Update in ASTHMA and COPD: Clearing the Air

What Works and What Doesn't?

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Community Faculty Development Symposium
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Knowing is not enough: we must apply.
Willing is not enough: we must do.

Goethe


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Overview of talk

- Asthma
  - Diagnosis
  - Chronic treatment
  - Acute exacerbation treatment
- COPD
  - Chronic treatment
  - Acute exacerbations
    - Diagnostic testing
    - Treatment

Epidemiology of asthma

- Prevalence
  - 5-12% US adult population or >200,000 adults
  - Prevalence increased 74% over 20 yrs
- Financial impact
  - 11 billion annual costs attributed to asthma
  - 465,000 hospitalizations per year
  - 1.8 million ER visits (20-30% admission rate)
  - 10.4 million MD office visits
  - Pts w/ exacerbations use 3.5-18x health care dollars
- Mortality
  - 4487 deaths in 2000 (61% increase over past 20 yrs)

Health Disparity and Asthma

- African Americans
  - Hospitalization rates 1.4-4x higher
  - More ED visits for asthma
  - Mortality rates 1.3-5.5x higher
  - Less likely to use inhaled steroids in MC setting
- Women
  - Lower quality of life with asthma
  - Hospitalization rate 2.5x higher

Why the Disparities

- SES?
- General Access to health care?
- Race specific barriers?
- Educational Level?

Asthma Case #1

45 yo M with new onset SOB, chest tightness, intermittent wheezing.

No CP, h/o CAD, reflux symptoms, no prior h/o dx asthma. Non – smoker

Mild productive cough with wheezing white sputum, no infection.

Exam – Normal except minimal end expiratory wheezing.

Audience Question #1

What would your next diagnostic step be? (choose one)

- History is sufficient diagnose asthma
- History and wheezing on exam is sufficient
- Need to perform Peak Expiratory Flow Rate
- Need to perform PFTs

Accuracy of Hx and PE in Diagnosing Asthma?

- Clinicians:
  - Disagree about presence or absence of respiratory signs 55-89% of the time
  - Correctly predict PFT findings 50%
  - Correctly diagnose asthma based on Hx and PE 63-74%

Ann All Asthma Immunology 1996;76:1.

Diagnostic Accuracy of Asthma History

SYMPTOM	SENSITIVITY
Persistent wheeze	35%
Chronic cough	24%
Chronic Dyspnea	29%

	PPV	NPV
Dyspnea + h/o asthma	48%	76%
Dyspnea + wheezing	42%	83%

Are PFTS Accurate/Useful?

- Spirometry
  - Reproducible (variation <5%)[1]
  - Accurate (sensitive to airflow obstruction)[2]
- Response to bronchodilators
  - Consensus as to cutoff for + test => increase by 12%, or >200 ml
- Methacholine challenge
  - Sensitivity >95%; Specificity ??
- **Peak Expiratory Flow Rate (PEFR)**
  - 30% variability between individuals
  - < 10% variability within patient (>5%)[3]
  - Requires pt understanding and cooperation

[1] NEJM 1994;331:25
[2] Am J Respir Crit Care Med 1995;152:1107
[3] Chest 2003;124:501

NAEPP Expert Panel: Diagnostic Testing Recommendations

- Hx and PE
- Spirometry with response to bronchodilators
- Methacholine challenge test if above is neg and suspicion is high


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No-show check-in counter

Chronic Asthma: Treatment

What are the 4 categories of chronic asthma?

- Mild intermittent
- Mild persistent
- Moderate persistent
- Severe

AR question #2

There is good evidence that early administration of inhaled corticosteroids: (check all that apply)

