Next-generation Allergic Rhinitis and Its Impact on Asthma (ARIA) guidelines for allergic rhinitis based on Grading of Recommendations Assessment, Development and Evaluation (GRADE) and real-world evidence

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Abstract

The selection of pharmacotherapy for patients with allergic rhinitis aims to control the disease and depends on many factors. GRADE (Grading of Recommendations Assessment, Development and Evaluation) guidelines have considerably improved the treatment of allergic rhinitis. However, there is an increasing trend to use real-world evidence to inform clinical practice, especially as randomized controlled trials are often limited with regards to the applicability of results. The MACVIA (*Contre les MAladies Chroniques pour un VIeillissement Actif*) algorithm has proposed an allergic rhinitis treatment by a consensus group. This simple algorithm can be used to step-up or step-down allergic rhinitis treatment. Next-generation guidelines for the pharmacologic treatment of allergic rhinitis were developed using existing GRADE-based guidelines for the disease, real-world evidence provided by mobile technology and additive studies (allergen chamber studies) to refine the MACVIA algorithm.

Key words

Allergic rhinitis, ARIA, GRADE, guidelines, real-world evidence

Abbreviations

AIRWAYS ICPs: Integrated care pathways for airway diseases
ARIA: Allergic Rhinitis and Its Impact on Asthma
Aze: Azelastine hydrochloride
DG Santé: European Commission's Directorate-General for Health and Food Safety
FF: Fluticasone furoate
FP: Fluticasone propionate
GRADE: Grading of Recommendations Assessment, Development and Evaluation
MACVIA: Contre les MAladies Chroniques pour un VIeillissement Actif
MASK: Mobile Airways Sentinel NetworK
MF: Mometasone furorate
mHealth: Mobile health
MPAzeFlu: Azelastine-Fluticasone propionate combination
MPR: Medication Possession Ratio
OTC: Over-the-counter
PDC: Proportion of days covered
RWE: Real-world evidence
VAS: Visual analogue scale
WHO: World Health Organization

Introduction

The selection of pharmacotherapy for patients with allergic rhinitis aims to control the disease and depends on (i) patient empowerment, preferences and age, (ii) prominent symptoms, symptom severity and multimorbidity, (iii) efficacy and safety of treatment (1), (iv) speed of onset of action of treatment, (v) current treatment, (vi) historic response to treatment, (vii) impact on sleep and work productivity (2, 3), (viii) self-management strategies and (ix) resource use (4, 5).

An algorithm was devised (5) and digitalized (6) to step-up or step-down allergic rhinitis treatment based on control. However, its use varies depending on the availability of medications and resources. Algorithms require testing with real-world evidence (RWE) that includes randomized controlled trials and observational research with real-world data (7-9).

To evaluate estimates of effects, the GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodology explicitly considers all types of study designs from Randomized Control Trials to case reports, although guideline developers often restrict guidelines to Randomized Control Trials (10-12). GRADE also considers evidence on prognosis, diagnosis, values and preferences, acceptability and feasibility or directness of findings. There is an increasing trend to use real-world data to inform clinical practice, especially as Randomized Control Trials are often limited to the applicability of results (13). The trade-off that is made is one between risk of bias, primarily selection and confounding bias, and applicability. Ideally, both types of evidence are merged.

Guidelines are not sufficiently followed because they are not close enough to patients' needs and probably do not reflect real life. In cluster-randomized trials, guideline-driven treatment is more effective than free-treatment choice (14, 15). Moreover, guidelines (in rhinitis but also in asthma) have led to a better understanding of the treatment of the disease and have had an important teaching role which has led to change management (16).

In addition, there is a need to support the transformation of the health care system for integrated care with organizational health literacy (17, 18). During a recent meeting held in Paris (December 3, 2018) for chronic disease care, MASK (Mobile Airways Sentinel NetworK) (19) and POLLAR (Impact of Air POLLution on Asthma and Rhinitis, EIT Health: European Institute for Innovation and Technology-Health) (20), in collaboration with professional and patient organizations in the field of allergy and airway diseases (Figure 1), recommended the evaluation of real-life care pathways (ICPs) centred around the patient with rhinitis and asthma.

