

Yellow Zone Practice Parameters for Management of Acute Loss of Asthma Control

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Disclosures

- Drs. Katkin and Stukus have no relevant financial relationships with the manufacturer(s) of any commercial product(s) and/or provider(s) of commercial services discussed in this CME activity.
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Objectives

- Utilize the yellow zone practice parameters to discuss an individualized approach to asthma therapy for patients in clinical practice
- Improve use of written asthma action plans for all patients with asthma
- Apply new concepts regarding use of inhaled corticosteroids into clinical practice

Who Created the Update?

- Joint Task Force (JTF) on Practice Parameters
 - 13-member task force (AAAAI, ACAAI, JCAI)
- 1st JTF Practice Parameter
 - Diagnosis and Treatment of Asthma 1995
- 1st JTF Update
 - Attaining Optimal Control 1998
- Workgroup Formed
 - Systematic literature review
 - Expert opinion

1. Dinikar C, et al. Management of acute loss of asthma control in the yellow zone: a practice parameter. *Ann Allergy Asthma Immunol*. 2014 Aug;113(2):143-59.

Why the Update?

- Most recent EPR-3 guidelines (2007) emphasized attainment of control and strategies to treat variations in symptoms that occur over months
- Most patients experience intermittent loss of control over shorter time frame
 - Exposure to acute trigger
 - Symptoms worsening over hours to days
- Physician-patient partnership to promote self-management lies at heart of asthma management
- Empower patients to monitor asthma and take action when control deteriorates

How Can This New Information Be Applied?

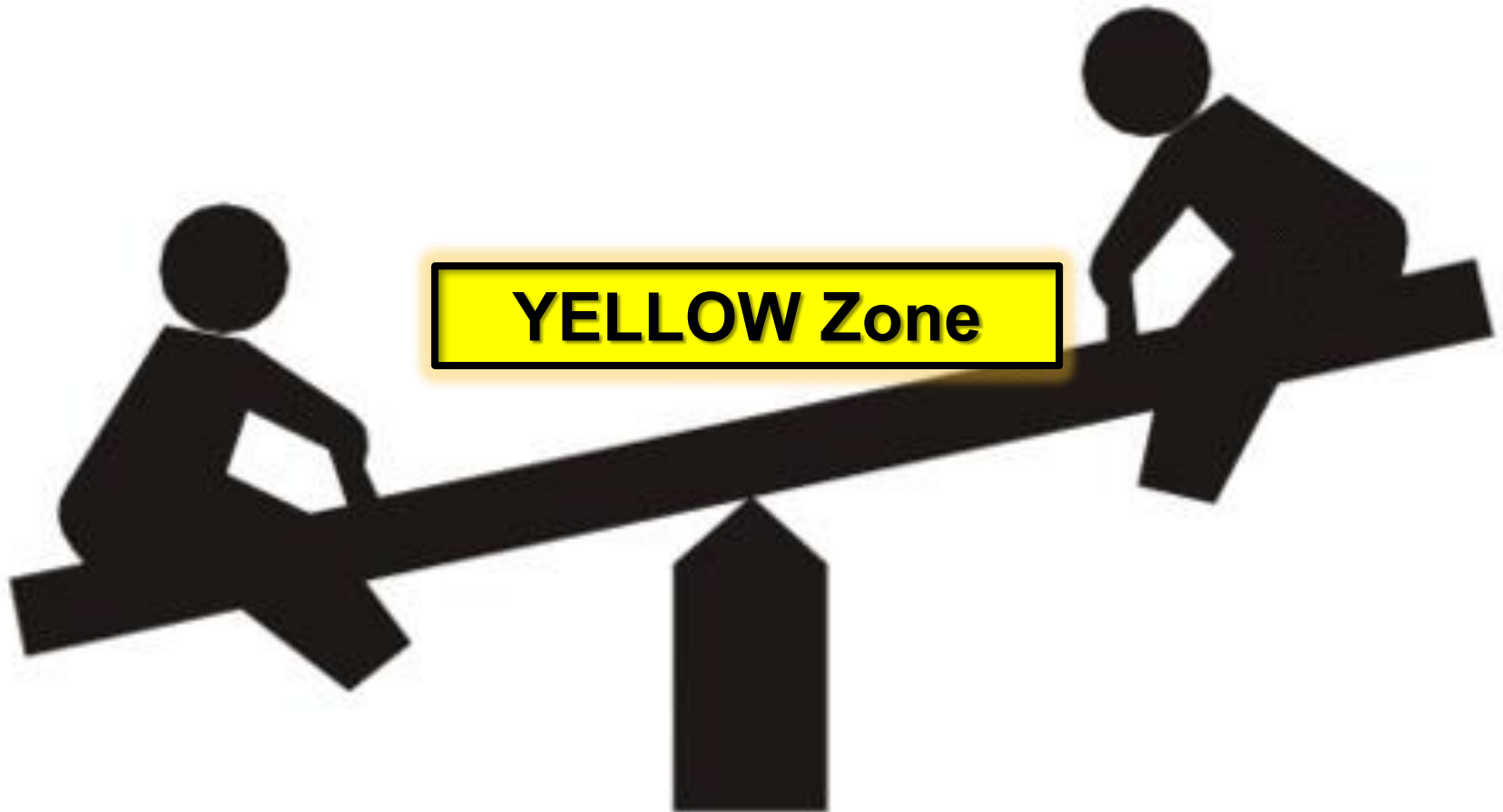
- Assist self-management when patients begin to experience acute loss of asthma control
- We will be focused on the **YELLOW ZONE** only
- Recommendations are intended to apply in the HOME (school, work) setting only
 - Does not apply to office, emergency department, or hospital
- Can be used to help tailor individual therapy
- Hallmark is use of an individualized asthma action plan for every patient
- **GOAL** = prevent deterioration to **RED Zone** and need for systemic corticosteroids and/or urgent medical care

How Can This New Information NOT Be Applied?