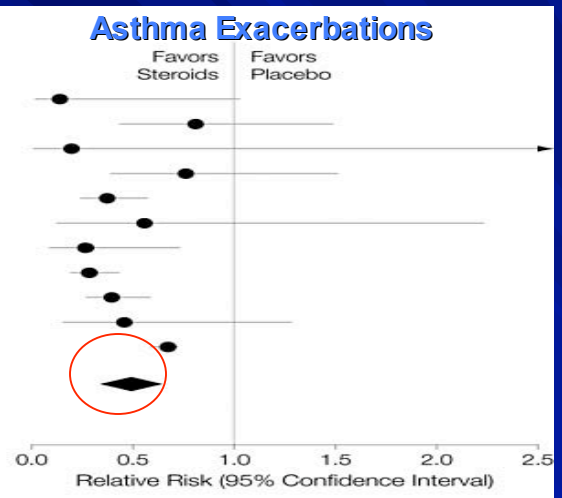
- Reduces asthma exacerbations
- Prevents airway remodeling
- Are cost – effective
- Can be safely reduced in moderate asthma

Do Inhaled Corticosteroids reduce exacerbations? – a Meta-analysis

A Inhaled Corticosteroids vs Placebo

Study	Participants, No.	Age, y, Mean (SD)*	FEV, % Predicted, Mean (SD)*
Juniper,[18] 1990	32	39 (14)	91 (13)
Haahtela,[17] 1991	103	38 (12)	87 (14)
Osterman,[20] 1997	75	34	NR
Nathan,[24] 1999	258	30 (12)	79 (12)
Malmstrom,[27] 1999	508	36	66 (11)
Kavuru,[22] 2000	172	37	64
Lazarus,[23] 2001	110	31 (11)	94 (9)
Nathan,[19] 2001	227	40	76
O'Byrne,[25] 2001	465	31	90 (15)
Busse,[26] 2001	227	NR	66
Pauwels,[21] 2003	7241	24 (15)	86 (14)

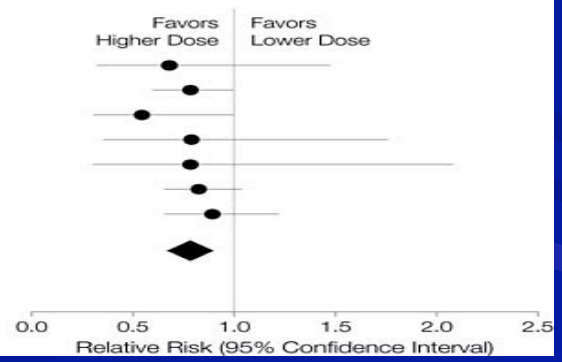
Pooled Summary
(RR, 0.46; 95% CI, 0.34-0.62;
Test for Heterogeneity: $\chi^2 = 32.15$, $P < .001$)



B Higher Dose vs Lower Dose Inhaled Corticosteroids

Study	Participants, No.	Age, y, Mean (SD)*	FEV, % Predicted, Mean (SD)*
Hummel,[31] 1992	142	43	NR
Pauwels,[28] 1997	427	43	76
Foresi,[30] 2000	142	38 (14)	74 (11)
Lim,[32] 2000	106	40 (14)	NR
Nathan,[19] 2001	113	40	76
O'Byrne,[25] 2001	629	37	86 (17)
Ind,[29] 2003	325	45 (15)	2.3 (0.9) L†

Pooled Summary
(RR, 0.77; 95% CI, 0.67-0.89;
Test for Heterogeneity: $\chi^2 = 2.81$, $P = .83$)



Inhaled steroids reduce exacerbations by 55%

Sin, D. D. et al. JAMA 2004;292:367-376.

Do inhaled steroids reduce exacerbations? One study in mild persistent asthma

- Patients: START Trial- 7241 pts with mild persistent asthma
- Design: 3 year, multinational, double blind, placebo RCT
- Intervention : QD budeniside vs. placebo

Outcome	EER Budeneside	CER Placebo	RRR	NNT
>1 Asthma Exacerbation in 3 years	117/3597 3.3%	198/3568 5.5%	46%	45 pts

Need to treat 45 pts with mild persistent asthma for 3 years to save one asthma exacerbation

Lancet 2003;361:1071

Does early administration of inhaled steroids delay airway remodeling?

- Data is not definitive
- Most benefit from inhaled steroids accrued in 1st 3 months (300-400 ml FEV1)
- Delayed use of inhaled steroids results in prolonged airway hyper-responsiveness – even after 6 months of therapy
  - This may result in more remodeling

Chest 1996;110:35

Are inhaled corticosteroids cost effective?

