EPR4 Guidelines:
What's New and What's Missing?

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Disclaimer

- I have received honoraria from, have carried out clinical research with, and/or have served as a consultant for: AstraZeneca, Genentech, NIAID, WebMD.

- My presentation will include discussion of off-label uses of FDA approved products, but not agents that are not FDA-approved.

Learning Objectives

After participation, the learner will be able to:

- Relate key updates in recommendations for asthma management based on EPR4 guidelines.
- Recognize the strengths and limitations of the GRADE approach for developing guideline recommendations, as reflected in EPR4 guidelines.

Guidelines

Institute of Medicine Definition

- "Statements that include recommendations, intended to optimize patient care, that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options"

Qaseem A, et al,. Ann Intern Med 2012; 156: 525-31.

“Trustworthy” Guidelines

- Utilize systematic reviews
- Multidisciplinary development group
- Disclose/manage COI
- Clear & unambiguous recommendations
- Rating system for evidence and recommendations
- Transparency
- External peer review
- Updated regularly

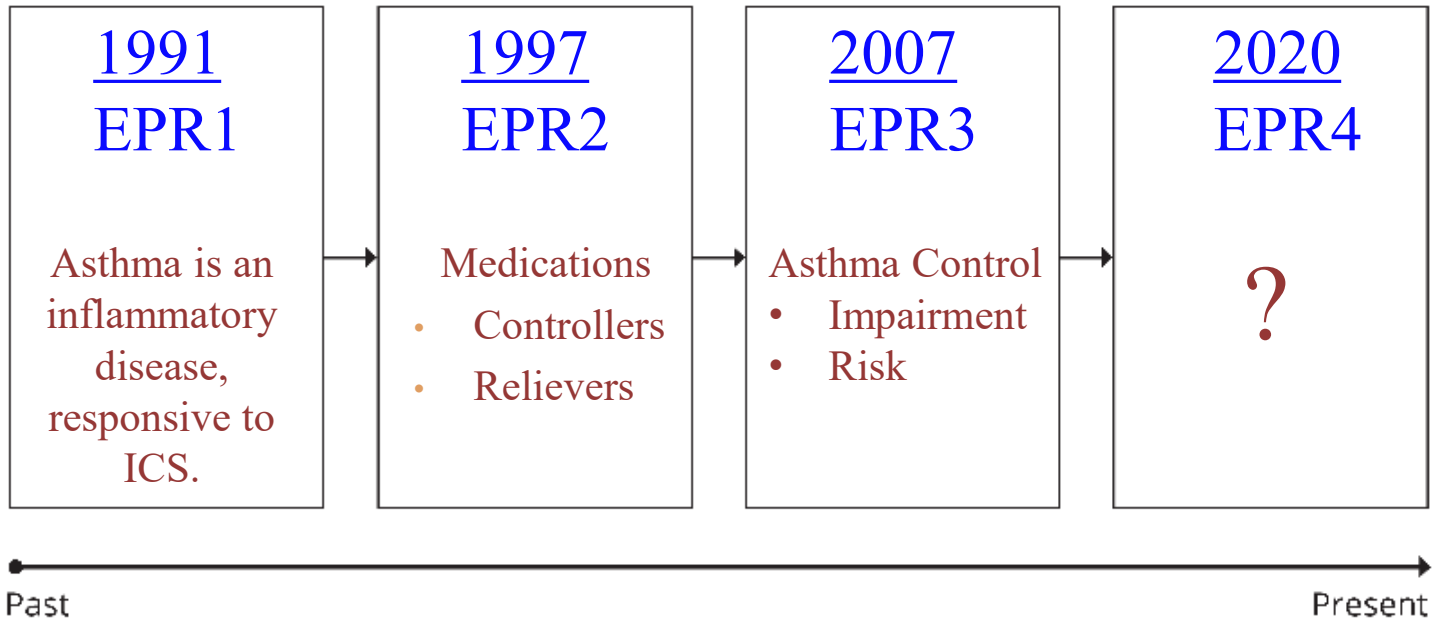
Qaseem A, et al,. Ann Intern Med 2012; 156: 525-31.

Timeline Template

Name _____ Date _____

Asthma Guidelines

Title: _____



Key Points About EPR4

- Enhanced appreciation that asthma is complex.
- PICO questions developed a priori; i.e., *not after a review of the literature*.
- Not too many strong recommendations.
- Expert panel more diverse.
- External input.

J Allergy Clin Immunol. 2020 Dec;146(6):1217-1270

Most Desired Outcome

- " … relief from symptoms that limit what people with asthma can do"
- Among both adults with asthma and caregivers

J Allergy Clin Immunol. 2020 Dec;146(6):1217-1270

Outcomes

Condition	Surrogate Outcomes	Patient-Centered Outcomes
Asthma	FEV1, exhaled nitric oxide	Asthma control days, exacerbations
CVID	Serum IgG level	Infections
Diabetes	Blood sugar, glycosylated hemoglobin	Visual impairment, neuropathy, renal failure
Hypertension	Blood pressure	Myocardial infarction, Cerebrovascular event
Osteoporosis	Bone density	Fractures

Timeline

Journal of Allergy and Clinical Immunology 2020 1461217-1270DOI: (10.1016/j.jaci.2020.10.003)

Grading of Recommendations Assessment, Development and Evaluation

Allergy and immunology practice parameters and guidelines: The new normal

David M. Lang, MD [*], Jay M. Portnoy, MD [†]

+ Author Affiliations & Information

It's spring break, and you're seeing a college student who has a history of moderate-to-severe spring and summer rhinoconjunctivitis. Skin testing shows remarkable wheal and flare reactions to tree and grass pollens. In addition to recommending aeroallergen avoidance measures, which initial treatment has the highest likelihood of helping this patient: intranasal corticosteroid monotherapy or intranasal corticosteroid combined with intranasal antihistamine? Previous practice parameters tended

Advantages of GRADE Approach

- Systematic approach to collecting evidence.
- Clear separation of quality of evidence and strength of a recommendation.
- Focus on patient important outcomes.
- Explicit consideration of patients' values & preferences.
- Transparent description of decision-making process.

