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Expert Consensus on the Tapering of Oral Corticosteroids for the Treatment of Asthma

A Delphi Study

Carey M. Suehs¹, Andrew Menzies-Gow², David Price^{3,4}, Eugene R. Bleeker⁵, Giorgio Walter Canonica⁶, Mark Gurnell^{7,8}, and Arnaud Bourdin^{1,9}; on behalf of the Oral Corticosteroids Tapering Delphi Expert Panel

¹Département des Maladies Respiratoires and ⁹PhyMedExp, Université de Montpellier, Institut National de la Santé et de la Recherche Médicale, Centre National de la Recherche Scientifique, Centre Hospitalier Universitaire Montpellier, Montpellier, France; ²Royal Brompton and Harefield National Health Service Foundation Trust, London, United Kingdom; ³Observational and Pragmatic Research Institute, Singapore; ⁴Division of Applied Health Sciences, Centre of Academic Primary Care, University of Aberdeen, Aberdeen, United Kingdom; ⁵Department of Medicine, University of Arizona, Tucson, Arizona; ⁶Personalized Medicine, Asthma and Allergy Center, Humanitas University and IRCCS Research Hospital, Milan, Italy; and ⁷Wellcome Trust–Medical Research Council Institute of Metabolic Science and ⁸Cambridge National Institute for Health Research Biomedical Research Centre, University of Cambridge and Addenbrooke's Hospital, Cambridge, United Kingdom

Abstract

Rationale: There is a need to minimize oral corticosteroid (OCS) use in patients with asthma to prevent their costly and burdensome adverse effects. Current guidelines do not provide recommendations for OCS tapering in patients with asthma.

Objectives: To develop expert consensus on OCS tapering among international experts.

Methods: A modified Delphi method was used to develop expert consensus statements relating to OCS use, tapering, adverse effects, adrenal insufficiency, and patient–physician shared decision-making. Initial statements proposed by experts were categorized, filtered for repetition, and presented back to experts over three ranking rounds to obtain consensus ($\geq 70\%$ agreement).

Measurements and Main Results: One hundred thirty-one international experts participated in the study, and 296 statements were ranked. Numerous recommendations and guidance regarding

appropriate OCS use were established. Experts agreed that OCS tapering should be attempted in all patients with asthma receiving maintenance OCS therapy, with personalization of tapering rhythm and speed. The importance of recognizing individual adverse effects was also established; however, a unified approach to the assessment of adrenal insufficiency was not reached. Shared decision-making was considered an important goal during the tapering process.

Conclusions: In this Delphi study, expert consensus statements were generated on OCS use, tapering, adverse-effect screening, and shared decision-making, which may be used to inform clinical practice. Areas of nonconsensus were identified, highlighting uncertainty among the experts around some aspects of OCS use in asthma, such as adrenal insufficiency, which underscores the need for further research in these domains.

Keywords: adrenal insufficiency; adverse effects; shared decision-making; biological treatments

Author Contributions: The study facilitator (C.M.S.) designed the study, developed the protocol and data-collection tools, classified hundreds of raw brainstorming statements, organized survey logistics, collected and analyzed the data, and wrote the report. The steering committee (A.M.-G., D.P., E.R.B., G.W.C., M.G., and A.B.) provided initial recommendations of experts invited to enroll in the study and provided guidance to C.M.S. on study design, data collection, survey logistics, data analysis, and report writing. Expert panel members who contributed complete questionnaires to the study are listed in the online supplement.

Correspondence and requests for reprints should be addressed to Carey M. Suehs, Ph.D., Department of Respiratory Diseases, Hôpital Arnaud de Villeneuve, 371, Avenue du Doyen Gaston Giraud, F-34295 Montpellier Cedex 5, France. E-mail: c-suehs@chu-montpellier.fr.

At a Glance Commentary

Scientific Knowledge on the

Subject: Cumulative oral corticosteroid (OCS) treatment for asthma is associated with costly and burdensome side effects and comorbidities. “OCS stewardship” is advocated to protect patients from inappropriate OCS use and its consequences. The advent of effective OCS-sparing biological therapies also fosters new opportunities for tapering. Currently, evidence-based guidelines for OCS use, tapering, and associated comorbidity screening in asthma are lacking.

What This Study Adds to the Field:

In the absence of clinical data to develop evidence-based guidelines, this modified Delphi consensus study brought together experts with relevant knowledge and clinical experience to generate a high-quality expert consensus statement on OCS use and tapering. The recommendations thus generated support for minimizing OCS use as much as possible. A cumulative yearly dose of 0.5 or 1 g of prednisolone equivalents would be indicative of poor asthma control. They also provide a first step toward development of an OCS-tapering algorithm, as well as a minimum OCS adverse-event screening list. Little consensus was achieved concerning the assessment and management of adrenal insufficiency, supporting a need for future related research in this specific domain. Finally, the experts strongly support shared decision-making during OCS tapering.

corticosteroid (OCS) use compared with mild and/or moderate asthma (5–8).

Early use of OCSs in emergency-department asthma treatment reduces hospital admission rates (9), supporting its routine guideline-recommended use for asthma exacerbations (4). Indeed, during acute exacerbations, OCSs have been observed to provide rapid benefit (10). Nevertheless, such benefits may be dose- or duration-dependent, and the current guidance remains somewhat empirical. Long-term, low-dose OCS add-on therapy is restricted to Global Initiative for Asthma (GINA) step 5 and is positioned after trials of other more preferential add-on treatments (e.g., tiotropium and biologicals), with consideration of side effects (4). However, long-term OCS therapy continues to be widely used in severe asthma, with global usage estimated at 20–60% (11).