Patients: mild persistent asthma, n=7165
Design: 3 yr, blinded, multi-center international RCT
Intervention: Daily inhaled steroid vs usual care

Patients	***Direct cost effectiveness***	***Indirect cost effectiveness***
Mild Persistent Asthma **Budeniside vs Usual care**	$9.40/SFD	$3.40/SFD

Direct cost = Health care related costs. Indirect cost = Lost wages, societal cost
SFD = Symptom Free Day

- *Second study - $13,500 incremental cost /QALY attributable to inhaled steroids*

J Allergy Clin Immunol 2003;112:1229
J Allergy Clin Immunol 2003;108:39

What is the NNT (days of steroid treatment) to achieve a Symptom Free Day?

Same trial:

Outcome	EER **Inhaled Steroid**	CER **Usual Care**	RRR	NNT*
Symptom Free Day	**319 SFD/yr** **88%d/yr**	**289 SFD/yr** **82%d/yr**	6%	18

Need to treat a patient 18 days on average to add one symptom free day

J Allergy Clin Immunol 2003;112:1229

Can you safely reduce inhaled corticosteroids?

- Patients: 259 pts, moderate asthma, high dose inhaled steroids
- Design: 12 mo multi-center, blinded, RCT
- Intervention: Continued high dose vs reduction to 50% dose

	Stepdown group (n=130)	Control group (n=129)	Odds ratio (95% CI)	P value (χ^2 test)
Asthma exacerbations	40 (31)	33 (26)	1.29 (0.75 to 2.23)	P=0.354
Asthma related events:				
Visit to general practice	45 (35)	41 (32)	1.14 (0.68 to 1.91)	P=0.629
Home visit by general practitioner	3 (2)	6 (5)	0.48 (0.12 to 1.98)	P=0.304
Visit to accident and emergency department	2 (2)	1 (1)	2 (0.18 to 22.3)	P=0.567
Admission to hospital	4 (3)	1 (1)	4.06 (0.45 to 36.86)	P=0.179

Nonsignificant differences between patients with reduced doses and those with high dose steroids.

BMJ 2003;326 (7399):1115

AR question #3

What one medication has the greatest efficacy as a monotherapy in managing moderate persistent asthma?

- Leukotrienes inhibitors
- Long acting B2 Agonists
- Inhaled corticosteroids
- Ipatropium

Are long acting B2 agonists better than inhaled steroids as monotherapy?

- Patients: 164 pts with mild-moderate persistent asthma
- Design: 28 wk blinded placebo controlled 6 center RCT
- Intervention: Inhaled triamcinolone vs salmeterol vs placebo

Outcomes	EER Steroids	CER Salmeterol	RRR	NNT
Asthma exacerbations	7%	20%	65%	5.5

Steroids are better than B2 agonists in all categories. Both medications better than placebo.

JAMA 2001;285 (20):2583

Are leukotriene inhibitors better than inhaled steroids as monotherapy?

- Patients: 895 Mild – Moderate Asthma age 15-85
- Design: 12 week, multi-center, double blind, placebo, RCT
- Intervention: Montelukast vs inhaled beclamethasone

Outcomes	EER (steroids)	CER LI (only)	RRR	NNT
Asthma Exacerbation	10%	15.6%	32%	18

Cochrane Data Base meta-analysis also concludes Leukotriene inhibitors are not as efficacious ICS therapy as first line therapy.

AIM 1999;130(6):487

ACP Journal Club 2003:138 (2):42

Are Leukotriene Inhibitors better than Salmeterol as second line therapy?

- Patients: 1490 chronic (>1 yr) mild to moderate asthma
- Design: 1yr double blind multi-center RCT
- Intervention: Inhaled steroids + montelukast or salmeterol

Outcomes	EER Steroids + LI's	CER Steroids + LABA	RRR	NNT
Asthma Exacerbation	20%	19%	5%	NS

- *Quality of Life and FEV1 were the same as well.*
- *No difference between the two adjunct therapies except cost.*

BMJ 2003:327: 891

AR Question #4

In what severity of asthma can Omalizumab recommended as an adjunct therapy?
(May choose more than one)

- Mild Intermittent
- Mild persistent
- Moderate persistent
- Severe

Does Anti IGE therapy work?