Omissions

- Biologic agents
- ACOS
- Action Plans
- Acute Exacerbations
- Adherence
- Assessment tools
- Asthma heterogeneity
- Biomarkers (except for FENO)
- EIB
- Hospital & ED management
- LABA safety
- Montelukast – neuropsychiatric effects
- Pregnancy
- Prevention
- Stepping down from maintenance therapy

SPECIALIST CARE; SEVERE ASTHMA CLINIC IF AVAILABLE

Assess and treat severe asthma phenotypes *cont'd*

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

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

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

Which biologic is appropriate to start first?

Anti-IgE

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

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

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

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

no / no

Anti-IL5 / Anti-IL5R

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

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

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

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

no / no

Anti-IL4R

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

… for severe eosinophilic asthma?

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

… or because of need for maintenance OCS?

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

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

Anti-IL4R may also be used to treat

- Moderate/severe atopic dermatitis
- Nasal polyposis

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

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

Good asthma response?

- *yes* → Good response to T2-targeted therapy
- *unclear* → Extend trial to 6-12 months
- *no* → **STOP add-on**

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

no → Little/no response to T2-targeted therapy

Priority Topics

- FENO in diagnosis, medication selection, and monitoring of treatment response.
- Remediation of indoor allergens (e.g., HDM).
- Adjustable medication dosing.
- LAMA as add on to ICS
- Immunotherapy
- Bronchial Thermoplasty

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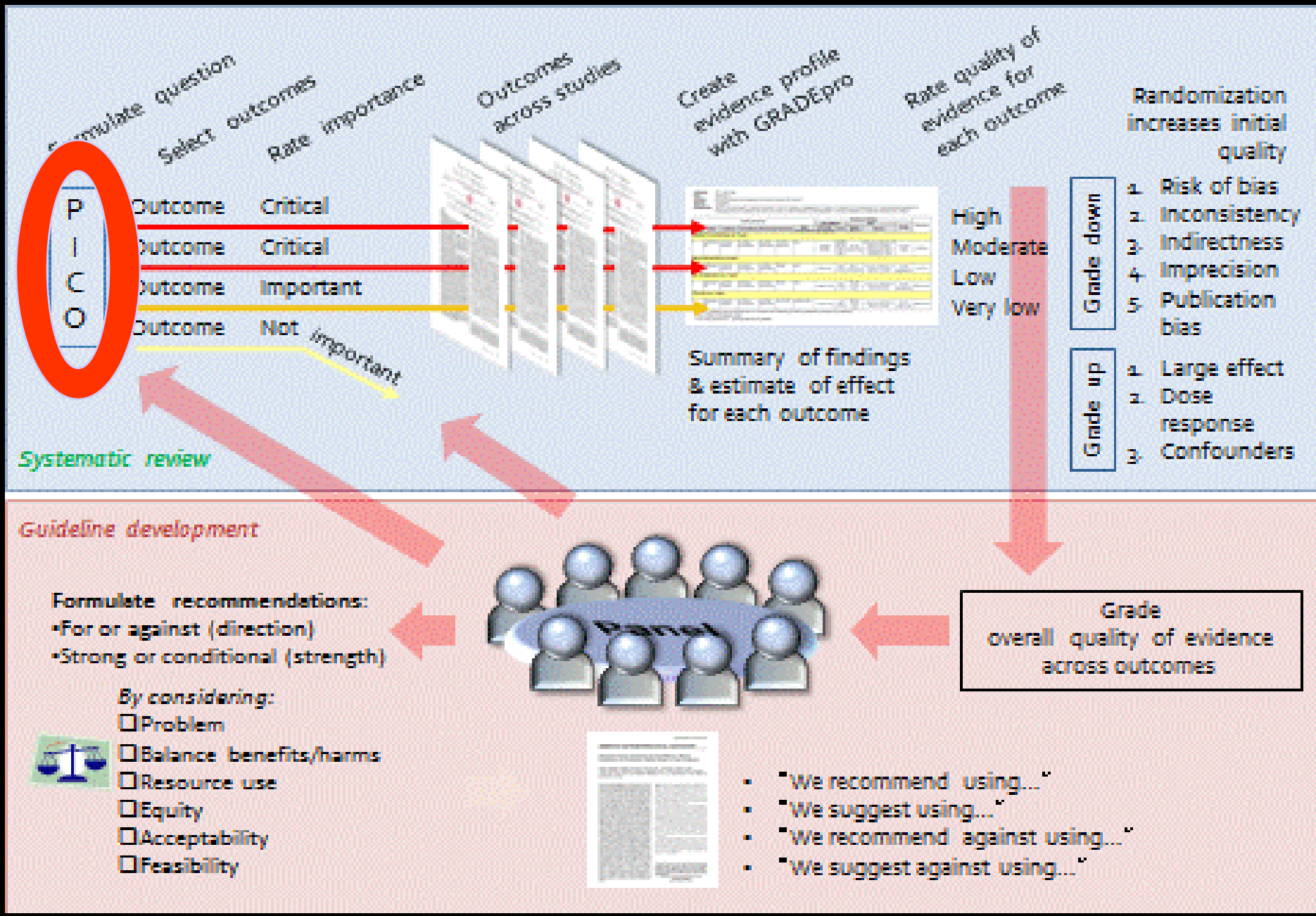
Rockhallizumab Therapy for Chronic Refractory Asthma

Developing Question using PICO Format

Rockhallizumab Therapy for Chronic Refractory Asthma

- TOO VAGUE: Is Rockhallizumab effective for chronic asthma?
- BETTER: What is the efficacy of Rockhallizumab for refractory chronic asthma?
- BETTER YET: In patients 12 years and older with severe persistent asthma that is refractory to high dose ICS/LABA, what is the effectiveness of add-on Rockallizumab compared with placebo for achieving control (e.g., ACT ≥ 20) and reducing exacerbations?