- Not intended to help establish a diagnosis of asthma
- Not intended to help initiate or guide stepwise adjustment to long term controller therapy
- Not intended to assist management in the emergency department
- Not intended to assist management in the hospital setting

GREEN Zone → All systems clear

RED Zone → Too late, seek care



Most Importantly...

- Asthma is NOT “one size fits all”
 - Heterogeneous disease that changes over time
 - Variable symptoms
 - Variable onset
 - Variable duration
 - Variable triggers
 - Variable response to therapy
 - So.....
 - Definition of loss of control
 - Management of loss of control
- } is NOT “one size fits all”

Summary Statement 1

- Asthma action plans typically follow a “traffic light” model
 - **Green – daily management when symptoms are well controlled**
 - **YELLOW – FOREWARNS ACUTE LOSS OF CONTROL AND IMPENDING EXACERBATION**
 - **Red – onset of severe exacerbation requiring course of systemic corticosteroids and contact with health care provider**
- *Every* patient should be provided with an asthma action plan
- Include instructions for recognition of loss of control AND activation of the yellow zone intervention plan

Written Asthma Action Plans

- Providing patients with individual written plans:
 - Decreases symptoms
 - Reduces unscheduled health care visits
 - Improves quality of life
 - Empowers patients to guide self-management
- Written action plans are recommended in all iterations of NHLBI guidelines
- Often under utilized
 - 25% of 18,000 asthmatic children in Chicago schools have plan³

1. Gibson PG, Powell H. Cochrane Database Syst Rev. 2003;1:CD001117.
2. Thoonen BP, et al. Thorax. 2003;58:30-6.
3. Gupta RS, et al. Pediatrics. 2014 Oct;134(4):729-36.

Child Asthma Action Plan

0–5 years of age

Patient Name: _____

Medical Record #: _____


Health Care Provider's Name: _____ DOB: _____

Health Care Provider's Phone #: _____ Completed by: _____ Date: _____

Long-Term-Control Medicines (Use Every Day To Stay Healthy)	How Much To Take	How Often	Other Instructions (such as spacers/masks, nebulizers)
		_____ times per day EVERY DAY!	
		_____ times per day EVERY DAY!	
		_____ times per day EVERY DAY!	
		_____ times per day EVERY DAY!	
Quick-Relief Medicines	How Much To Take	How Often	Other Instructions
		Give ONLY as needed	NOTE: If this medicine is needed often (_____ times per week), call physician.

GREEN ZONE

Child is well and has no asthma symptoms, even during active play.



PREVENT asthma symptoms every day:

- Give the above long-term-control medicines every day.
- Avoid things that make the child's asthma worse:
 - Avoid tobacco smoke; ask people to smoke outside.
 - _____
 - _____

YELLOW ZONE

Child is not well and has asthma symptoms that may include:

- Coughing
- Wheezing
- Runny nose or other cold symptoms
- Breathing harder or faster
- Awakening due to coughing or difficulty breathing
- Playing less than usual
- _____
- _____

Other symptoms that could indicate that your child is having trouble breathing may include: difficulty feeding (grunting sounds, poor sucking), changes in sleep patterns, cranky and tired, decreased appetite.

CAUTION. Take action by continuing to give regular asthma medicines **every day** AND:

- Give _____
(include dose and frequency)

If the child is not in the **Green Zone** and still has symptoms after 1 hour, then:

- Give more _____
(include dose and frequency)
- _____
(include dose and frequency)
- Call _____
(include dose and frequency)

RED ZONE

Child feels awful! Warning signs may include:

- Child's wheeze, cough, or difficulty breathing continues or worsens, even after giving yellow zone medicines.
- Child's breathing is so hard that he/she is having trouble walking/talking/eating/playing.
- Child is drowsy or less alert than normal.

MEDICAL ALERT! Get help!

- Take the child to the hospital or call 9–1–1 immediately!
- Give more _____ until you get help. (include dose and frequency)
- Give _____ (include dose and frequency)

Call 9–1–1 if:

- The child's skin is sucked in around neck and ribs, or
- Lips and/or fingernails are grey or blue, or
- Child doesn't respond to you.

Danger! Get help immediately!

My Asthma Action Plan

Patient Name: _____

Medical Record #: _____


Physician's Name: _____ DOB: _____

Physician's Phone #: _____ Completed by: _____ Date: _____

Long-Term-Control Medicines	How Much To Take	How Often	Other Instructions
		_____ times per day EVERY DAY!	
		_____ times per day EVERY DAY!	
		_____ times per day EVERY DAY!	
		_____ times per day EVERY DAY!	
Quick-Relief Medicines	How Much To Take	How Often	Other Instructions
		Take ONLY as needed	NOTE: If this medicine is needed frequently, call physician to consider increasing long-term-control medications.

Special instructions when I feel ● *good*, ● *not good*, and ● *awful*.

I feel *good*.
(My peak flow is in the **GREEN** zone.)



GREEN ZONE

I do *not* feel *good*.
(My peak flow is in the **YELLOW** zone.)

My symptoms may include one or more of the following:

- Wheeze
- Tight chest
- Cough
- Shortness of breath
- Waking up at night with asthma symptoms
- Decreased ability to do usual activities

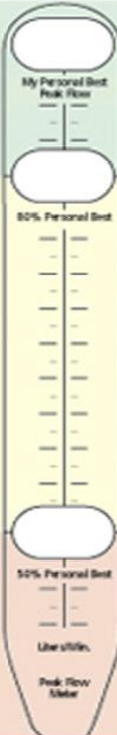
YELLOW ZONE

I feel *awful*.
(My peak flow is in the **RED** zone.)

Warning signs may include one or more of the following:

- It's getting harder and harder to breathe
- Unable to sleep or do usual activities because of trouble breathing

RED ZONE



PREVENT asthma symptoms everyday:

- Take my long-term-control medicines (above) every day.
- Before exercise, take _____ puffs of _____
- Avoid things that make my asthma worse like: _____

CAUTION. I should continue taking my long-term-control asthma medicines every day AND:

- Take _____

If I still do not feel good, or my peak flow is not back in the **Green Zone** within 1 hour, then I should:

- Increase _____
- Add _____
- Call _____

MEDICAL ALERT! Get help!

- Take _____ until I get help immediately.
- Take _____
- Call _____

Danger! Get help immediately!

Call 9-1-1 if you have trouble walking or talking due to shortness of breath or lips or fingernails are gray or blue.

Controversy: Are Asthma Action Plans Useful?

- Despite widely adopted use of asthma action plans, there is no evidence in the literature that use of asthma action plans are associated with decreased use of acute resource for asthma care
- Asthma action plans are not uniform across states, school districts or doctor's offices – and can't be
- Patients are mandated to receive a new plan with each encounter, which can lead to the generation of contradictory information that is more confusing than useful

Summary Statement 2

- Instruct patients to activate the yellow zone intervention plan when there is acute loss of asthma control in a setting outside a medical care facility, i.e. home
- Yellow zone is defined as:
 - An increase in asthma symptoms
 - An increase in use of reliever medications
 - A peak flow rate decrease of at least 15% or lower than 80% of personal best
 - The presence or increase in nocturnal asthma symptoms

***Need to consider patient variability in baseline symptoms**

What if Yellow Zone is Started Too Early?

- A **“false”** start may lead to initiation of management when not necessary

BUT...

- Risk of a **“late”** start may result in episode progression and need for systemic corticosteroids/ER care

Don't want to be late!



How Much Time From Yellow to Red?



- Substantial variability in literature and real life
- Mean time from 1st appearance to peak of symptoms 5.1 days (range <30 min to >2 weeks)¹
- Mean interval peak of symptoms to recovery 6.2 days¹
- Often lead time of days to peak of exacerbation
 - Window of opportunity to intervene
- Symptoms may recover before lung function improves
 - Prudent to continue yellow zone management ~2 weeks

Controversy: What About Peak Flow Monitoring?

- Fallen out of favor by many physicians
- Evidence that measurement may not be better predictor than monitoring symptoms^{1,2}
- Use of PEF should be individualized
- Ideal for subset of asthmatics: “poor perceivers”
 - More ER visits, hospitalizations, near-fatal & fatal exacerbations³

1. Bhogal S, et al. Cochrane Database Syst Rev. 2006 Jul 19;(3):CD005306.
2. Buist AS, et al. Am J Respir Crit Care Med. 2006 Nov 15;174(10):1077-87.
3. Magadle R, et al. Chest. 2002 Feb;121(2):329-33.



Summary Statement 3

- Instruct patients to activate the yellow zone plan at the **onset** of an upper respiratory tract infection
 - If this is a previously identified trigger
- URIs one of most common triggers in children
 - May be only trigger
 - In young children, difficult to distinguish WARI from asthma

Controllers at Start of URI

- Montelukast
 - Not effective in preventing exacerbation requiring steroids¹
 - With chronic use, can reduce symptom severity and health care usage during URI²
 - Mainly when used in children with + modified API
 - Recommended in Europe for episodic viral wheeze³
- Inhaled Corticosteroids
 - Fluticasone 750 mcg BID at onset of URI in preschool children⁴
 - 50% reduction in need for oral steroids
 - Decreases in height and weight gains
 - Budesonide 1 mg BID x 7 days⁵
 - Not better than placebo
 - Comparable to 0.5 mg daily

1. Bacharier LB, et al. J Allergy Clin Immunol. 2008 Dec;122(6):1127-1135.
2. Robertson CF, et al. Am J Respir Crit Care Med. 2007 Feb 15;175(4):323-9.
3. Brand PL, et al. Eur Respir J. 2008 Oct;32(4):1096-110.
4. Ducharme FM, et al. N Engl J Med. 2009 Jan 22;360(4):339-53.
5. Zeiger RS, et al. N Engl J Med. 2011 Nov 24;365(21):1990-2001.

Summary Statement 4

- Instruct patients to escalate asthma therapy when they experience a loss of asthma control that puts them in the yellow zone

What Are Our Patients Actually Doing?

- Not uncommon for patients to adjust medications on their own
- Large study of 3,415 adults
 - 29% were given acute care plan by MD advising increasing controller meds
 - 52% did so anyway
 - Increase use of both rescue and controller medications
- Patients utilize dynamic dosing on their own to match symptom severity
- Often without direction and inappropriately

Intervention Strategies to Start in Yellow Zone

- Not “one size fits all” – no ideal single strategy
- Consider timing of loss of control
 - Over days (URI)
 - Over hours (exposure to known allergen or irritant)
- Start at onset of symptoms → continue until full recovery (1-2 weeks)
 1. Repetitive use of inhaled SABA
 2. Scheduled dosing step up
 1. Increasing total ICS dose (at least quadrupling)
 3. Dynamic dosing step up
 1. ICS and SABA
 2. ICS and LABA

Summary Statement 5

- Advise patients to use a short acting β_2 agonist (SABA) for reliever use in yellow zone
- Dose: 2 to 4 puffs every 4 to 6 hours
 - In addition to their escalated yellow zone treatment
- If SABA use exceeds 12 puffs per day → advise patients to contact their provider for guidance



SABA Use

- 2007 NHLBI Guidelines
 - 2-6 puffs of SABA every 3-4 hours for 24-48 hours for home use
 - No evidence of explanation for category A rec is provided
- 2011 Global Strategy for Asthma Management and Prevention
 - 2-4 puffs of SABA every 20 min for 1 hour
 - 2-4 puffs of SABA every 3-4 hours with good response
 - 6-10 puffs for moderate exacerbation

MDI vs. Nebulizer

- For mild-to-moderate exacerbation (yellow zone)
- Cochrane Review in 2013¹
 - 1897 children, 729 adults in 39 trials mainly ED setting
- Use of MDI with spacer equivalent to nebulizer
 - Various markers of clinical outcomes
- Nebulizers associated with more adverse events
 - Tachycardia
 - Tremor
 - Longer LOS

1. Cates CJ, et al. Cochrane Database Syst Rev. 2013 Sep 13;9:CD000052
2. Schuh S, et al. J Pediatr. 1999 Jul;135(1):22-7.
3. Chou KJ, et al. Arch Pediatr Adolesc Med. 1995 Feb;149(2):201-5.

Summary Statement 6

- Advise patients currently treated with daily low-to-moderate dose inhaled corticosteroid (ICS) to consider:

Increasing the total ICS dose per 24 hours
(quadrupling) for managing loss of asthma
control in yellow zone

Doubling Dose of ICS

- Previous studies suggested doubling dose of current ICS controller may reduce duration of symptoms, less need for oral steroids
- Recent studies have not demonstrated significant benefit from doubling dose
- However...
 - Significant methodological differences
 - Definition of exacerbation
 - Timing of onset & duration for intervention
 - Primary outcome measures
- So...
 - This may be effective for some patients at certain times
 - Difficult to make blanket recommendations with available data

Quadrupling Dose of ICS

- EPR3 states that quadrupling dose of ICS at start of symptoms and continuing for 7 days may reduce exacerbations
- Similar issues with varying methodologies for studies
- Several demonstrate reduced need for oral steroids, less duration of symptoms
- **But...Gasp! That's a lot of steroids!**
 - Typical systemic steroids dosed 2 mg/kg/day, max 60 mg
 - Moderate dose inhaled steroids baseline ~500 mcg/day
 - $500 \text{ mcg} \times 4 = 2000 \text{ mcg} = 2 \text{ mg}$

Controversy: Increased Inhaled Steroids

- Using very high doses of ICS at first sign of exacerbation requires EARLY recognition of symptoms. This is really difficult with children, who may not recognize or report early signs (especially teens).
- Increased symptoms in very young children must first be recognized by adult caretakers, which will lead to a delay in therapy
- Not all respiratory infections are associated with wheezing – chance for unnecessary exposure to really high doses of ICS, particularly for very young children

Summary Statement 7

- For children younger than 6 years with
 - Recurrent wheezing
 - Risk factors for subsequent asthma (positive modified asthma predictive index)
- Consider initiating high-dose ICS *or* oral montelukast at the early signs of wheezing illnesses to decrease intensity of symptoms



Asthma Predictive Index

- Primary: ≥ 4 wheezing episodes per year
- Secondary:

At least 1 Major:

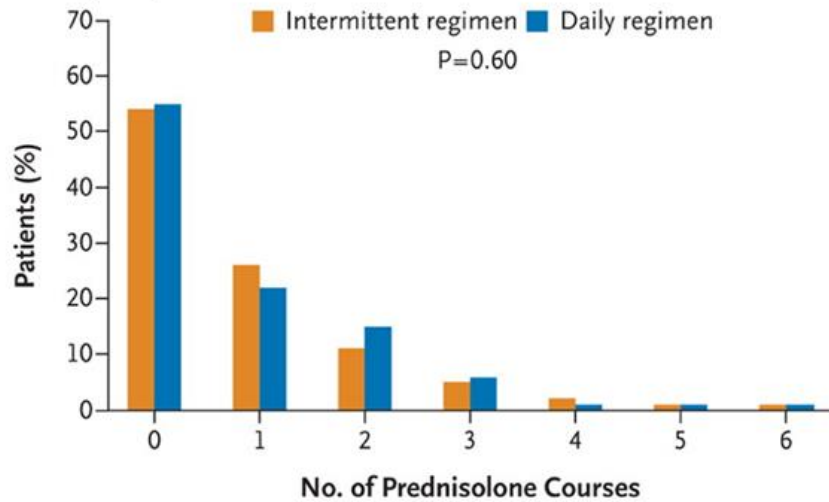
- Parental asthma
- Physician diagnosed eczema
- +IgE to at least aeroallergen

At least 2 Minor:

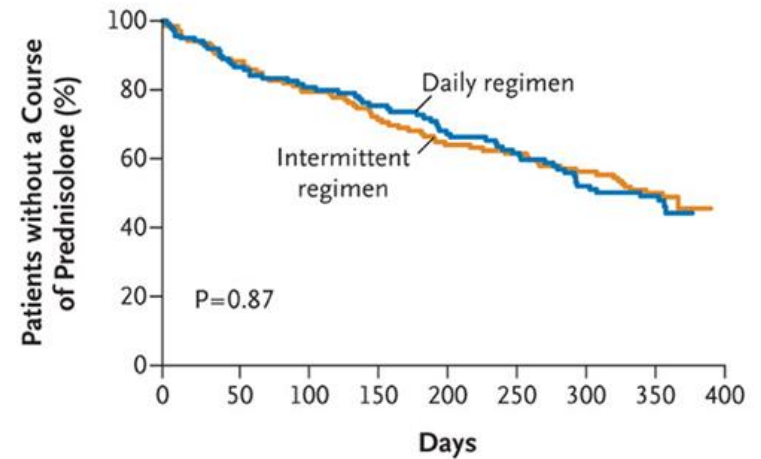
- Wheezing apart from colds
- Peripheral eosinophils $\geq 4\%$
- +IgE to milk, egg, or peanut

Positive mAPI identifies young children more likely to develop true asthma in later childhood

A Frequency of Exacerbations



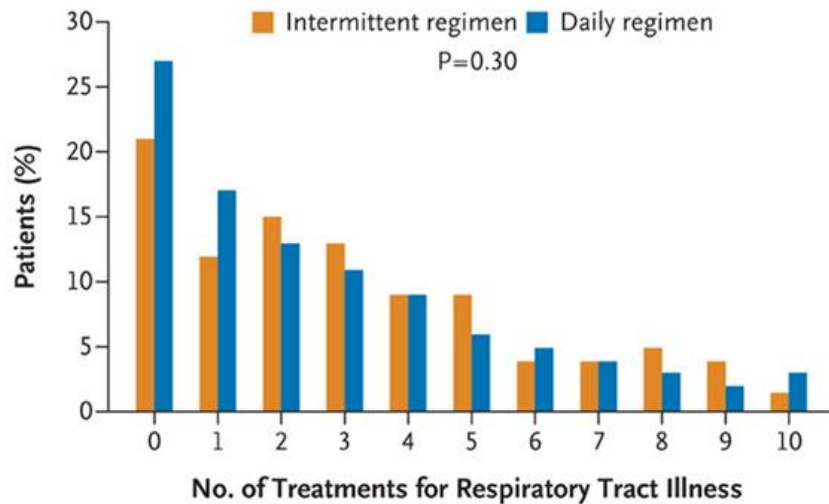
B Time to First Exacerbation



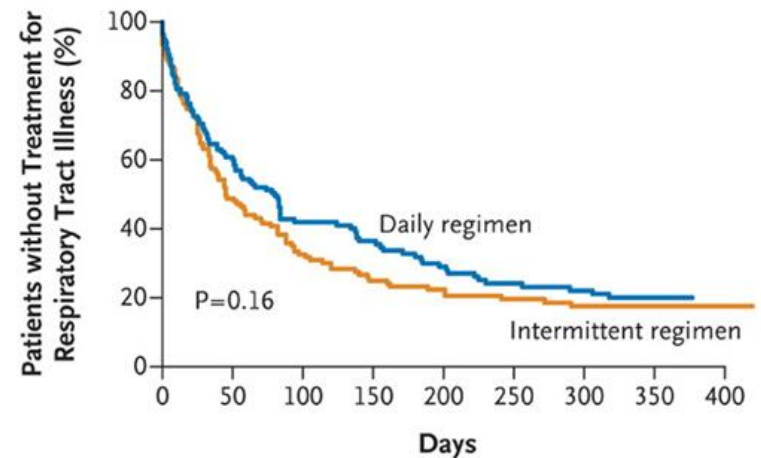
No. at Risk

Intermittent regimen	139	114	100	89	78	71	64	50
Daily regimen	139	114	93	84	74	66	54	40

C Frequency of Treatments for Respiratory Tract Illness



D Time to First Treatment for Respiratory Tract Illness



No. at Risk

Intermittent regimen	139	61	39	29	24	19	17	15
Daily regimen	139	78	46	39	30	23	20	16

Controversy: Montelukast

- Evidence for montelukast as a useful agent for viral induced wheezing is very thin; use in Europe is based on only a couple of studies
- Use in this manner presumes that one is not on montelukast as daily controller therapy , which is usually how it is used in this country
- At recent Celebration of Pediatric Pulmonology, a group of pediatric pulmonologists voted use of montelukast to treat virus associated wheezes as a good candidate for elimination as part of the “Choosing Wisely” campaign
- Clearly, there are broad differences of opinion here based on experience, and little data

Controversy: Increased ICS with Illness for Toddlers

- Not every child with a cold will go on to wheeze
- Limited studies available, but those suggest that only 50% of young children who increase ICS with illness escape the need for oral steroids. Potential for “double exposure” to ICS + oral steroids, and delay in treatment
- Total dose of ICS can be higher for episodic use than with daily low dose ICS, and there is no decrease in frequency of exacerbation requiring OCS
- Decreased growth rate with high dose episodic ICS in young children
- I don't see any benefit here

Summary Statement 8

- For patients with mild to moderate asthma, consider:
 - Symptom driven use of ICS with concomitant inhaled β agonist for control of yellow zone symptoms
- Dynamic dosing step-up with ICS plus albuterol may be considered an option for children and adults whose asthma is mildly persistent

Symptom Driven ICS with or w/o SABA

- **IMPACT Trial**

- Adults not on ICS: ICS 200 mcg BID vs zafirlukast 20 mg vs placebo
- Told to start budesonide 800 mcg BID or prednisone with symptoms
- Budesonide PRN group (placebo)
 - Similar morning PEF and exacerbations
- Daily ICS
 - Better results for lung function, symptoms, biomarkers, QoL

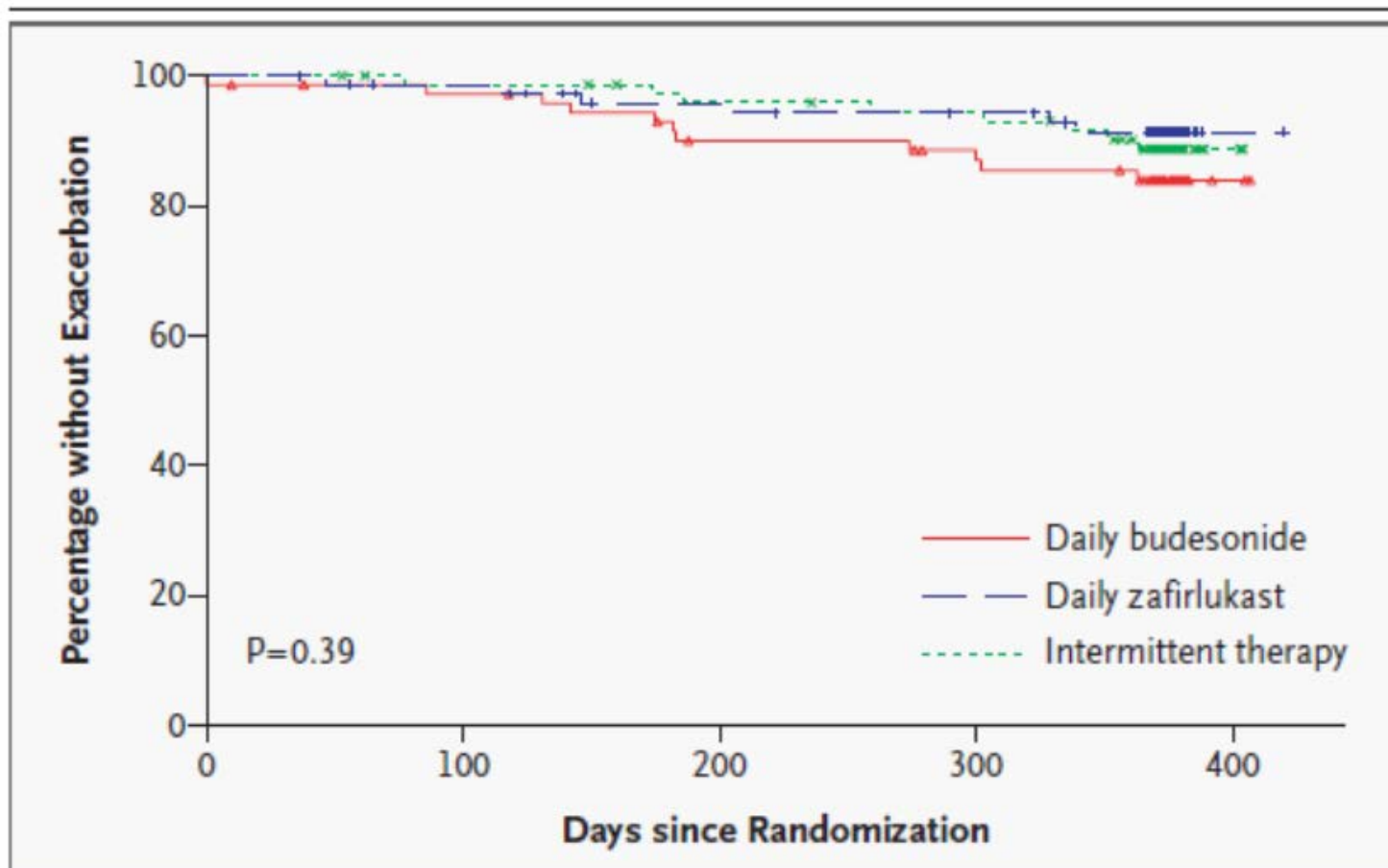


Figure 3. Kaplan–Meier Estimates of the Time to a First Exacerbation of Asthma. There was no significant difference among the groups ($P=0.39$).

TREXA

- Treating Children to Prevent Exacerbations of Asthma
- Study design:
 - 288 children 5 – 18 years old
 - 44 week, randomized, double blind, placebo controlled trial
 - Patients had mild persistent asthma; well controlled & stable on step 2 therapy = low dose ICS
- Randomized into four treatment arms:
 - **Combined:** Beclomethasone 40 mcg twice daily with ICS 80 mcg + albuterol as needed
 - **Daily:** Beclomethasone 40 mcg twice daily with albuterol + placebo ICS as needed
 - **Rescue:** Placebo twice daily with ICS 80 mcg + albuterol as needed
 - **Placebo:** Placebo twice daily with placebo ICS + albuterol as needed

TREXA

- Primary outcome:
 - Time to first exacerbation requiring treatment with systemic corticosteroids
- Primary outcome results:
 - Compared with the placebo group (49%, 95% CI 37-61), frequency of exacerbations was lower in the **daily** (28%, 18-40, $p=0.03$), **combined** (31%, 21-43, $p=0.07$), and **rescue** (35%, 24-47, $p=0.07$) groups
 - Frequency of treatment failure was 23% (95% CI 14-43) in the placebo group, compared with 5.6% (1.6-14) in the combined ($p=0.012$), 2.8% (0-10) in the daily ($p=0.009$), and 8.5% (2-15) in the rescue ($p=0.024$) groups
- Secondary outcome:
 - Linear growth
- Secondary outcome results:
 - Linear growth was **1.1 cm (SD 0.3) less** in the **combined and daily arms** ($p<0.0001$), but not the rescue group ($p=0.26$)