- Patients: 2037 pts in 8 studies
- Design: Meta-analysis – Cochrane. Only blinded RCTs
- Intervention: Omalizumab (Xolair)

Outcomes	EER Omalizumab	CER Placebo	RRR	NNT
Asthma Exacerbation	14%	26%	46%	9

- *Omalizumab helps in selected patients with atopic hx, moderately high IGE reduce steroids, improve sxs*
- *$12,000/yr*

Cochrane Data Base Syst Rev 2003(3) CD003559

Does Immunotherapy work?

- Patients: 3506 in 75 RCTs
- Design: Meta-analysis by Cochrane Collaboration
- Intervention: Specific immunotherapy

Outcomes	EER Immunotherapy	CER Placebo	RRR	NNT
Symptom improvement	29%	60%	51	3.2

- *Also demonstrated improvement in FEV1 and reduction in medication with IT*
- *$800 =>$170/yr*

Cochrane Syst Rev 2003; 4: CD001186

AR question #5

Which strategy is best for using B-blockers in patients with asthma?

- Avoid non-selective B-Blockers
- Avoid selective B-Blockers
- Avoid both selective and non-selective
- Can use B-blockers in most asthmatics without increasing asthma sxs

What is the impact of B Blockers on Asthmatic patients?

Patients: 400 pts with mild to moderate asthma, COPD w/ 15% improvement in FEV1 after bronchodilator rx

Design: Meta-analyses

Intervention: Selective beta blockers

RESULTS

- Single dose use
  - 8% decrease FEV1
- Sustained use
  - No increase in SXS, FEV1 or beta agonist inhaler use

Selective B1 Beta blockers are safe in mild to moderate asthma

Ann Int Med 2002;137:715
Cochran Database Syst Rev 2001;2:CD002992)

What about theophylline?

- Only one study showing theophylline better than short acting beta agonists in pts on inhaled steroids.

Am J Resp Crit Care 1995;151:325

Acute Asthma Exacerbations: Treatment

34 yo obese woman with h/o asthma presents to ED with progressive SOB/ wheezing, h/o uri sxs in past week, no f/c/sputum production/chest pain.

PE – 150/100 w/ pulsus of 22. P 120 RR 32 36.9 89% on RA

Using accessory muscles. Cant talk in complete sentences. Prolonged expiratory phase. Wheezes throughout (or silent).

AR question #6

In managing acute asthma exacerbations in the emergency room, which treatment(s) is **NOT** supported by evidence?

1. B2 agonists (inhaler, nebulized)
2. Ipatropium
3. Theophylline
4. Steroids (oral, parenteral)

Does Ipatroprium improve acute asthma exacerbation outcomes?

- Patients: 172 ED pts with acute asthma exacerbations
- Design: RCT, Double Blind (short term)
- Intervention: Triple therapy vs Ipatropium and Steroids vs B2 Agonists and steroids

Outcomes	EER Triple rx[1]	CER Steroid, B2	CER Steroid, Ipat	RR	NNT
FEV1	2.1	1.7	1.8	NS	NS
Hospital Admissions	11%	20%	25%	45%, 56%	11, 7

[1]Triple Rx= Inhaled steroid, Ipatropium, B2 agonist

- *Triple Therapy outperforms double therapy.*
- *Ipatropium has greater benefit in more severe disease.*

Chest 2003; 123:1908.

Effect of Inhaled Anticholinergic Agents in the Treatment of Adult Patients With Acute Asthma

Study	Patients, No.	Jadad Score	Anticholinergic Protocol	Difference in Hospital Admissions (95% CI)	Change in Pulmonary Function (95% CI)
Owens and George[37]	37	3	AT (2.5 mg × 1) NEB	Trend favorable to IB group (12% vs 20% [NS])	NS
Cydulka and Emerman[38]	125	3	GL (2 mg × 1) NEB	NA	Favorable to control group (FEV_1, 52% vs 82% of predicted; $p < 0.05$)
Diaz et al[40]	126	3	AT (2.0 mg × 2) NEB	NS	NS
Kamei et al[27]	69	2	OB (200 μg × 5) MDI + spacer	Trend favorable to IB group (6.5% vs 12.1% [NS])	Favorable to IB group: mean PEF difference, 51.0 L/min (1.7–100.6)
Nakano et al[30]	74	3	OB (200 μg × 5) MDI + spacer	Trend favorable to IB group (13.2% vs 27.8% [NS])	Favorable to IB group: mean PEF difference, 37.8 L/min (15.9–59.8)
Rodrigo and Rodrigo[29]	180	4	IB (24 puffs/h × 3) MDI + spacer	20% vs 36% favorable to IB group ($p = 0.01$); RR, 0.51 (0.31–0.83); NNT, 5 (3–17)	All patients: favorable to IB group: mean PEF difference, 52.3 L/min (27–77.6)

*AT = atropine sulfate; GL = glycopyrrolate; OB = oxitropium bromide. See Table 1 for abbreviations not used in the text.

Trend across studies favoring Ipatropium over placebo

Chest, 2002;121(6):1977.

Do oral or inhaled steroids in ED improve outcomes in acute asthma exacerbations?

- Patients: 352 ED pts in 7 trials
- Design: Meta-analysis
- Intervention: Inhaled corticosteroids vs placebo

Outcomes	EER Inhaled steroids	CER Placebo	RRR	NNT
Hospital admission	10%	27%	61%	6

Steroids (oral/parenteral) reduce hospital admissions.

Ann Emerg Med 2002; 40:145

Are parenteral steroids more effective than inhaled steroids?

- Patients: 313 pts in 4 studies with asthma exacerbations
- Design: Meta-analysis
- Intervention: Inhaled vs parenteral steroids

- *No difference in hospital admission rates.*
- *No clinically significant different outcomes.*
- *Slightly later (1-2 hrs) improvement in FEV1 with IV.*

Ann Emerg Med 2002; 40:145

Do **oral** + inhaled steroids improve outcomes in acute asthma exacerbations?

- Patients:191 ED pts, PEFR <80%
- Design: Single site, blinded, placebo controlled RCT
- Intervention: 7 d oral steroids vs 7d oral + 3 wks inhaled steroids

Outcomes	EER **Oral + inhaled steroids**	CER **Oral steroids**	RRR	NNT
Relapse	13%	25%	48%	9

Inhaled steroids reduce relapse rate in acute setting.

JAMA 1999;281:2119

Are B2 Agonist **MDIs** more effective than **Nebulizers**?

- No

Chest 1993;104:835

AR question #7

Which of the following treatments have evidence to justify their use in severe asthma exacerbations? (May choose more than 1)

1. Mg SO4
2. Leukotrienes
3. Heliox
4. Theophylline
5. Glucagon

Other therapies for acute asthma exacerbations

- MgSO4
  - May have efficacy in some severe situations.
- Leukotriene Inhibitors
  - Not effective
- Heliox
  - No evidence
- Theophylline
  - Not effective and has side effects
- Glucagon
  - No evidence

Other therapies for chronic and acute asthma exacerbations

- Nebulized furosemide, heparin , lidocaine
- Methotrexate, gold, cyclosporine, colchicine hydroxychloroquine, IVIG
- Macrolides
- Acupuncture, chiropractic manipulation, massage
- Dietary manipulations, antioxidants
- Breathing exercises

Treatment of COPD

Stepwise Chronic COPD Treatment

Stage 0 At Risk	Stage 1 Mild	Stage 2 Moderate	Stage 3 Severe	Stage 4 Very Severe
FEV_1 Normal Chronic Symptoms (Cough and Sputum Production)	$FEV_1 \geq 80\%$ Predicted	FEV_1 50% to 79% Predicted	FEV_1 30% to 49% