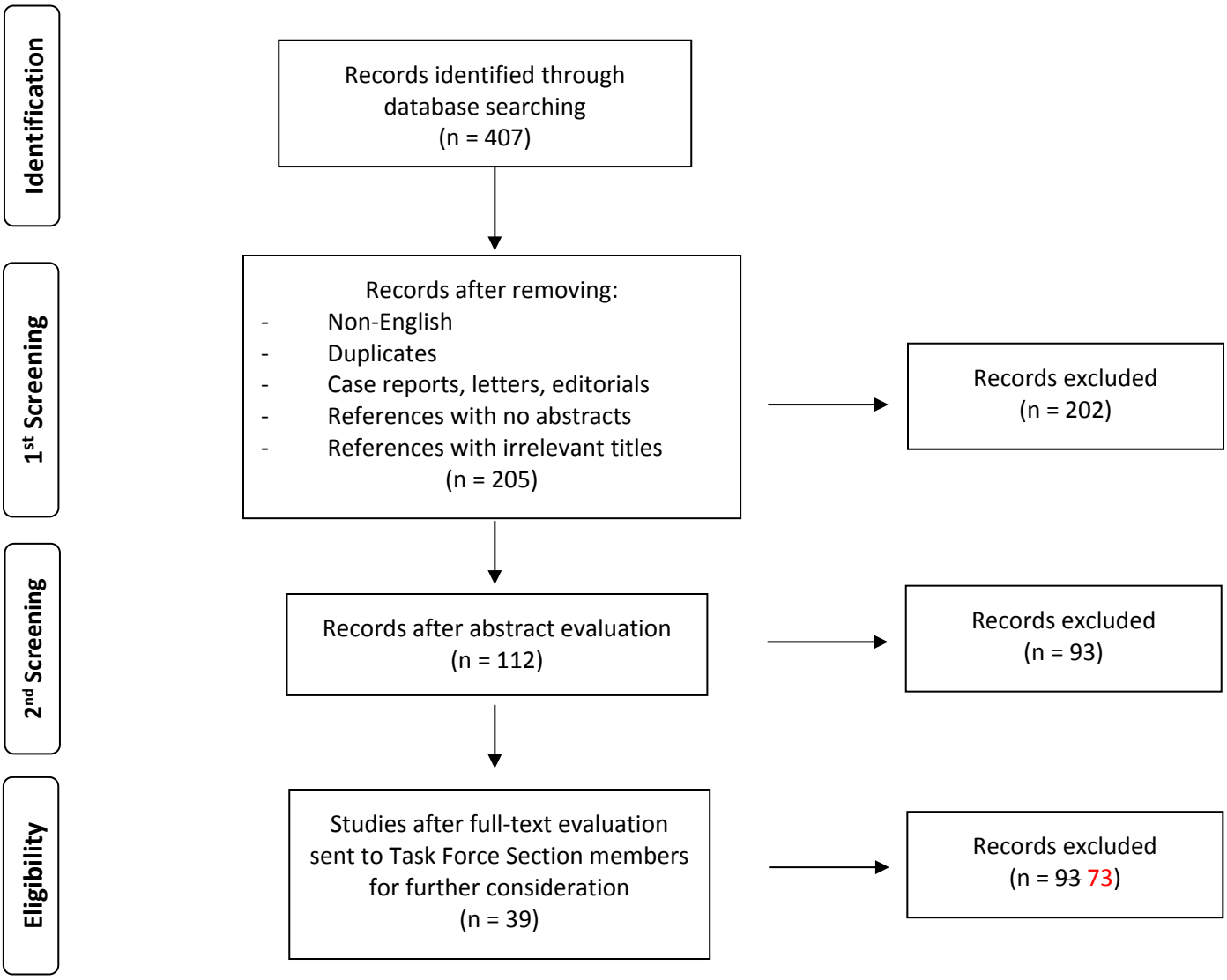
FLOW CHART: SECTION 4