Recent studies across multiple therapeutic areas demonstrate that cumulative OCS use (including long-term and intermittent use) is associated with a dose- and duration-dependent risk of potentially serious adverse effects, including osteoporosis, hypertension, diabetes mellitus, cataracts, fractures, obesity, and gastrointestinal disorders (6, 11–13). Risk of adverse effects is evident at relatively low cumulative and mean daily OCS doses (12). Furthermore, long-term OCS use is associated with increased risk of mortality, reduced quality of life, and increased healthcare resource use and costs (5, 6, 14–16).

The costly and burdensome adverse effects associated with OCS use have prompted international respiratory experts to call for a structured “OCS-stewardship” approach to protect patients from inappropriate OCS use and its consequences (16, 17). Tapering has been strengthened by the availability of effective OCS-sparing biological therapies; however, the process should still be approached with caution to prevent symptom recurrence and to avoid risking unrecognized adrenal insufficiency (12, 18). Reporting on successful OCS-tapering protocols is most often indirect (i.e., the tapering algorithm is not the subject of study *per se*) and results in a diverse selection of study-specific algorithms (19–26), whose detail varies significantly between published studies. Current recommendations (4, 27) do not provide guidance on the choice of OCS-tapering protocol or how to taper otherwise. From a clinical perspective, the lack of asthma-specific guidelines on OCS

tapering and the systematic screening of adverse events represent key barriers to reducing OCS use (16). In the absence of clinical data to develop evidence-based guidelines, this modified Delphi consensus study aimed to bring together experts with relevant knowledge and clinical experience to generate a high-quality expert consensus statement on OCS use and tapering.

Methods

Study Design

An international panel of experts participated in a four-round Delphi study to develop a systematic consensus on OCS tapering. The protocol was approved by the Institutional Review Board, University Hospital of Montpellier (reference number 2019 IRB-MTP 04-12) and was registered on clinicaltrials.gov (NCT 03934801). Surveys were administered anonymously to the expert panel using SurveyMonkey online software (www.surveymonkey.co.uk). Statistical analyses were performed using the R programming environment (version 3.6.1; R Foundation for Statistical Computing) (28).

Participants and Expert Recruitment

The study steering committee (E.R.B., A.B., G.W.C., M.G., A.M.-G., and D.P.) provided initial recommendations of experts (on the basis of their professional and/or association networks) to be invited to enroll in the study, and eligible and/or responding experts were asked to recommend additional experts in the field. Pulmonologists and/or respiratory-disease specialists, allergists, endocrinologists, pediatricians, rheumatologists, and patient advocacy-organization representatives were eligible for study enrollment. Clinicians were required to manage patients on a weekly basis and have clinical experience in managing disease after OCS tapering and/or withdrawal to ensure a high degree of knowledge in OCS management. Patient advocacy organization representatives were required to represent an asthma patient-advocacy group. Experts were excluded if they were currently, or due to be (in the following 12 mo) employed by a pharmaceutical company or if they had ownership in a pharmaceutical company. Participants were encouraged to provide

Asthma is a chronic inflammatory disease, characterized by reversible airway obstruction and airway hyperresponsiveness (1), which affects ~339 million individuals worldwide (2). Approximately 5–10% of the overall asthma population has severe asthma (3), defined as uncontrolled asthma despite adherence to maximal optimized therapy and treatment of contributory factors (4). Severe asthma is associated with greater asthma-related morbidity, increased healthcare costs, more frequent exacerbations, and greater oral

complete responses to all survey rounds, and reminders were delivered daily.

Round 1: expert demographics and brainstorming. Participants completed an electronically administered questionnaire to provide demographic information, including age, sex, qualifications, practice environment, specialty, years since training completion, time spent caring for patients treated with OCSs, and number of patients seen per year. To initiate the brainstorming process, the questionnaire included open-ended questions to generate an initial list of statements pertaining to six categories: appropriate OCS use, OCS tapering, addressing adverse effects, adrenal insufficiency, patient-physician shared decision-making, and other aspects they believed to be important. Experts were informed that all OCS dosages should be expressed as prednisone-equivalent dosages, as reported in GINA guidelines (4). Raw statements (which refer to adult patients unless otherwise indicated) were categorized, filtered to avoid repetition, and amended for clarity (if necessary) to generate a final list of statements for ranking. The demographics plus brainstorming and ranking questionnaires are available on the Open Science Framework platform (<https://osf.io/wrdbu/>).

Rounds 2, 3, and 4: ranking. The final list of statements was presented to experts for ranking using a predefined Likert scale ranging from “strongly disagree” (−2 points) to “strongly agree” (+2 points). Experts were also asked to select specific responses for treatment duration, threshold values, and assessment frequencies. A stopping rule was enforced for a given statement when $\geq 70\%$ of experts indicated “agree” or “strongly agree” (positive consensus) or when $\geq 70\%$ indicated “disagree” or “strongly disagree” (negative consensus) during any round. For statements requiring a specific response, consensus was defined as 70% of experts providing an identical response. Items that achieved consensus were not re-presented in subsequent ranking rounds.

Results

Participants

Of the 363 experts invited to participate in this Delphi study, 169 were enrolled in the expert panel and 131 completed at least one of the four survey rounds (Figure 1A). Participant attrition rates during the ranking process were low; of the 108 experts who participated

in the first ranking round, 96 proceeded to complete all three rounds of ranking (Figure 1B). Most experts were pulmonologists (73%) or allergists (18%); however, a wide range of specialties were represented in the study. Demographics and professional characteristics of the expert panel are provided in Table 1.

Ranking Results

The initial brainstorming survey was completed over a 2-month period (April to May of 2019), and three rounds of ranking surveys (rounds 2–4) were completed between August 31 and September 26, 2019. Ninety-one experts provided at least one brainstorming statement, and 1,447 statements were generated in total. Raw statements were categorized and filtered to avoid repetition, resulting in a final list of 296 statements. The following sections summarize key points of consensus but do not cover all 296 items presented to the experts. For the full ranking results for all 296 statements, see pp. 1–21 in the online supplement.

Section 1: appropriate OCS use for the treatment of asthma. Over 95% of experts agreed or strongly agreed with the following statement: “In general, our goal should be not to use OCSs. When nevertheless required, dose and duration should be minimized.”

SHORT-TERM OCS USE. Positive consensus was reached for five out of six statements regarding appropriate short-term OCS use (see numbers 1.2.a–1.2.f on p. 1 of the online supplement). Short-term OCS use (<15 d) was deemed appropriate in patients experiencing acute nonresolving or life-threatening exacerbations and in patients experiencing eosinophilic or allergic exacerbations. Experts also agreed that short-term OCS use was appropriate within an asthma-management plan or to avoid hospitalization. No consensus was reached on whether short-term OCS use was appropriate to palliate unavailability of hospitalization services. Experts agreed that 5–7 days constitutes the usual maximal duration for a short course of OCSs for treatment of an exacerbation and that the optimal dosage of a short course of OCSs should be 0.5 mg/kg/d. Items that remained controversial included whether dosages for short courses of OCSs for treatment of an exacerbation should remain stable and whether the need for individual tailoring of the OCS dose would render systematic application of “ideal” doses unlikely.

MAINTENANCE OCS USE. Nine statements were proposed regarding

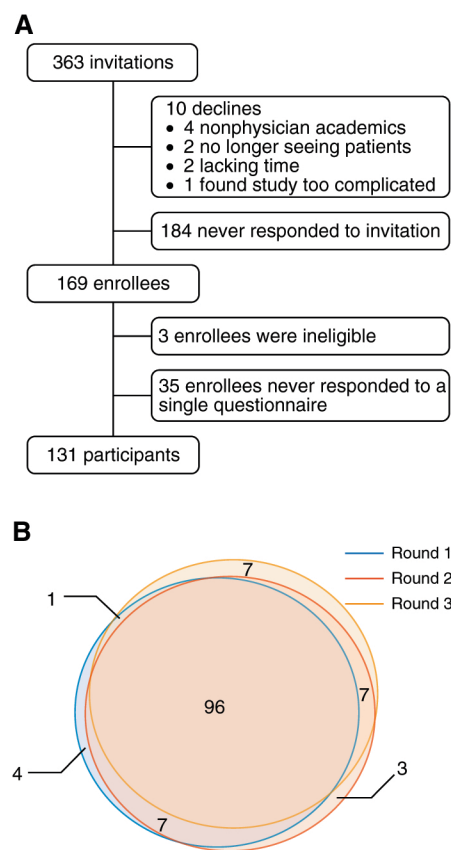


Figure 1. (A) Study flow diagram. (B) Expert participation in three statement-ranking rounds.

appropriate use of OCS as a maintenance (long-term) treatment, with five statements reaching consensus (see numbers 1.6.a–1.6.i on pp. 1–2 of the online supplement). Maintenance OCS use was considered appropriate in patients with severe asthma experiencing inadequate control despite optimization of GINA step 5 treatments or when adverse effects that could not be managed by another treatment presented during a tapering attempt. Consensus was also reached on 8 of 13 statements characterizing an adequate response to long-term OCS use (see numbers 1.9.a–1.9.m on pp. 2–3 of the online supplement). In situations in which OCS maintenance treatment is appropriate, experts considered ≤ 5 mg/d to be an acceptable dose (Figure 2).

Maintenance OCS use remained controversial in the context of adrenal insufficiency and to reduce overall OCS exposure. There was no consensus on whether maintenance OCS use is appropriate on the basis of a patient's type 2 (T2) phenotype.

Table 1. Expert-Panel Demographic Data

Variable	Sample Size (n)	Mean ± SD, Median (IQR), or Percentage
Age, yr	131	50.6 ± 9.64
Sex	131	—
F	35/131	26.72%
M	96/131	73.28%
Academic qualification	131	—
M.D. (or equivalent)	129	98.47%
Ph.D.	71	54.20%
Master's degree	8	6.11%
Practice environment	131	—
University hospital	117	89.31%
Private practice	11	8.40%
Academic environment	37	28.24%
Patient-care environment	13	9.92%
Medical-practice environment	14	10.69%
Other	7	5.34%
Specialty	131	—
Allergist	24	18.32%
Endocrinologist/metabolic	8	6.11%
Pediatrician	1	0.76%
Patient advocacy–organization representatives	2	1.53%
Pulmonologist/respiratory-disease specialist	95	72.52%
Rheumatologist	1	0.76%
Years since completion of training	131	19 (10–27)
Approximate percentage of work spent in caring for patients treated with OCSs	131	15 (5–30)
How often tapering is attempted in patients receiving OCSs	131	—
NA (patient advocacy–organization representative)	2	1.53%
Occasionally	4	3.05%
Frequently	48	36.64%
Systematically	77	58.78%
Participation in studies with aim of OCS tapering	80	61.07%
Concerning OCS		
Protocols, no.	131	2 (1–4)
Scientific articles, no.	131	2 (0–5)
Patients seen/yr, no.	131	50 (25–100)
Concerning asthma		
Protocols, no.	131	10 (4–20)
Scientific articles, no.	131	30 (6–60)
Patients seen/yr, no.	131	300 (100–500)
In all		
Protocols, no.	131	20 (10–40)
Scientific articles, no.	131	67 (25–132)
Patients seen/yr, no.	131	600 (400–1,200)

Definition of abbreviations: IQR = interquartile range; NA = not applicable; no. = number; OCS = oral corticosteroid.

Over 90% of experts agreed or strongly agreed that the annual cumulative OCS dose should be monitored as a marker of asthma control. Over 75% of experts selected a threshold of 0.5 g or 1 g as the annual cumulative OCS dose indicative of poor control in ranking round 3 (Figure 3).

It was agreed that biological therapies are useful OCS-sparing agents and that patients should be systematically assessed

for suitability for biological therapy. The daily OCS dose may represent a reliable marker for the evaluation of the biological treatment response (*see numbers 1.16.g and 1.17.a–1.17.c on p. 5 of the online supplement*).

Section 2: OCS tapering. Two general statements reached positive consensus in the first round of ranking: 1) “Tapering (down to a minimal efficacious dose or complete

weaning, if possible) should be attempted in all patients with asthma receiving maintenance OCS therapy, regardless of comorbidities” and 2) “The rhythm and speed of OCS tapering requires individualization for each patient.”

Multiple statements reached positive consensus on when it may be appropriate to attempt OCS tapering and when cautious slow attempts of tapering and complete OCS cessation are appropriate (Table 2). Tapering was deemed appropriate in multiple cases (*see numbers 2.2.a–2.2.f on p. 5 of the online supplement*), including when the intensity or duration of OCS use is a cause for concern or when a patient exhibits OCS-related adverse effects or a lack of response to OCSs, holds a reasonable likelihood of hypothalamic–pituitary–adrenal axis recovery, or experiences improved asthma control after initiation of biological therapy. Tapering was also deemed appropriate in patients experiencing asthma control with OCS maintenance therapy for a minimum agreed-on time; however, the duration of the minimum length of time remained controversial.

Tapering attempts were deemed inappropriate in patients with eosinophilic granulomatosis with polyangiitis or allergic bronchopulmonary aspergillosis that relapses during tapering (*see numbers 2.4.b–2.4.c on p. 6 of the online supplement*). Further statements that remained controversial included tapering in patients who demonstrated potentially harmful effects during previous tapering attempts and whether tapering should be attempted in patients with adrenal insufficiency (*see numbers 2.4.a and 2.4.d on pp. 5–6 of the online supplement*).

Experts agreed that OCS tapering should incorporate some aspect of individualization, and multiple factors were considered that may influence the rhythm and speed of OCS tapering (*see numbers 2.5.a–2.5.g on p. 6 of the online supplement*); such factors included duration of previous maintenance OCS treatment, history and future risk of adverse effects, and type of adverse effect present. Three statements that remained controversial concerned the speed of OCS tapering in patients with a fast or slow response to OCSs, whether OCS tapering should be guided by biomarkers at each weaning step, and whether the speed of tapering should be dependent on the known rapidity of action of the OCS-sparing drug introduced.

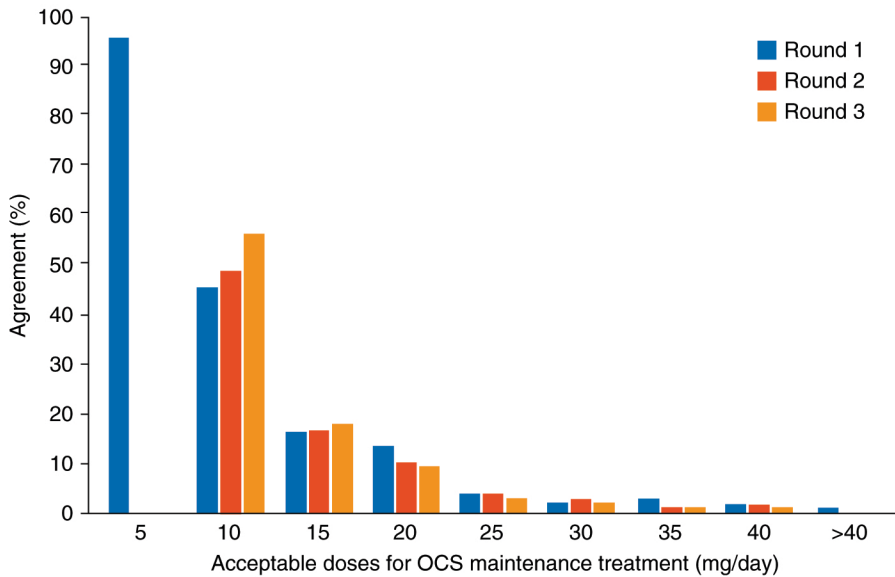


Figure 2. Percentage of agreement among experts on acceptable doses for maintenance OCS treatment. OCS = oral corticosteroid.

Five statements concerning the characteristics of an acceptable OCS-tapering algorithm reached positive consensus, and three statements remained controversial (Table 3). Experts agreed that biologicals should play an important role in OCS tapering and that failure to achieve a $\geq 50\%$ OCS dose reduction indicates failure of the biological and may warrant

switching strategies (see numbers 2.11.c and 2.11.e on p. 9 of the online supplement); furthermore, when writing prescriptions, the option to reduce the dose should be considered (see number 2.12.c on p. 9 of the online supplement).

Section 3: addressing OCS-related adverse effects. All five general statements concerning adverse effects reached positive

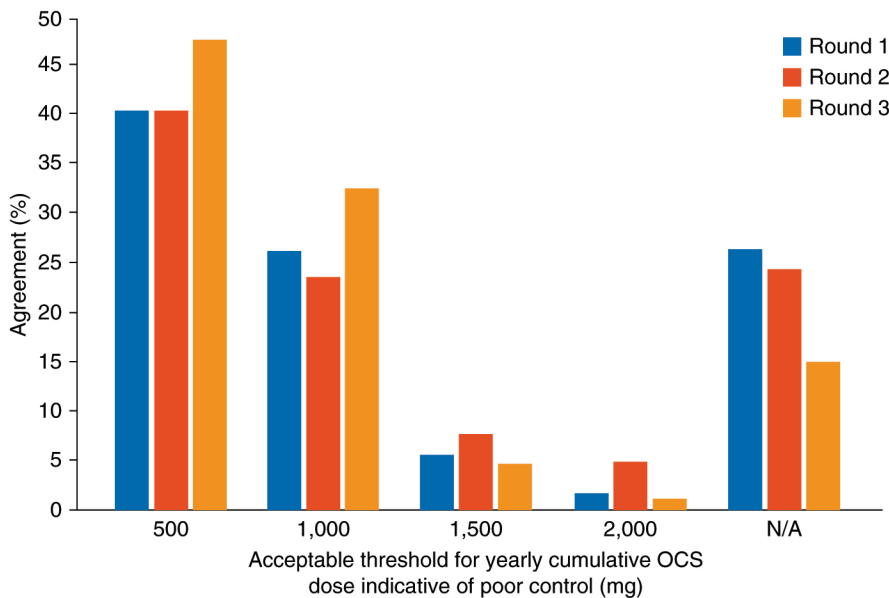


Figure 3. Percentage of agreement among experts for threshold options indicating a yearly cumulative OCS dose that is suggestive of poor asthma control. N/A = not applicable; OCS = oral corticosteroid.

consensus in the first round of ranking (see numbers 3.1.a–3.1.e on p. 9 of the online supplement). Experts agreed that patients receiving OCS were at greater risk of adverse effects compared with patients receiving no OCS, and adverse effects should always be addressed but should not preclude attempting to taper OCSs to the lowest possible dose.

Experts reached positive consensus on two of three adverse-effect subsets of patients for whom OCS tapering should be a priority (see numbers 3.4.a–3.4.c on pp. 10–11 of the online supplement). A positive consensus was achieved in the first round of ranking for 7 of 10 elements that should be included in a minimum checklist for adverse-effect screening in patients receiving OCS therapy, and three statements remained controversial (Table 4).

Section 4: managing adrenal insufficiency. The majority of statements (44/55 [80%]) concerning adrenal insufficiency failed to reach consensus after three ranking rounds. Many statements that remained controversial concerned the subpopulations in which adrenal insufficiency should be assessed (see numbers 4.3.a–4.3.f and 4.4.a–4.4.d on pp. 13–14 of the online supplement). Experts agreed that adrenal insufficiency should be assessed in individuals on regular, long-term OCS therapy. In addition, a positive consensus was almost reached (69% agreement) on statements indicating that adrenal insufficiency should be assessed in patients exceeding an OCS dose of 2 g/yr or in patients receiving more than four repeated OCS short courses per year.

Experts agreed that adrenal insufficiency is inadequately assessed (see number 4.11.a on p. 16 of the online supplement) and should be assessed regularly (see number 4.1.a on p. 12 of the online supplement) and when OCS tapering has failed in OCS-treated patients (see number 4.5.b on p. 14 of the online supplement). Experts also agreed that signs of adrenal insufficiency should be symptomatically treated as much as possible during the tapering process and should not be viewed as a reason to give up on tapering altogether (see number 4.1.b on p. 12 of the online supplement). Experts agreed that adrenal insufficiency should be assessed using fasting morning cortisol and, in case of intermediate results, follow-up with a (short) tetracosactide/cosyntropin

Table 2. Consensus Statements on OCS Tapering

	Strongly Disagree (%)	Disagree (%)	Neutral (%)	Agree (%)	Strongly Agree (%)	Weighted Mean Rank*
Proceeding toward a tapering attempt is particularly appropriate when:						
Biological treatment has been initiated and results in asthma control	0.00	0.95	0.95	25.71	72.38	1.70
The patient does not appear to respond to OCS treatment	0.00	0.95	0.95	35.24	62.86	1.60
A patient exhibits symptoms/comorbidities likely linked to OCSs	0.00	1.90	2.86	41.90	53.33	1.47
Patients receiving maintenance OCS treatment have gained control (for a minimum agreed-on time)	0.00	0.00	3.81	59.05	37.14	1.33
The intensity or duration of OCS treatment gives reason for concern	0.00	0.00	3.81	59.05	37.14	1.33
There is reasonable likelihood of hypothalamic–pituitary–adrenal axis recovery	0.00	1.90	11.43	54.29	32.38	1.17
Tapering should not be attempted in patients who:						
Have EGPA that relapses during tapering (and no other changes can be proposed)	0.95	3.81	12.38	66.67	16.19	0.93
Have ABPA that relapses during tapering (and no other changes can be proposed)	0.00	9.52	19.05	61.90	9.52	0.71
Cautious slow tapering is particularly appropriate for patients who:						
Have had life-threatening attacks	0.95	3.81	3.81	60.00	31.43	1.17
Have been dependent on systemic steroids for an extended period (e.g., 6 mo or more)	0.00	2.86	6.67	63.81	26.67	1.14
Have comorbidities that respond to OCSs	0.00	3.81	9.52	70.48	16.19	0.99
Complete OCS cessation (weaning) can be implemented:						
After a short course of OCS treatment that lasted for 5–7 d	0.95	1.90	1.90	44.76	50.48	1.42
After a short course of OCS treatment if patients are receiving inhaled antiinflammatory therapy	1.90	1.90	2.86	48.57	44.76	1.32
When a sparing strategy has been initiated	0.95	2.86	14.29	54.29	27.62	1.05
When there is no evidence of adrenal insufficiency	0.95	6.67	13.33	59.05	20.00	0.90
When the patient has agreed to cessation	1.90	4.76	20.00	50.48	22.86	0.88
When there is no evidence of EGPA or ABPA	0.00	7.62	19.05	56.19	17.14	0.83
When the OCS dose is ≤5 mg of prednisolone	0.95	15.24	13.33	53.33	17.14	0.70

Definition of abbreviations: ABPA = allergic bronchopulmonary aspergillosis; EGPA = eosinophilic granulomatosis with polyangiitis; OCS = oral corticosteroid.