During the ICPs meeting in Paris**, next-generation guidelines** for the pharmacologic treatment of allergic rhinitis were developed using existing GRADE-based guidelines for allergic rhinitis (5, 21-23),

RWE provided by Randomized Control Trials, real-world data using mobile technology (24, 25) and chamber studies (Figure 2). These recommendations were used to refine the algorithm for allergic rhinitis treatment proposed by a consensus group (5).

The present report describes the process of next-generation ARIA-GRADE guidelines for the pharmacologic treatment of allergic rhinitis.

1- Documents considered for the development of ARIA care pathways

1-1- MACVIA algorithm proposing a stepwise approach for allergic rhinitis pharmacologic treatment

An algorithm based on the visual analogue scale (VAS) (26) has been devised by the ARIA (Allergic Rhinitis and its Impact on Asthma) expert group (i) for the selection of pharmacotherapy for allergic rhinitis patients and (ii) to step-up or step-down treatment depending on control (5) (Figures 3a and 3b).

The ARIA algorithm for allergic rhinitis was revised by an expert group and a proposal was made to classify allergic rhinitis treatments (Table 1) (6).

1-2- ARIA 2010, 2016 revision and US Practice Parameters 2017

Although few head-to-head comparisons of medications during Randomized Control Trials are available (27-30), the comparison of allergic rhinitis medications has been proposed by several reviews (1) and guidelines (5, 21-23). A Health Technology Assessment evaluation concluded that most allergic rhinitis medications had a similar effect (31). However, this study used a method that did not enable differentiation between medications.

The ARIA revision 2016 (22) and the US Practice Parameters 2017 (23) were developed independently and used the same methodological approach: GRADE (10-12). Interestingly, the same questions were considered. Two major outcomes were considered in the treatment of moderate-severe rhinitis: efficacy and speed of action (Table 2).

Although the GRADE approach suggests the use of all relevant evidence, developers of recommendations have focused on Randomized Control Trials .

ARIA 2016 revision (22) and US Practice Parameters 2017 (23) mainly based on Randomized Control Trials support the MACVIA algorithm (5)

1-3- Speed of onset of action of medications

The US Food and Drug Administration has proposed three study types to assess the onset of action of allergic rhinitis medications (32, 33): the standard Phase III double-blind Randomized Control Trial, park setting studies and allergen exposure chamber (AEC) studies (34). Randomized Control Trials are informative but cannot provide sufficient precision to assess the onset of efficacy as they cannot allow repeated timing over short periods of time (minutes). Allergen exposure chambers offer some advantages over Randomized Control Trials in assessing the onset of action of medications which can be demonstrated in minutes (34). The allergen exposure chamber allows consistent allergen exposure. However, it is a manipulated *in vivo* procedure, while the park study mirrors real-life exposure. Park studies have not captured the early time as well as the allergen exposure chamber. It appears that a cross-over trial would be difficult with a park study due to variations of allergen exposure between days. On the other hand, the allergen exposure chamber cannot replace real-world allergen exposure but only complement it. Allergen exposure chamber studies appear more robust than park studies. To date, the allergen exposure chamber studies that have been conducted have been monocentric and have followed protocols unique to each centre. Because there are technical differences in each allergen exposure chamber, it is not easy to compare the results obtained in the different allergen exposure chambers (35) although standardization has begun for some of them (36).

In the Ontario and Vienna allergen exposure chambers, several medications have been tested (Tables 3A and B).

The Ontario Chamber studies show the rapid onset of efficacy for Azelastine and its combinations. There does not seem to be a difference between Azelastine alone or in combination. Other intranasal H_1-antihistamines have a slower onset of action. INCS (alone or with oral H_1-antihistamines) are not effective before 2 hrs.

The Vienna chamber studies show that Azelastine and Levocabastine/FF are the fastest-acting medications by comparison with oral H_1-antihistamines.