Accessed DEC 8, 2018 at: http://gdt.guidelinedevelopment.org/central_prod/_design/client/handbook/handbook.html

PICO

Rockhallizumab Therapy for Chronic Refractory Urticaria

- P: (Severe) Asthma
- I: Rockhallizumab
- C: Placebo
- O: Exacerbations

Barlam T, et al. Clin Infect Dis. (2016) doi: 10.1093/cid/ciw118

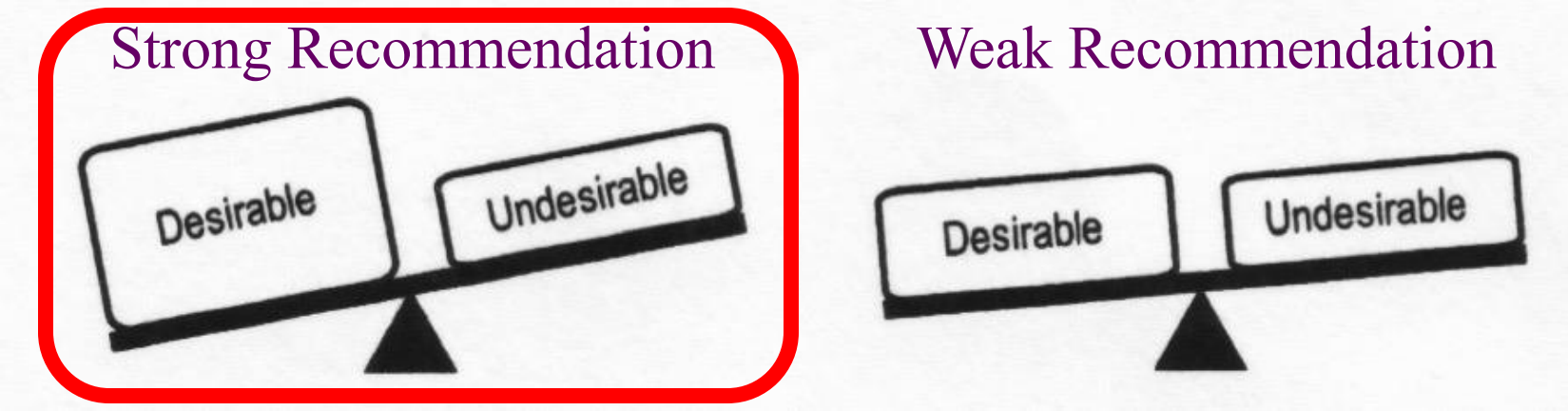
Classifying Recommendations

- Strong / Weak
- Unconditional / Conditional
- Unqualified / Qualified
- We Recommend… / We Suggest…
- Clinicians should … / Clinicians might …

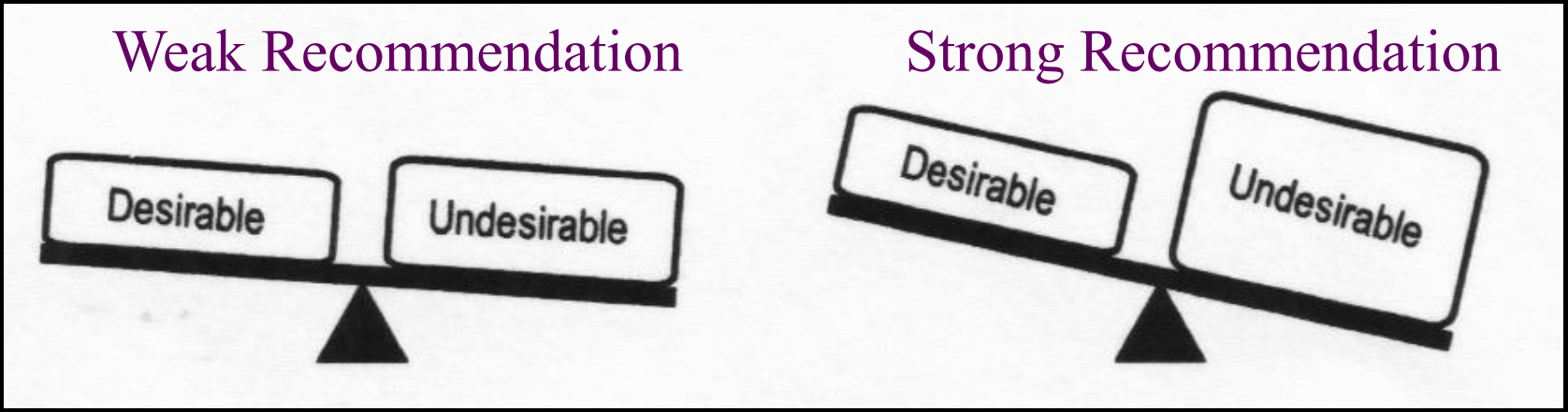
Implications

	Patients	Clinicians	Policy Makers
Strong	Most people in this situation would want recommended treatment, only a small proportion would not	Most patients in this situation should receive recommended treatment	Recommended treatment can be adopted as policy in most situations
Weak	Most people in this situation would want recommended treatment, but many would not	Recognize difference choices are appropriate for different patients based on their values and preferences	Policy making will require substantial debate and involvement of many stakeholders

Brozek J, et al . Allergy 2011; 66: 588-95.



Balance: Desirable vs Undesirable Outcomes



Brozek J et al. Allergy 2011;66:588-95

Strong Recommendation

- In individuals age 4 years and older with moderate-severe persistent asthma, the Expert Panel recommends ICS-formoterol in a single inhaler used as both daily controller and reliever therapy compared to either:
  - Higher dose ICS as daily controller therapy with SABA for quick relief therapy
  - Same-dose ICS-LABA as daily controller therapy and SABA for quick relief therapy

J Allergy Clin Immunol 2020; 146: 1217-20

Stepwise Approach for Managing Asthma in Youths ≥12 Years of Age & Adults

Intermittent Asthma

Persistent Asthma: Daily Medication

Consult asthma specialist if step 4 care or higher is required.
Consider consultation at step 3

Step 1
Preferred:
SABA PRN

Step 2
Preferred:
Low dose ICS

Alternative:
Cromolyn, LTRA, Nedocromil or Theophylline

Step 3
Preferred:
Low-dose ICS + LABA
OR – Medium dose ICS

Alternative:
Low-dose ICS **+** either LTRA, Theophylline, or Zileuton

Step 4
Preferred:
Medium Dose ICS **+** LABA

Alternative:
*Medium-dose ICS **+** either LTRA, Theophylline, or Zileuton*

Step 5
Preferred
High Dose ICS **+** LABA

AND

Consider Omalizumab for patients who have allergies

Step 6
Preferred
High dose ICS **+** LABA **+** oral corticosteroid

AND

Consider Omalizumab for patients who have allergies

Step up if needed

(first check adherence, environmental control & comorbid conditions)

Assess control

Step down if possible

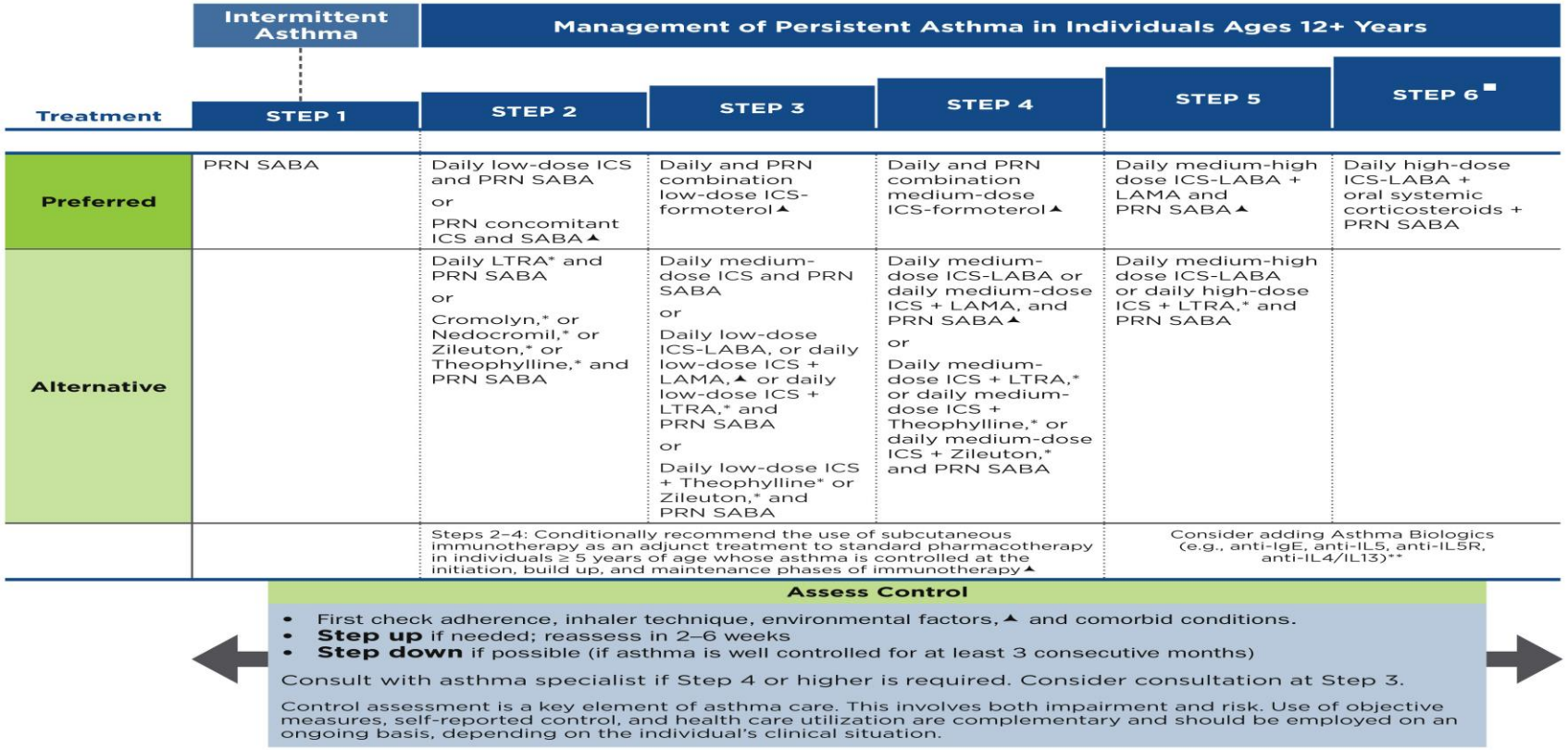
(and asthma is well controlled at least 3 months)

Each Step: **Patient Education and Environmental Control and management of comorbidities**
Steps 2 – 4: Consider subcutaneous allergen immunotherapy for patients who have allergic asthma

- Quick-relief medication for ***ALL*** patients -SABA as needed for symptoms: up to 3 tx @ 20 minute intervals prn. Short course of systemic corticosteroids may be needed.
- Use of SABA >2 days a week for symptom relief (not prevention of EIB) generally indicates inadequate control & the need to step up treatment.

www.nhlbi.nih.gov/guidelines/asthma/epr3/index.htm; accessed September 13, 2018

AGES 12+ YEARS: STEPWISE APPROACH FOR MANAGEMENT OF ASTHMA



Abbreviations: ICS, inhaled corticosteroid; LABA, long-acting beta$_2$-agonist; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; SABA, inhaled short-acting beta$_2$-agonist

▲ Updated based on the 2020 guidelines.

* Cromolyn, Nedocromil, LTRAs including Zileuton and montelukast, and Theophylline were not considered for this update, and/or have limited availability for use in the United States, and/or have an increased risk of adverse consequences and need for monitoring that make their use less desirable. The FDA issued a Boxed Warning for montelukast in March 2020.

** The AHRQ systematic reviews that informed this report did not include studies that examined the role of asthma biologics (e.g. anti-IgE, anti-IL5, anti-IL5R, anti-IL4/IL13). Thus, this report does not contain specific recommendations for the use of biologics in asthma in Steps 5 and 6.

■ Data on the use of LAMA therapy in individuals with severe persistent asthma (Step 6) were not included in the AHRQ systematic review and thus no recommendation is made.

December 2020

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ICS/FORM – Systematic Review/Meta-analysis

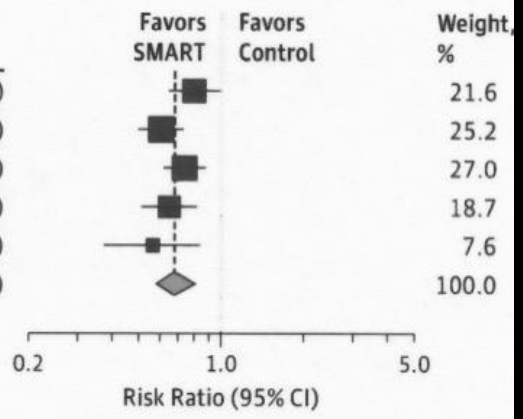
- 16 RCTs involving 22,748 subjects
- Combination ICS/FORM associated with
  - Reduced number of subjects having exacerbations compared with:
    - Same dose of ICS/LABA as controller therapy (RR = 0.68, 95% CI = 0.58-0.80)
    - Higher dose of ICS/LABA as controller therapy (RR = 0.77, 95% CI = 0.60-0.98).

Sobieraj w, et al. JAMA; 2018; 3191485-96

ICS/FORM – Systematic Review/Meta-analysis

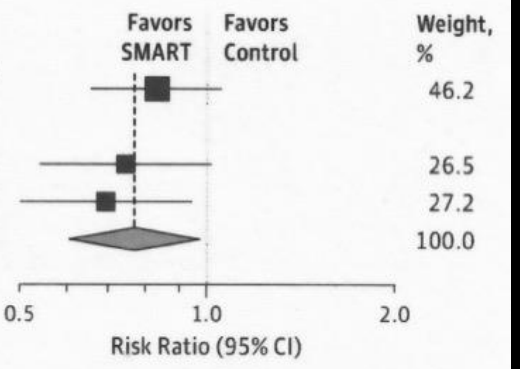
Source	SMART Group: Total No. of Participants	SMART Group: No. With Event	Control Group: Total No. of Participants	Control Group: No. With Event	Absolute Risk Difference (95% CI), %	Risk Ratio (95% CI)
Vogelmeier et al,[23] 2012	1067	132	1076	167	-3.1 (-6.1 to -0.2)	0.80 (0.64 to 0.99)
Rabe et al,[25] 2006	1107	143	1138	245	-8.6 (-11.7 to -5.5)	0.60 (0.50 to 0.72)
Atienza et al,[24] 2013	1049	170	1042	229	-5.8 (-9.1 to -2.4)	0.74 (0.62 to 0.88)
Papi et al,[26] 2013	852	99	849	152	-6.3 (-9.6 to -2.9)	0.65 (0.51 to 0.82)
Patel et al,[27] 2013	151	28	152	50	-14.4 (-24.1 to -4.6)	0.56 (0.38 to 0.84)
Overall (random-effects model)	4226	572	4257	843	-6.4 (-10.2 to -2.6)	0.68 (0.58 to 0.80)

Heterogeneity. $I^2 = 29\%$, $P = .23$
Test for overall effect: $t_4 = -6.44$, $P < .001$



Source	SMART Group: Total No. of Participants	SMART Group: No. With Event	Control Group: Total No. of Participants	Control Group: No. With Event	Absolute Risk Difference (95% CI), %	Risk Ratio (95% CI)
Bousquet et al,[32] 2007	1151	108	1153	130	-2.7 (-5.2 to 0.6)	0.83 (0.65 to 1.06)
Kuna et al,[33] 2007						
Comparison 1	552	47	1099	126	-2.9 (-5.9 to 0.1)	0.74 (0.54 to 1.02)
Comparison 2	552	47	1119	138	-3.8 (-6.8 to -0.8)	0.69 (0.50 to 0.95)
Overall (random-effects model)	2254	202	3371	394	-2.7 (-5.2 to -0.3)	0.77 (0.60 to 0.98)

Heterogeneity: $I^2 = 0\%$, $P = .64$
Test for overall effect: $t_2 = -4.71$, $P = .04$

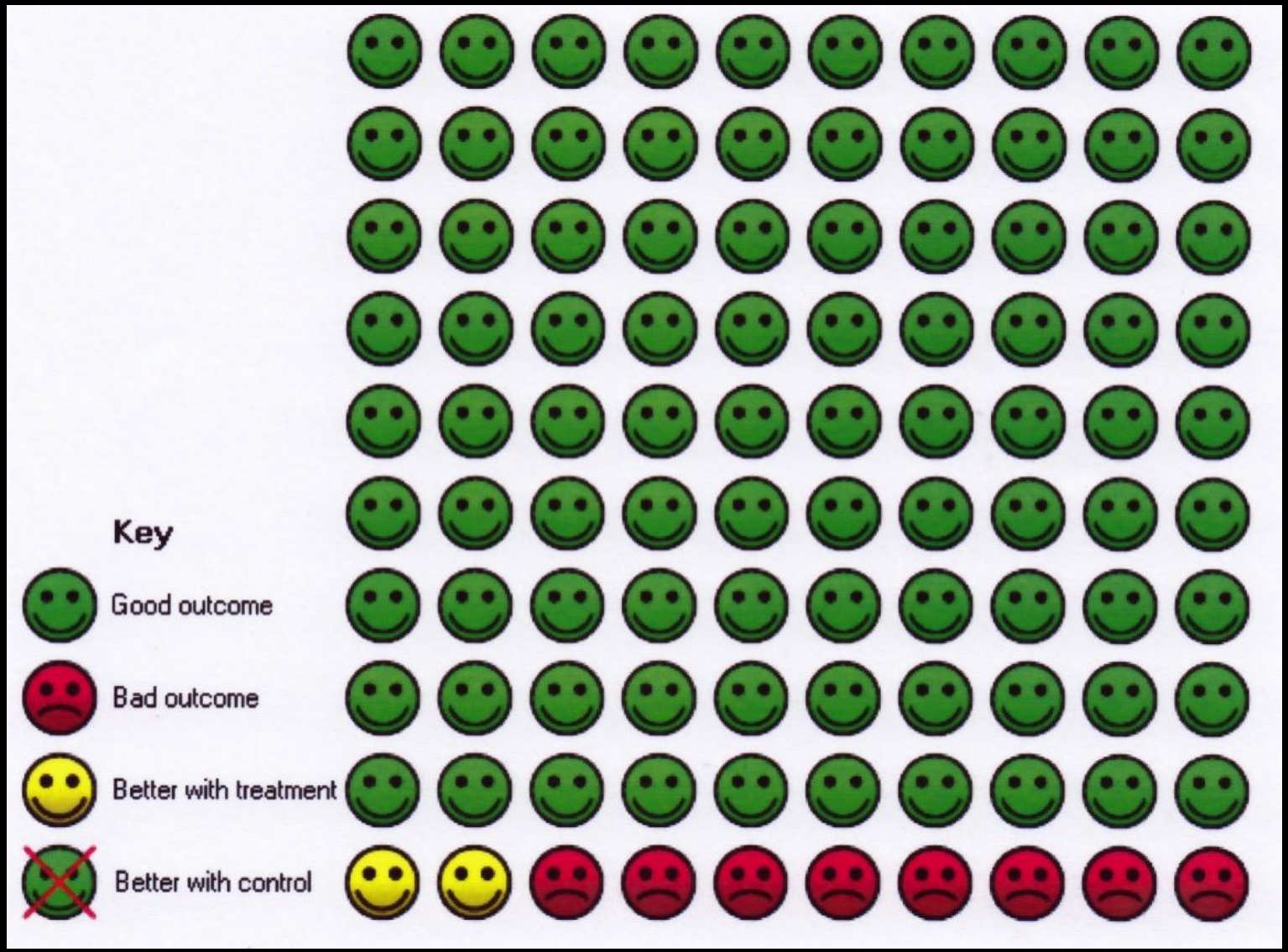


Sobieraj w, et al. JAMA; 2018; 3191485-96

ICS/FORM – Cochrane Review

- 4 studies involving 9130 subjects
  - Two were 6 month DB trials
  - Two were 12 month open label studies
- Combination ICS/FORM associated with:
  - Reduced number of subjects having exacerbations compared with fixed dose combination inhalers
  - Mean daily ICS dose always lower than other combination groups.

Kew, et al. Cochrane Database of Systematic Reviews 2013; 12: Art No. CD009019.



Kew, et al. Cochrane Database of Systematic Reviews 2013; 12: Art No. CD009019

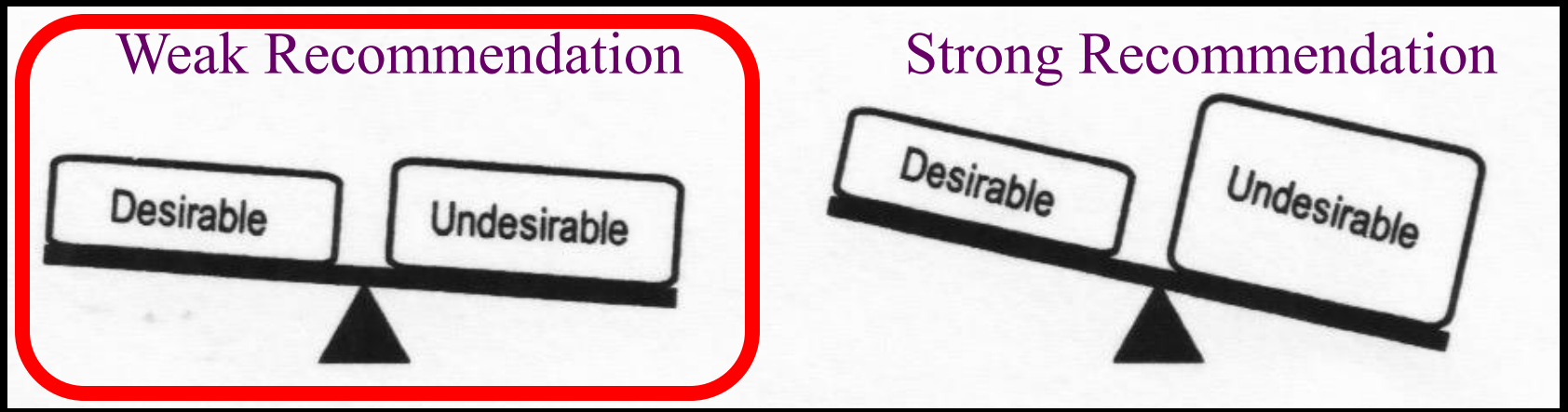
ICS Exposure

Lazarus S. N Engl J Med 2018; 378: 1940-2.