*Note that statements are ordered by mean rank score.

(e.g., Synacthen) test should be used (*see* number 4.9.c on p. 15 of the online supplement). An additional general statement regarding whether hydrocortisone replacement is preferred to continued prednisolone almost reached positive consensus, with 65% of experts agreeing with the statement and 8% disagreeing; the remaining percentage remained neutral on the subject (*see* number 4.1.c on p. 12 of the online supplement).

Consensus was reached on the need for the treating respiratory physician to assess for adrenal insufficiency in patients with severe asthma, and it was agreed that management of adrenal insufficiency in

patients with severe asthma should involve an endocrinologist or a multidisciplinary approach (*see* numbers 6.1.c–6.1.d on p. 20 of the online supplement).

Section 5: patient–physician shared decision-making. Experts agreed that shared decision-making should be a systematic practice and that self-management should be limited to individuals with good levels of comprehension (*see* numbers 5.1.a and 5.1.d on p. 17 of the online supplement). Eight statements achieved positive consensus on the importance of shared decision-making (*see* numbers 5.2.a–5.2.h on p. 17 of the online supplement), and 14 statements reached positive consensus concerning the content to be included in

the shared decision-making process (*see* numbers 5.3.a–5.3.n on pp. 17–18 of the online supplement).

Section 6: miscellaneous. Experts agreed that primary care physicians prescribing at least three courses of OCSs per year to a patient should consider specialist referral (*see* number 6.2.a on p. 20 of the online supplement). Experts also achieved positive consensus on 16 of 17 statements concerning future research of OCS tapering (*see* numbers 6.3.a–6.3.q on pp. 20–21 of the online supplement). The only subject that remained controversial concerning future work was the efficacy of internet-provided algorithms for delivering

Table 3. Consensus Statements Concerning Development of an OCS-Tapering Algorithm

Positive Consensus	Controversial
<ul style="list-style-type: none"> • The initial tapering of high OCS doses (e.g., >20 mg/d) can proceed at a faster pace (e.g., –10 mg/wk or 30–50% reductions every 2–4 wk). • OCS tapering should be gradual, with 2.5- to 5-mg steps every 0.5–2 wk until an agreed-on threshold is achieved (e.g., 5–10 mg/d), and should then proceed at a slower pace (1–2.5 mg every 1–2 wk). • When a reduction in the OCS dose by 5 mg/wk fails, a slower and lower dose reduction of 1 mg/wk should be attempted. • If mild symptoms occur, maintain the current dosage; they are likely to resolve as endogenous-axis recovery occurs. • If intolerable symptoms occur, return to the previous (efficacious) dose and then later consider reattempting tapering at a slower pace. 	<ul style="list-style-type: none"> • In general, the speed of tapering should not exceed a reduction of 5 mg/wk. • OCS tapering should incorporate every-other-day OCS reductions (especially before discontinuation) to allow recovery of the endogenous axis. • OCS tapering should be gradual by reducing the OCS dose by 30–50% every 2–4 wk.

Definition of abbreviation: OCS = oral corticosteroid.

symptom-driven OCS-tapering guidance to patients with asthma.

Discussion

This Delphi study generated expert consensus and recommendations on numerous statements concerning appropriate OCS use, OCS tapering, adverse effects, patient–physician shared decision-making, and future research domains. Consensus was reached on general statements concerning adrenal insufficiency; however, beyond generalities, consensus was not reached. Hence, improving the assessment of adrenal insufficiency was one of multiple domains identified as requiring future research.

To our knowledge, no existing asthma-specific guidelines are currently available to guide OCS tapering in clinical practice. Consensus stated that tapering should be attempted in all patients with asthma receiving maintenance OCS therapy, regardless of comorbidities; however, the speed and rhythm of tapering should be

individualized. Furthermore, expert consensus was reached on characteristics of an acceptable OCS-tapering algorithm (Table 3), which constitutes a first step toward the development of OCS-tapering algorithms for use in clinical practice. These consensus and related information are summarized in Figure 4.

Successful OCS-tapering algorithms have been reported in the past (19–25, 29, 30) but vary greatly in content and reporting quality. Currently, the most detailed and recent OCS-tapering algorithm is being tested in the eagerly awaited PONENTE study (26). Certain previous studies also demonstrate that prescribing treatment guided by eosinophil levels can improve control while simultaneously resulting in some corticosteroid sparing (31–33). Current GINA guidelines suggest that OCS dose adjustment may be supported by internet-based monitoring of symptom control and exhaled nitric oxide; however, the latter contributed little to algorithm decisions, in favor of asthma control–questionnaire scores (34). In the current study, only asthma-control

questionnaires reached positive consensus as a useful tool during OCS tapering. The need for laboratory tests or at-home lung-function measurements may render many biomarker approaches impractical for patients and clinicians. In addition, GINA recommends gradually decreasing or stopping OCSs in patients with a good response to biological therapies. Successful corticosteroid reduction after initiation of biological therapies, using preset tapering protocols, has been demonstrated in multiple studies (18). However, the latter are often short-term in nature, with little focus on adrenal-function assessments, and the full potential of tapering was therefore not achieved/documentated. As the use of biological therapies increases, studies evaluating OCS-tapering regimens on a longer basis, which can be personalized on the basis of factors such as baseline OCS dosage and degree of asthma control, will become increasingly important (e.g., the PONENTE study) (26). The current consensus statement provides broader guidance on when and how to taper OCSs in patients with asthma (Figure 4), regardless of whether a biological therapy has been initiated.

Regarding appropriate OCS use, experts believed that long-term use is not appropriate in situations in which other treatment options are available. However, if no alternative treatment options are available, experts considered ≤ 5 mg/d to be an acceptable dose. This threshold is considerably lower than the definition in current GINA guidelines, which defines low-dose maintenance OCS use as ≤ 7.5 mg/d (4), and this may result from the way the question was designed to span the range of thresholds mentioned during the

Table 4. Minimal Checklist for Adverse-Effect Screening

Positive Consensus	Controversial
<ul style="list-style-type: none"> • Growth (pediatric population) • Glycemic control • Bone density • Blood pressure • Cataracts and glaucoma • Weight change • Fracture risk score (e.g., FRAX) 	<ul style="list-style-type: none"> • Cardiovascular risk score • Lipid panel • Fluid retention

Definition of abbreviation: FRAX = Fracture Risk Assessment Tool.

Adverse effects are not ordered/hierarchized and should be given equal consideration.

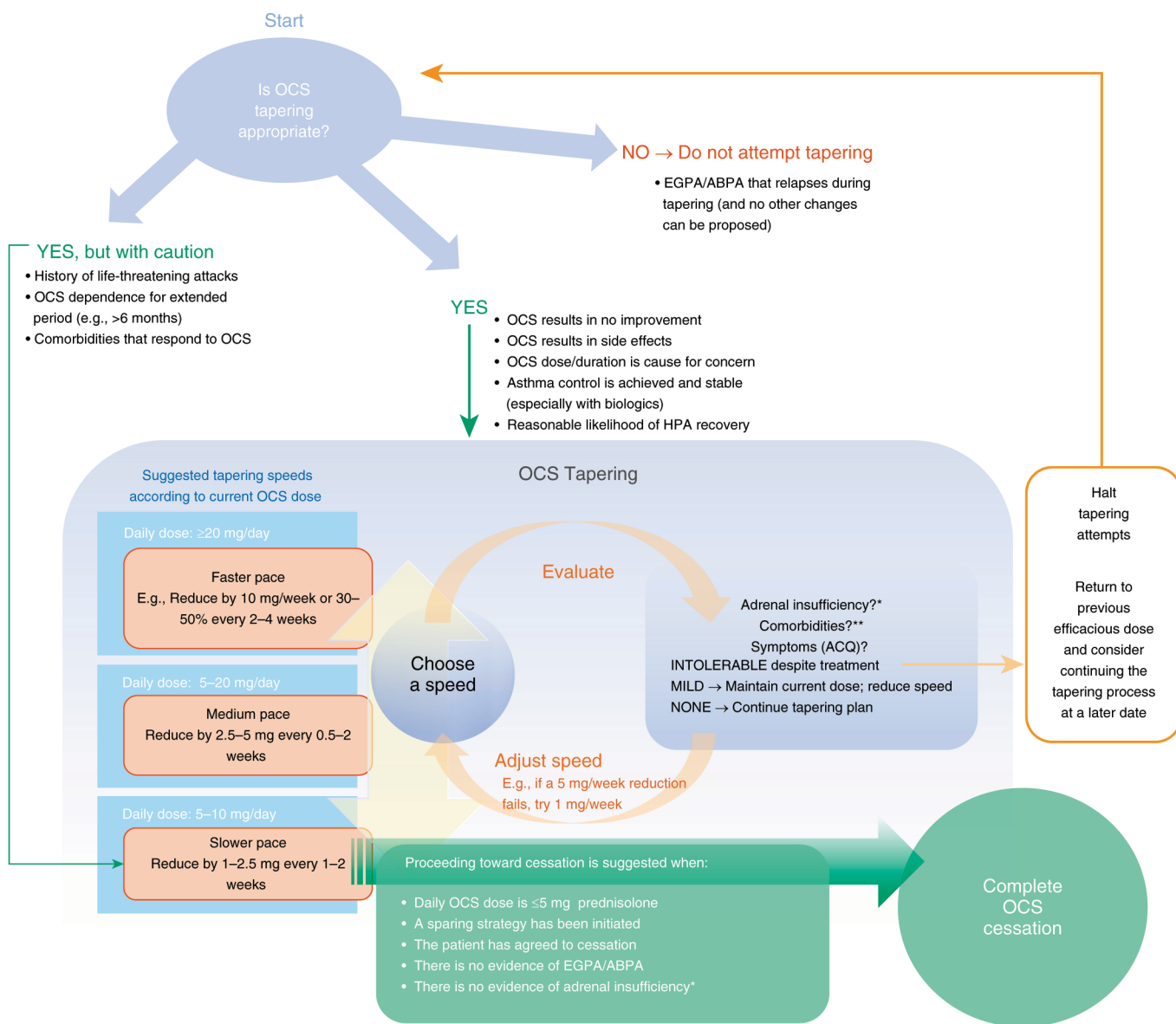


Figure 4. Graphic summary of consensus information on OCS tapering. ^{*}Adrenal insufficiency should be regularly assessed using fasting morning cortisol. In case of intermediate results, follow up with a (short) tetracosactide/cosyntropin test. Adrenal-insufficiency management should be multidisciplinary, involving an endocrinologist. ^{**}Comorbidity screening should include at least the following: glycemic control, bone density, blood pressure, cataracts and glaucoma, weight change, fracture risk score, and growth in pediatric populations. However, no consensus was achieved concerning the periodicity of comorbidity-screening measures. ABPA = allergic bronchopulmonary aspergillosis; ACQ = asthma-control questionnaire; EGPA = eosinophilic granulomatosis with polyangiitis; HPA = hypothalamic-pituitary-adrenal axis; OCS = oral corticosteroid.

brainstorming phase of the study. The reader should note that nonconsensus fractions of experts are willing to use 10 mg/d doses and higher, suggesting that there is considerable non-guideline-conforming OCS usage in the field, even among experts. The low consensus threshold at 5 mg may also reflect the increasing importance of biologics in the domain and the resulting opportunities for

tapering down to the lowest efficacious dose possible or complete cessation. Regardless, the reader should also keep in mind that a 5 mg/d OCS dose amounts to a cumulative dose exceeding 1.8 g/yr.

In this study, when experts were asked to consider cumulative OCS doses, they voted that 0.5 or 1 g/yr would be indicative of poor asthma control. This would correspond to approximately 3.5–7 months

of maintenance treatment at 5 mg/d. A previous study by Price and colleagues demonstrated that diabetes associated with OCS use emerged at lifetime cumulative systemic corticosteroid exposures of 0.5 to <1 g, with most other adverse events emerging at 1.0 to <2.5 g (12). Furthermore, a 2020 study stated that a yearly cumulative OCS dose above 1 g should be considered unacceptable in

severe asthma treatment and indicates the need for specialist referral (35). Even a short-term use, which amounts to a median of 20 mg/d for approximately 6 days in a large database study, is associated with an increase in sepsis, venous thromboembolism, and fracture in the next 30 days (36). These studies highlight the need for earlier specialist referral and earlier consideration of OCS-sparing strategies in patients receiving OCSs.

Biological therapies were a common subject among the experts, and the initiation of a successful biological therapy was the highest-ranked situation appropriate for initiating OCS tapering (Table 2). The reader should keep in mind that there are other important reasons for initiating tapering, such as side effects or nonresponse (Table 2). Key criteria for success of a biological therapy include maintenance of asthma control, a reduction in exacerbations, and a decrease in the dose of OCSs (27, 37). However, there is no clear guidance on the magnitude of OCS reduction that constitutes success or failure of a biological therapy. In this study, consensus stated that failure to achieve a $\geq 50\%$ reduction in the OCS dose indicates failure of the biological therapy and may warrant a switch in strategy. The guidance provided here will support clinical decision-making.

Items included on the minimal checklist for adverse-effect screening (Table 4) have been well documented in the literature among individuals receiving OCSs. Early detection of adverse effects has been shown to be important in the treatment and management of OCS-related complications; the items on the checklist provide a basis for adverse-effect screening in clinical practice (6, 11, 12, 38). This checklist further underlines the importance of adverse-effect prevention measures, including calcium and vitamin D supplementation and appropriate prescribing of bisphosphonates for osteoporosis, optimizing the inhaled-corticosteroid dose and medication adherence. The latter may in addition allow further reduction in the OCS dose.

Previous studies have shown that adrenal insufficiency is common among frequent users of OCSs after tapering (39);

however, the lack of clear guidance for clinicians on how to manage adrenal insufficiency may hinder OCS reduction in patients with severe asthma (16). Experts agreed on the need to regularly assess for adrenal insufficiency and agreed that fasting morning cortisol tests may be used (followed up with a [short] tetracosactide/cosyntropin test in case of intermediate results). Experts also highlighted the need for a process to be in place for referral to an endocrinologist alongside further research and potential education in this domain. The majority of experts agreed that use of hydrocortisone replacement therapy is preferential to continued prednisolone use to aid the tapering process in the case of adrenal insufficiency; however, consensus was not reached. The lack of consensus on this point is not surprising, given that the optimal strategy for glucocorticoid replacement in patients with adrenal insufficiency remains controversial in the literature. In the United Kingdom, hydrocortisone is the first-line treatment in management of adrenal insufficiency, followed by prednisolone (40). Prednisolone is less expensive, and some experts contend it may mimic the circadian rhythm more closely than the standard thrice-daily hydrocortisone therapy; however, prednisolone may also be associated with an increased relative risk of cardiovascular disease (40–42). Results of ongoing head-to-head studies will improve understanding regarding this issue (43).

Shared decision-making in OCS tapering was viewed positively by the experts. The consensus was that although the OCS-tapering process should be primarily driven by the physician, patients should contribute to the decision-making process and be educated on OCS use and tapering. Patients' perceptions are frequently ambivalent toward OCSs, and how they navigated previous tapering attempts should be taken into account. This is in line with emerging evidence showing that shared decision-making is becoming more common in asthma management and has been shown to improve patient adherence, outcomes, and satisfaction with care (44). Shared decision-making tools and/or platforms to facilitate this process (e.g., in References 45

and 46) require further development and validation for general populations with asthma.

The strengths of this study include participation of 131 experts across a range of specialties, ensuring that a wide breadth of knowledge and relevant expertise was represented among the expert panel. Results from this study also benefit from the anonymity of expert responses, alongside a clear, *a priori* definition of consensus criteria and controlled feedback. Importantly, a lack of participant attrition was observed throughout all three ranking rounds, increasing the validity of the consensus by avoiding suppression of minority opinions and minimizing potential for bias (47). A limitation of the study was the large number of raw statements that needed to be reduced and summarized; therefore, statements presented to experts were not fully representative of all the raw statements.

This Delphi consensus study provides expert consensus statements around OCS use and tapering, which may be used to inform clinical practice and optimize management of patients with severe asthma. The recommendations also provide a first step toward development of an OCS-tapering algorithm and support the ongoing OCS-stewardship effort by international respiratory experts to reduce the harm from inappropriate OCS use and its consequences. Although consensus was generated on numerous statements, many remained controversial, highlighting the existing uncertainty, even among international experts, around certain aspects of OCS use in asthma, such as assessment and management of adrenal insufficiency. These findings underscore the need for further research to inform clinical practice and drive future evidence-based guideline development.

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