1-4- Real-world evidence using mobile technology

According to the World Health Organization (WHO), mHealth (Mobile Health) has the potential to transform health service delivery globally (37). Next-generation ARIA guidelines should consider testing the recommendations based on the GRADE approach with direct RWE using data obtained by mHealth tools in order to confirm or refine current GRADE-based recommendations.

Although many mHealth tools are available for the assessment of allergic rhinitis (38), only MASK (Mobile Airways Sentinel networK) has reported data on medications that can be used in RWE. MASK, a new development of ARIA, is an information and communication technology (ICT) system centred

around the patient (adolescents and adults) (20, 39). MASK, freely available in Google Play and Apple Stores, can inform patient decisions on the basis of a self-care plan proposed by the health care professional (19, 20). It uses a treatment scroll list including all medications customized for each country as well as visual analogue scales (VASs) to assess rhinitis control and work productivity. MASK is ~~a Good Practice following CHRODIS recommendations~~ deployed in 23 countries and 17 languages (40) with over 30,000 users. It was selected by the European Commission's Directorate-General for Health and Food Safety (DG SANTE) and by the newly established Commission Expert Group "Steering Group on Health Promotion, Disease Prevention and Management of Non-Communicable Diseases" as a Good Practice (GP) that can be scaled up in the field of digitally-enabled, integrated, person-centred care (41).

1-4-1- Messages from MASK

Two studies in over 9,000 users and 22 countries (25, 42) confirmed a pilot study (24) and allowed differentiation between ALLERGIC RHINITIS treatments. They also showed that the assessment of days was useful in understanding treatment patterns. Their results combine to indicate that, in real life:

(i) Patients are poorly adherent to treatment (24, 42).

(ii) No treatment trajectory could be identified (25) and most patients self-medicate.

(iii) Most rhinitis patients use on-demand treatment when they are sub-optimally controlled. When uncontrolled, they change their medications daily in order to be controlled (24).

(iv) The vast majority of patients do not follow guidelines or physicians' prescriptions (24, 25, 42).

(v) When physicians are allergic, they behave like patients (43), suggesting the need for behavioural science to improve control.

(vi) Patients who do not take medications are usually well-controlled (24, 25).

(vii) Patients reporting monotherapy with intranasal corticosteroids (INCS)-containing medications have a similar control level (24, 25). However, MPAzeFlu (intra-nasal Azelastine-Fluticasone Propionate combination) is significantly more often administered as a single therapy than fluticasone Furoate (FF) or Mometasone Furoate (MF).

(viii) Patients reporting oral H_1-antihistamines monotherapy have a poorer level of control than those reporting INCS-containing medications (24, 25).

(ix) Most patients have a worse control level with increasing medications (24, 25) contradicting guidelines that propose to increase the treatment level to achieve control.

(x) These results indicate that when patients are controlled, either they do not take a medication or remain with a single treatment. When they are uncontrolled, they co-medicate.

(xi) Considering control level and co-medication, MPAzeFlu is more effective than INCS (24, 25).

(xii) Resistant hypertension is defined by the number of medications used to control the disease (44), and a similar classification may be proposed in allergic rhinitis confirming the SCUAD (severe chronic upper airway disease) concept (45).

1-4-2- Limitations of MASK

As for all studies using participatory data, potential biases include (i) the likelihood of sampling bias, which makes it difficult to assess generalizability of the study, (ii) outcome misclassification that cannot be assessed and (iii) due to ethical considerations, availability of very little information on patient (or day) characteristics. App users are not representative of all patients with rhinitis.

MASK studies have used days in cross-sectional analyses (19, 20) because there is no clear pattern for a defined treatment, and a longitudinal study was not feasible since users mostly use the App intermittently.

The diagnosis of allergic rhinitis was not supported by a physician but was a response to the question: "Do you have allergic rhinitis? Yes/No". Some users with no rhinitis may therefore have responded "Yes" to the question but >95% of responders declared symptoms of rhinitis by questionnaire. There are potential measurement biases when using apps including collection of information, education of the patient, age, availability and ability to use a smartphone (24). Precise patient characterization is impossible using an App, but every observational study using MASK has been able to identify days with poor control or criteria of severity (46-50).

Adherence to treatment is impossible to obtain directly as patients do not report data every day and may not report all medications used. Electronic counters on delivery devices could be used to obtain more complete data on adherence.

Nonetheless, mobile technology is becoming an important tool for better understanding and managing allergic rhinitis. It adds novel information that was not available with other methods (46-52). In addition, the mere number of observations that mobile technology can provide offers an unprecedented body of evidence that can complement conventional Randomized Control Trials for RWE.

1-4-5- Other real-world evidence studies using mobile technology

To our knowledge, no other mHealth study has assessed the efficacy of different medications at large scale.

1-5- Physician's perspectives

There is a complete disconnection between the physician's prescriptions and the patient's behaviour for the treatment of pollen-induced allergic rhinitis. The vast majority of allergists prescribe medications for the entire season, recommending the patient to use them regularly, even during days with few symptoms. Some allergists prescribe a pre-season treatment without clear evidence of efficacy. On the other hand, the vast majority of patients use their medications on-demand when their allergic rhinitis is not well controlled and they do not follow guidelines (19, 20).

When physicians are patients themselves, they behave like patients when they treat their own allergic rhinitis and do not follow the prescriptions, as recently reported (43). Health literacy is an important component of adherence to medications (53, 54), but, given the behaviour of allergists as patients, it appears that other factors are more important. Possibly, it is human nature that drives adherence to treatment whether or not the patient is a physician, and behavioural science is an important need to be considered in medical care.

Lack of adherence is very common in allergists who suffer from allergic rhinitis and prescribe long-term treatment

2- Next-generation ARIA-GRADE guidelines

Recommendations have been refined with RWE and chamber studies (Table 4). The algorithm proposed in Figure 3 is also supported by the present data.

The approach proposed in this paper confirms most GRADE recommendations for allergic rhinitis and the classification of allergic rhinitis treatments proposed by ARIA (Table 1 (6)). Some conditional evidence was supported by RWE. In particular:

- The combination of oral H_1-antihistamines with INCS was not found more effective than INCS alone
- The combination of intra-nasal H_1-antihistamines with INCS was found more effective than INCS alone and
- Intra-nasal H_1-antihistamine-containing medications are effective within minutes.

3- Next-generation ARIA algorithm

The overall ARIA algorithm (5) was found appropriate and no change is needed. The step-up and step-down approach proposed by ARIA experts (6) based on the ARIA algorithm has been confirmed (Table 5). However, the different steps need further validation with RWE.

Conclusions

In this report, we present the first GRADE-based guideline integrating RWE and supportive studies (chamber studies) in the management of allergic rhinitis. This approach could be considered as a model for chronic diseases.

These guidelines will inform ICPs and will be included in the DG Santé **digitally-enabled, integrated, person-centred care** (55). They will represent the Change Management strategy of ARIA Phase 4 (17).

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Figure 1: Organizations supporting the meeting (Paris, December 3, 2018)

POLLAR: Impact of Air POLLution in Asthma and Rhinitis, EIT Health: European Institute for Innovation and Technology, ARIA: Allergic Rhinitis and its Impact on Asthma, Euforea: European Forum for Research and Education in Allergy and Airways Diseases GA^{2}LEN: Global Allergy and Asthma European Network, CEmPac: Centre for Empowering Patients and Communities, EAACI: European Academy of Allergy and Clinical Immunology, EFA: European Federation of Allergy and Airways Diseases Patients' Associations, ERS: European Respiratory Society, ERS: European Rhinology Society, GARD: Global Alliance against Chronic Respiratory Diseases (WHO Alliance), GINA: Global Initiative for Asthma, MACVIA: Fondation MACVIA-LR, SPLF: Societé de Pneumologie de Langue Française, SFA: Société française d'Allergologie, WAO: World Allergy Organization

Figure 2: Development of next-generation ARIA guidelines

Figure 3a: Step-up algorithm in untreated patients using visual analogue scale (adolescents and adults) (from (5))

The proposed algorithm considers the treatment steps and the patient's preference
VAS levels in ratio
If ocular symptoms remain once treatment has been initiated: add intra-ocular treatment

Figure 3b: Step-up algorithm in treated patients using visual analogue scale (adolescents and adults) (from (5))

The proposed algorithm considers the treatment steps and the patient's preference
VAS levels in ratio
If remaining ocular symptoms: add intra-ocular treatment

749 **Table 1: Classification of treatments used in allergic rhinitis** (from 6)

T1	Non-sedating H1-antihistamine (oral, intra-nasal, ocular), leukotriene receptor antagonist (LTRA) or cromones (intranasal, ocular)
T2	Intranasal corticosteroids (INCS)
T3	INCS + intranasal Azelastine
T4	Oral corticosteroid as a short course and an add-on treatment
T5	Consider referral to a specialist and allergen immunotherapy

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Table 2: Overall recommendations using GRADE

A- ARIA 2016 (22)

1. In patients with SAR, we suggest either a combination of INCS + OAH or INCS alone, but potential net benefit may not justify spending additional resources.
2. In patients with PAR, INCS alone are recommended rather than a combination of INCS + OAH
3. In patients with SAR, we suggest either a combination of INCS + INAH or INCS alone, but the choice of treatment depends on patient preferences. At initiation of treatment (first 2 weeks), a combination of INCS + INAH might act faster than INCS alone and might therefore be preferred by some patients. In settings in which additional cost of combination therapy is not large, a combination therapy might be a reasonable choice.
4. In patients with PAR, we suggest either a combination of INCS + INAH or INCS alone.

For all of these recommendations, the level of evidence was low (2, 3) or very low (1,4).

B- US Practice Parameters 2017 (23)

For initial treatment of nasal symptoms of SAR in patients ≥12 years of age, clinicians:

- Should routinely prescribe monotherapy with an INCS rather than a combination of INCS and oral H_1-antihistamine.
- Should recommend an INCS over LTRA (for ≥15 years of age).
- For moderate to severe symptoms, may recommend the combination of an INCS and INAH.

Table 3: Comparison of the time of onset of action using environmental exposure chambers

A: Ontario environmental exposure chamber (from (56))

Drug (dose)	Formulation	Onset of Action	Parameter	Reference
Azelastine	Nasal spray	15 min	TNSS	(57)
MPAzeFlu	Nasal spray	5 min	TNSS	(56)
FP + oral Loratadine (10 mg)	Nasal spray + tablet	160 min		
Olopatadine	Nasal spray	90 min	TNSS	(58)
Ciclesonide	Nasal spray	60 min	TNSS	(59)
Budesonide	Nasal spray	8 h	TNSS	(60)
Budesonide & Azelastine	Nasal spray	20 min		
CDX-313 (solubilized Budesonide + Azelastine)	Nasal spray	20 min		
Levocetirizine	Tablet	160 min	MSS	(61)

TNSS: total nasal symptom score, MSC: mixed symptom score

B: Vienna environmental exposure chamber

Drug (dose)	Formulation	Onset of Action	Parameter	Ref
Astemisole-D, Loratadine-D	Tablet	65-70 min	No placebo MSS	(62)
Astemisole, Loratadine, terfenadine-forte	Tablet	107-153 min	No placebo MSS	(63)
Azelastine (IN), desloratadine	Nasal/ Tablet	Aze: 15 min DL: 150 min	TNSS	(64)
Bilastine, cetirizine, fexofenadine	Tablet	No assessment before 60 min	TNSS	(65)
Cetirizine-D, budesonide	Nasal/ Tablet		No placebo	(66)
Cetirizine-D, xylometazoline nasal spray	Nasal/ Tablet		No placebo	(67)
Desloratadine	Tablet	30 min	obstruction	(68)
Fluticasone furorate and levocabastine	Nasal spray	Combi: 15 min No data for FF or Levocabastine	TNSS	(69)
Levocetirizine, loratadine	Tablet	Levo: 45 min Lora: 60 min	MSS	(70)
Rupatadine	Tablet	15 min	TNSS	(71)

778 **Table 4: Information used to support the next-generation ARIA-GRADE guidelines**

	GRADE recommendation	mHealth RWE	Chamber studies
Oral H_1-antihistamines are less potent than INCS **BUT many patients prefer oral drugs**	(21) No information on patient's preference	(24)(25) No information on patient's preference	
Intra-nasal H_1-antihistamines are less effective than INCS	(21)		
Intra-nasal H_1-antihistamines are effective within minutes	(21)		(57, 64)
INCS should continue being prescribed as first line therapy in moderate-severe rhinitis	(21, 23)	(24, 25)	
The onset of action of INCS takes a few hours to a few days (ciclesonide has a faster onset)	(21)		(59, 60)
The combination of INCS and oral H_1-antihistamines offers no advantage over INCS	(22, 23)	(24, 25)	
The combination of INCS and intra-nasal H_1-antihistamines is more effective than INCS	YES in moderate-severe patients: (23) With restriction: (22)	(24, 25)	
The combination of INCS and intra-nasal H_1-antihistamines is effective within minutes			(56, 60, 69)
Leukotriene antagonists are less potent than INCS	(23)		(56, 60, 69)

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781 **Table 5: Consensus opinion for the different scenaria** (from 6)

	Patient VAS	Phenotype	Tx	Consensus
Part 1: Approach to treatment				
1	≥5	IAR or PER	Yes	Step-up
2	≥2 to <5	IAR	Yes	Continue
3	<2	IAR	Yes	Step-down
4	≥2 to <5	PER	Yes	Continue or Step-up
5	<2	PER	Yes	Step-down
6	≥5	IAR	No	Initiate
7	≥5	PER	No	Initiate
8	<5	IAR or PER	No	Initiate
Part 2: Specific treatment step-ups				
	Current Tx	**Step-ups**		**Notes**
9	T1	T2 or T3		
10	T2	T3		
11	T3	T3 + T4[a]		Consider T5[b]
12	T1 + T2	T3		Consider T5[b]
13	T1 + T3	T3 + T4[a]		Consider T5[b]
14	T2 + T3	T3 + T4		Consider T5[b]
15	T5 + VAS ≥5	T5 + T>2 or T3		
16	T5 + VAS ≥2 to <5	T5 + T1, T2 or T3		T5 + T2 or T3 if congestion
17	T5 + T1	T5 + T2 or T3		
18	T5 + T2	T5 + T3		
19	T5 + T3	Continue		Consider referral
Part 3: Specific treatment step-downs				
	Current Tx	**Step-down**		**Notes**
20	T3	T2 or T1		T2 if congestion
21	T2	T1		Continue T2 if congestion
22	T1	Stop		NOT exposed to allergen
23	T1	Continue		EXPOSED to allergen
24	T1 + T2	T1 or T2		T2 if congestion
25	T1 + T3	T1 or T3		T3 if congestion
26	T2 + T3	T2 or T3		
27	T5 + T3	T5 + T1 or T2		T5 + T2 if congestion
28	T5 + T2	T5 + T1		Continue T5 + T2 if congestion
29	T5 + T1	T5		NOT exposed to allergen
30	T5 + T1	T5 + T1		EXPOSED to allergen
31	T5	T5		Until end of course
Part 4: treatment initiation				

	Patients	Tx	Consensus	Note
32	IAR; VAS ≥5	No	T1,T2 or T3	T2 or T3 if congestion
33	PER; VAS ≥5	No	T2 or T3	
34	IAR or PER VAS <5	No	T1, T2 or T3	T2 or T3 if congestion

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783 VAS: visual analogue scale, Tx: treatment, IAR: Intermittent allergic rhinitis, PER: persistent allergic rhinitis, T1:
784 anti-histamine (oral, intranasal, eye drop), leukotriene receptor antagonist or cromones (intransal or eye
785 drops), T2 : intransal corticosteroids (INCS), T4 : INCS + intranasal antihistamine, T5 : consider referral and
786 allergen immunotherapy
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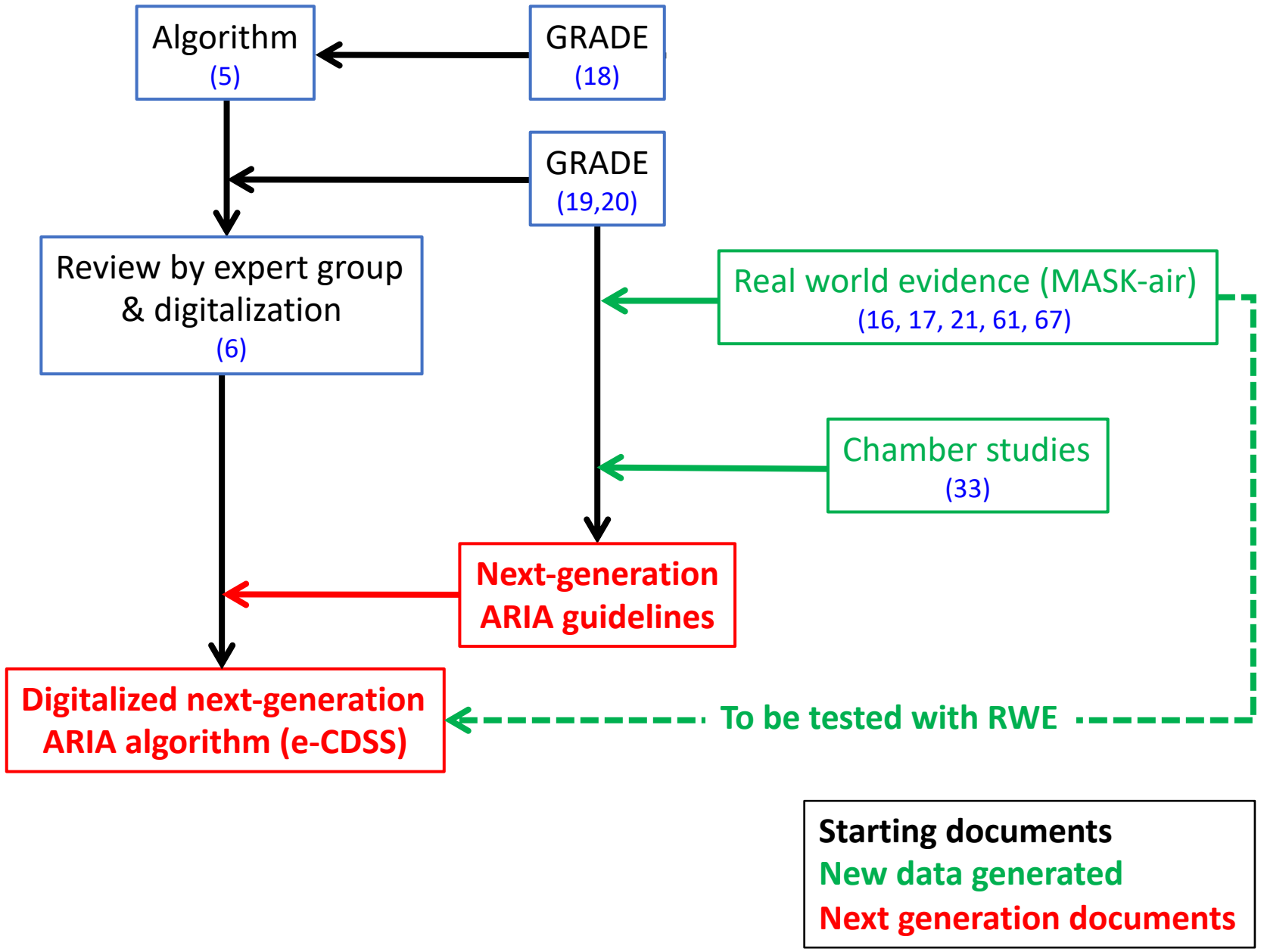
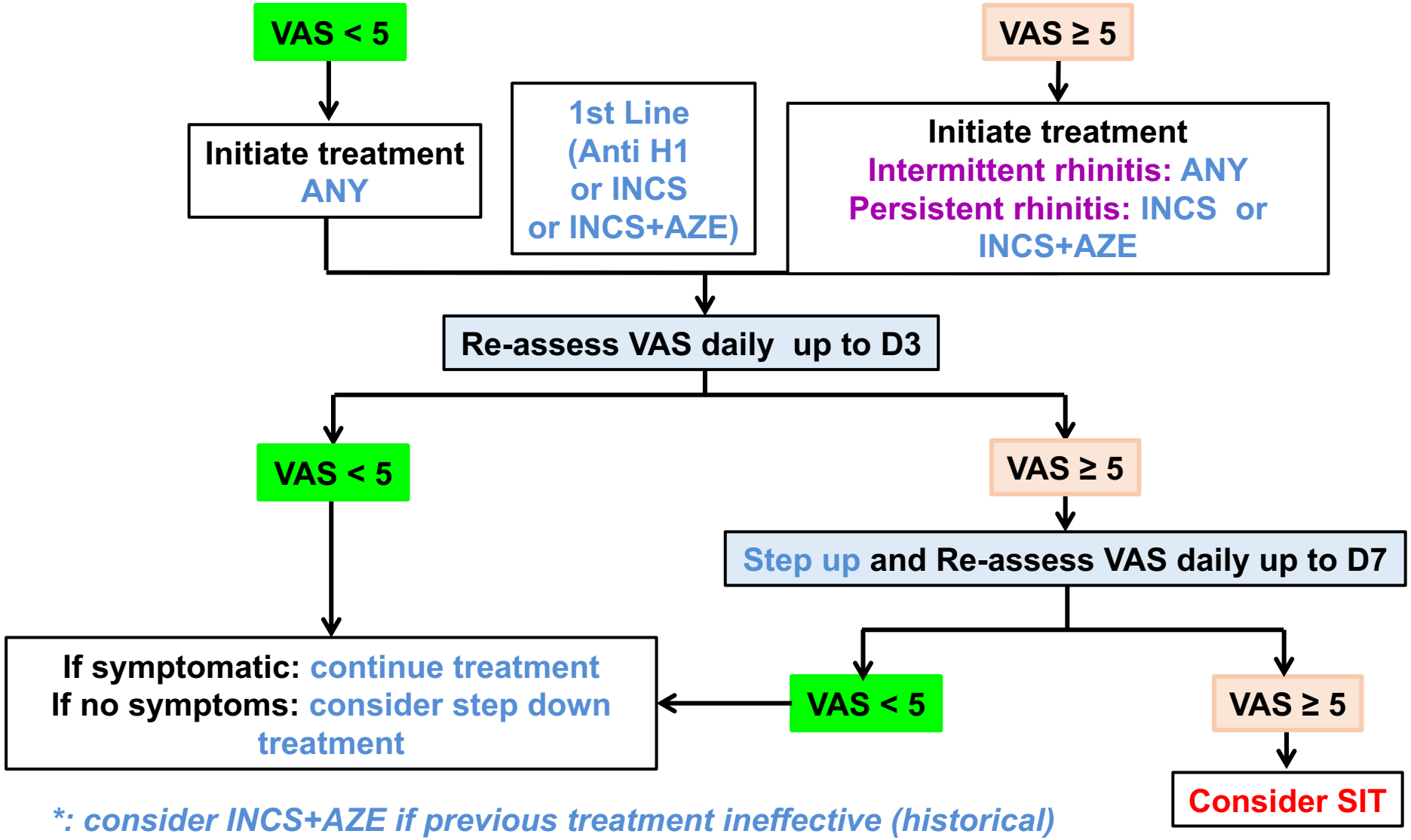
F2


Algorithm
(5)
GRADE
(18)
GRADE
(19,20)
Review by expert group
& digitalization
(6)
Real world evidence (MASK-air)
(16, 17, 21, 61, 67)
Chamber studies
(33)
Next-generation
ARIA guidelines
Digitalized next-generation
ARIA algorithm (e-CDSS)
To be tested with RWE
Starting documents
New data generated
Next generation documents

F3A

Assessment of control in untreated symptomatic patient



*: consider INCS+AZE if previous treatment ineffective (historical)

F3B

Assessment of control in treated symptomatic patient