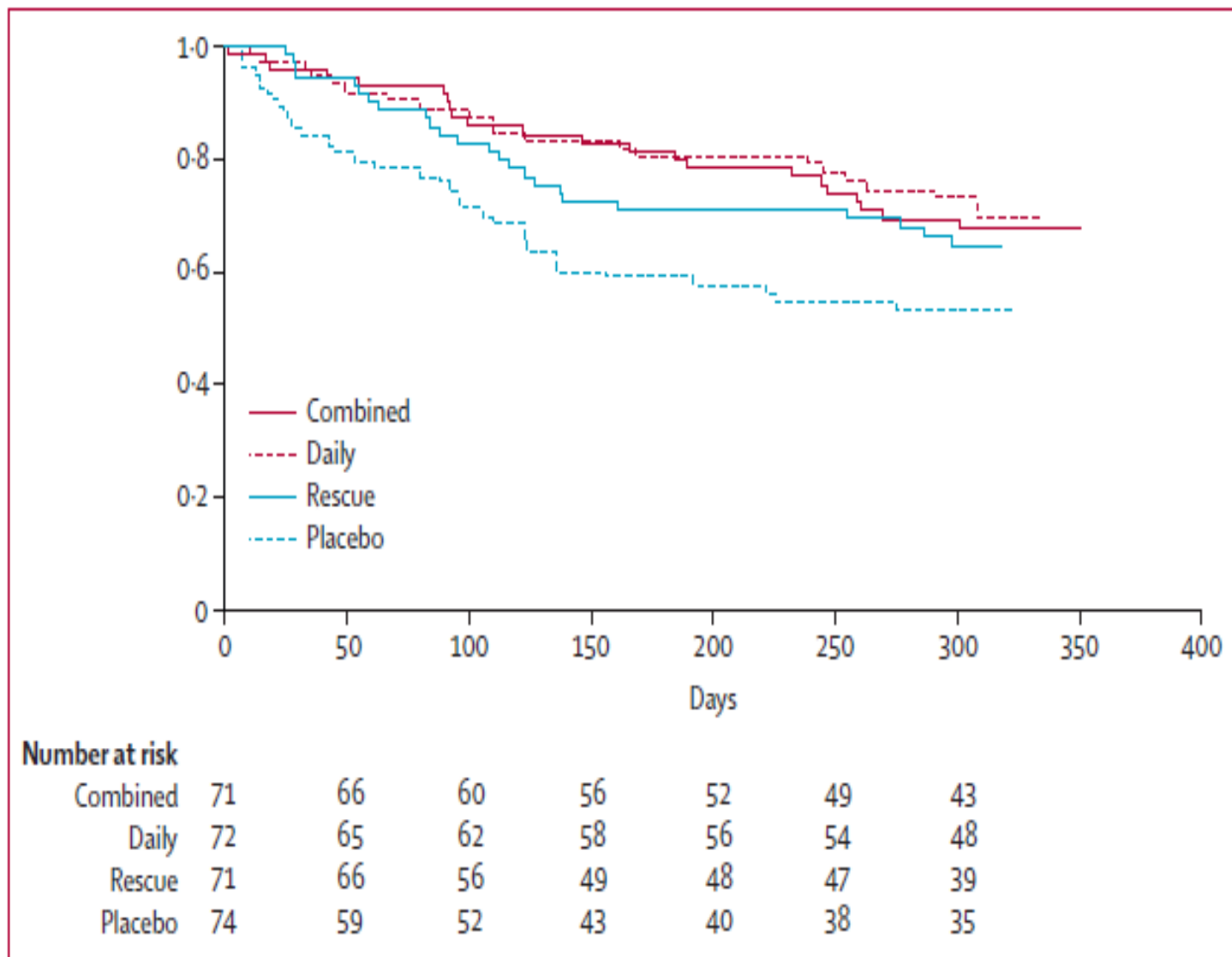


Figure 2: Kaplan-Meier curves showing the time to first exacerbation

1. Martinez, FD, et al. Lancet. 2011 Feb 19;377(9766):650-7.

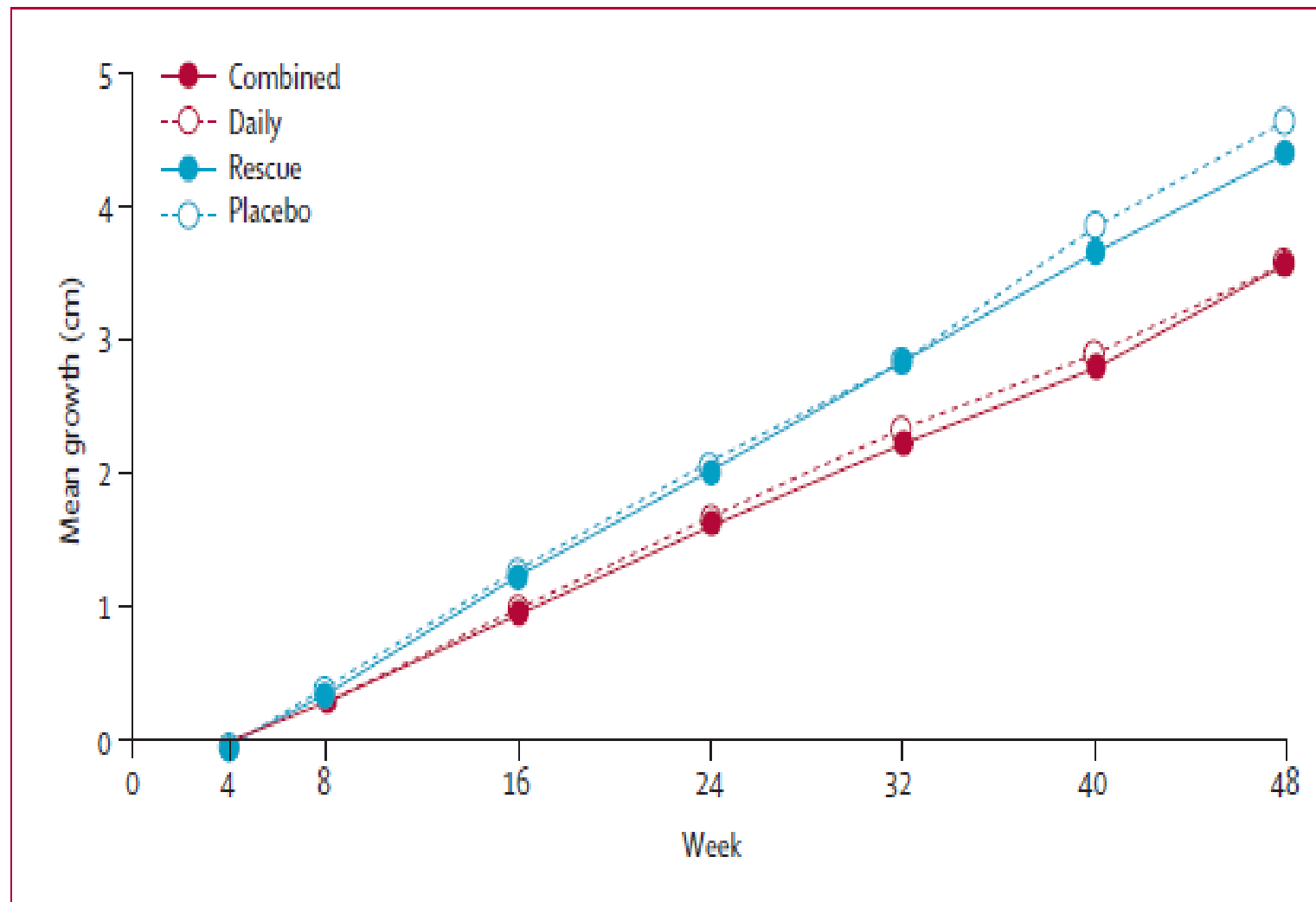


Figure 4: Linear growth by treatment group
Randomisation took place at week 4.

TREXA: Conclusions

- Children with mild persistent asthma should not be treated with rescue albuterol alone
- The **most effective** treatment to prevent exacerbations in persistent asthmatics is **daily** inhaled corticosteroids
- Inhaled corticosteroids as **rescue medication with albuterol** might be an effective step-down strategy; it is more effective at reducing exacerbations than is use of rescue albuterol alone and does not have associated growth effects

- **Why is this study important?**
 - 1st study to evaluate “real world” use of ICS therapy in children with intermittent dosing
 - Confirmed benefits of use of daily ICS as treatment for persistent asthma
 - But...also allowed for possibility of as needed ICS + albuterol in **mild** asthmatics
 - Confirmed 1.1 cm reduction in growth velocity with ICS use – now demonstrated with HFA formulation (all prior studies used CFC)

BASALT

- Best Adjustment Strategy for Asthma in Long Term
- Rationale:
 - To determine if adjustment of inhaled corticosteroid therapy based on exhaled nitric oxide or day-to-day symptoms is superior to guideline-informed, physician assessment-based adjustment in preventing treatment failure in adults with mild to moderate asthma.

BASALT: Conclusions

- Among adults with mild to moderate persistent asthma controlled with low-dose inhaled corticosteroid therapy, the use of either biomarker-based or symptom-based adjustment of inhaled corticosteroids was not superior to physician assessment-based adjustment of inhaled corticosteroids in time to treatment failure
- **Why is this important?**
 - Can patients improve asthma control with self-management?
 - Depends upon definition of 'failure'
 - One of first studies to begin to address 'real world' patient driven asthma management
 - Raises new questions re: dosing, end points, etc

Adjusted Maintenance Dosing(AMD): ICS and LABA

- Encourages patient to escalate therapy based upon symptoms by using single inhaler
 - Goal = decrease need for oral corticosteroids
- Multiple recent studies consistently demonstrate efficacy
- AMD therapy standard of care in Canada and Europe

*****Important Notation*****

This is NOT FDA approved
Many of these studies used Turbuhaler, not MDIs
FDA black boxed warning re: LABAs
NOT studied in children

Dynamic Dosing: Key Points

- Formoterol is the LABA component associated with efficacy
 - Similar to SABA reliever with time to onset of bronchodilation
 - Two current products:
 - Symbicort: budesonide/formoterol
 - Dulera: mometasone/formoterol
- Rationale – patients possess single inhaler to simplify regimen
- Ensures prompt increase in additional ICS dosing when using reliever more frequently
- Symptom driven approach assumes patients recognize worsening asthma symptoms
 - Not ideal for poor perceivers
 - Must have good provider-patient relationship, written action plan

Additional Considerations

- Yellow Zone parameters do not recommend use of ICS/LABA dynamic dosing in children < 18 years of age
- Options without much/strong evidence:
 - Single high dose of ICS
 - SABA plus anticholinergics
 - Montelukast

Controversy: Why Can't We Do This?

- Dynamic dosing of ICS + formoterol is better studied than most of the recommendations in this guideline, and is successfully implemented in Europe
- If we were going to have people dropping dead in emergency rooms because of LABA usage, we would be seeing them by now. The black box warning is academic
- Unfortunately, insurance companies will only pay for one inhaler a month. What do patients do for the rest of the month if they have an exacerbation?

Conclusion

- New efforts to focus on self-management at initial loss of asthma control can hopefully prevent progression to red zone
- Every patient should be given written individualized instructions
 - What to watch for
 - When to escalate therapy
 - What to do & for how long
- Asthma is a heterogeneous disease and treatment is not 'one size fits all'

THANK YOU FOR LISTENING