As-needed ICS-formoterol – maximum daily dose?

- As-needed low dose ICS-formoterol
  - Prescribed in maintenance and reliever therapy (Steps 3–5), or as-needed only (Steps 1–2), or within an asthma action plan
  - From product information, the maximum recommended total in one day is 72 mcg formoterol (12 inhalations of budesonide-formoterol Turbuhaler 200/6 mcg)
- As-needed low dose ICS-formoterol
  - Prescribed in maintenance and reliever therapy (Steps 3–5), or within an asthma action plan
  - From product information, the maximum recommended total in one day is 48 mcg formoterol (6 inhalations of beclometasone-formoterol pMDI100/6 mcg)

Balance: Desirable vs Undesirable Outcomes



Brozek J et al. Allergy 2011;66:588-95

https://health.clevelandclinic.org/allergy-shots-proven-solution-you-shouldnt-ignore/

Immunotherapy – EPR4

- In individuals age 5 years and older with mild to moderate allergic asthma, the Expert Panel conditionally recommends the use of SCIT as an adjunct treatment to standard pharmacotherapy in those individuals whose asthma is controlled at the initiation, build-up and maintenance phases of immunotherapy.

J Allergy Clin Immunol. 2020 Dec;146(6):1217-1270

Immunotherapy – EPR4

- In individuals age 5 years and older with mild to moderate allergic asthma, the Expert Panel ***conditionally*** recommends the use of SCIT as an adjunct treatment to standard pharmacotherapy in those individuals whose asthma is controlled at the initiation, build-up and maintenance phases of immunotherapy.
- Certainty of evidence: ***Moderate***

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Immunotherapy – EPR3

- Consider subcutaneous allergen immunotherapy for patients who have persistent asthma when there is clear evidence of a relationship between symptoms and exposure to an allergen to which the patient is sensitive. Evidence is strongest for use of subcutaneous immunotherapy for single allergens, particularly house dust mites, animal dander, and pollen.

Evidence Summary

- 3 *critical* outcomes
  - Exacerbations
  - Asthma control
  - QOL
- 3 *important* outcomes
  - Use of quick relief medications
  - Adverse events (harms)
  - Long term medication use

LOW

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Evidence Summary

- "The studies available for evaluation tended to have small samples, and study reports did not characterize the races of participants or the social determinants of health that they experienced."

- "The enthusiasm of the Expert Panel for recommending SCIT for allergic asthma management is reduced by the slight risk fo harms and variability in access (because of costs and geographical location); this variability in access can promote health inequities."

J Allergy Clin Immunol. 2020 Dec;146(6):1217-1270

Immunotherapy – Which 15%?

- "Delayed *systemic* reactions (those occuring more than 30 minutes after injection) occur in approximately 15% of individuals after injection."

J Allergy Clin Immunol. 2020 Dec;146(6):1217-1270
Epstein T, et al. J Allergy Clin Immunol Pract 2019; 7: 1996-2003.

Immunotherapy – Which 15%?

- "Delayed *systemic* reactions (those occuring more than 30 minutes after injection) occur in approximately 15% of individuals after injection."
- "*Among practices monitoring patients for at least 30 minutes, 15% of systemic reactions occurred after 30 minutes…*"

J Allergy Clin Immunol. 2020 Dec;146(6):1217-1270
Epstein T, et al. J Allergy Clin Immunol Pract 2019; 7: 1996-2003.

Immunotherapy – Systemic Reactions

- "Studies[5] have found systemic reactions with up to 12% of total injections…"

J Allergy Clin Immunol. 2020 Dec;146(6):1217-1270

Effective Health Care Program

Comparative Effectiveness Review
Number 111

Allergen-Specific Immunotherapy for the Treatment of Allergic Rhinoconjunctivitis and/or Asthma: Comparative Effectiveness Review

AHRQ

"… the highest rate of systemic allergic reactions was 11.7 percent of total injections given (203 reactions out of 1735 total injections)"[45]

EXPERIMENTAL AND THERAPEUTIC MEDICINE 7: 630-634, 2014

Efficacy analysis of three-year subcutaneous SQ-standardized specific immunotherapy in house dust mite-allergic children with asthma

YU HUI, LING LI, JUN QIAN, YUN GUO, XILIAN ZHANG and XIAOJUAN ZHANG

Department of Respiratory Medicine, Wuxi Children's Hospital Affiliated to Nanjing Medical University, Wuxi, Jiangsu 214023, P.R. China

Efficacy ana ndardized
specifi rgic

YU HUI, HANG

Department of Res iversity, Wuxi,

Adverse reactions following injection were monitored and it was identified that 203 out of the 1,735 injections were associated with an adverse reaction. One of the 203 injections was a systemic adverse reaction and the remainders were local adverse reactions.

Weak Recommendation

- Direction of the recommendation (i.e., for or against) frequently depends on assumed values and preferences of patients.
- Important for guideline panels to be transparent and be explicit in describing rationale for recommendation.
  - State values and preferences considered, and relative weights placed on each.

Weak Recommendation

- For interventions that merit weak recommendations, either related to low quality evidence or uncertainty as to whether the potential for harm/burden exceeds the likelihood of benefit, the clinician is required to carefully consider whether administration of the therapy is favorable from the standpoint of balancing the potential for benefit with the potential for harm, and discuss this openly with patients to determine that the treatment decision is consistent with their values and preferences

Bernstein JA, Lang DM, Khan D, eds. ***The Diagnosis and Management of Acute and Chronic Urticaria.*** ***J Allergy Clin Immunol*** *2014;133:1270-7.*

Whether to Use Immunotherapy …

Strength of Recommendation: CONDITIONAL
Certainty of Evidence: MODERATE

Timeline Template

Name _____ Date _____

Title: Asthma Guidelines

1991 EPR1	1997 EPR2	2007 EPR3	2020 EPR4
Asthma is an inflammatory disease, responsive to ICS.	Medications • Controllers • Relievers	Asthma Control • Impairment • Risk	ICS/LABA: Dynamic dosing

Strength of Recommendation: STRONG
Certainty of Evidence: High (Age ≥ 12), Moderate (Age 4-11)

ICS/FORMOTEROL

- Effective strategy for delivering maintenance anti-inflammatory and bronchodilator therapy.
- Flexibility in ICS dosing more effective than standard fixed-dose combination therapy, as it allows ICS to be increased when needed while keeping the maintenance dose low when asthma is stable.
- Potential for substantial savings in cost of asthma care in USA.

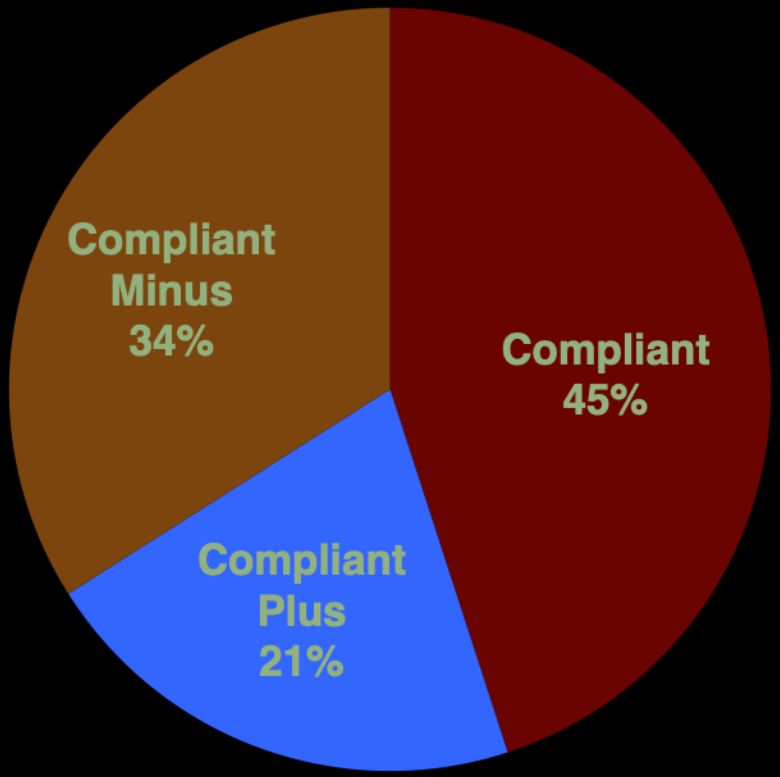
Inspire* Study: How Do Patients Respond to Worsening of Their Asthma?

- 3415 subjects with asthma, age ≥ 16, taking regular ICS or ICS/LABA, were interviewed regarding attitudes and actions to manage their asthma.
  - Mean Age (+/- SD)= 45.2 (16.7)
  - Cared for by PCP = 76%
- Worsening asthma: mean period between from onset to peak symptoms = 5.1 days.

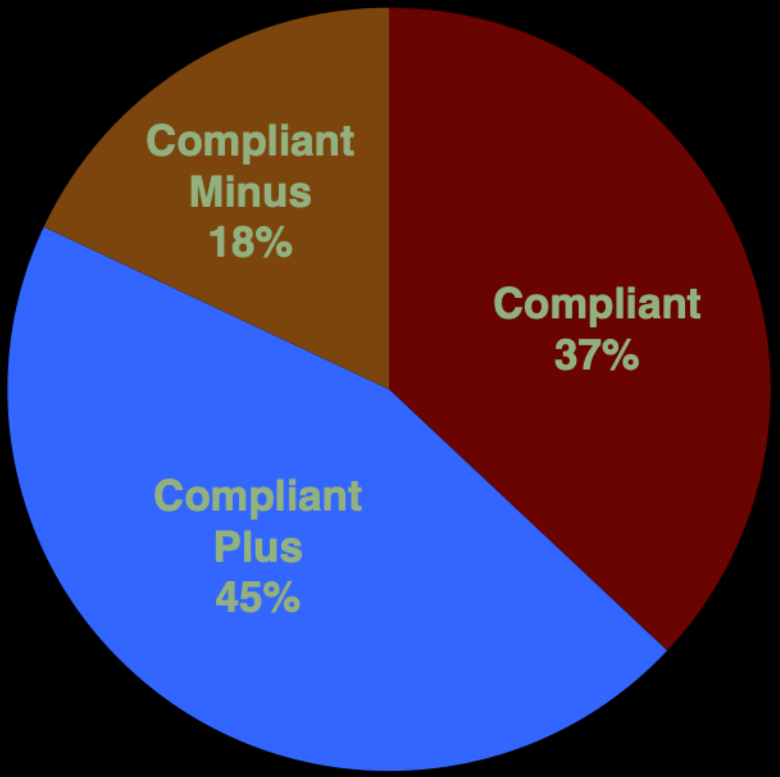
* Inspire: International Asthma Patient Insight Research

Partridge, et al. BMC Pulm Med 2006; 6: 13.

Missed Opportunities



When Well



During Worsening

Partridge, et al. BMC Pulm Med 2006; 6: 13.

Starting Early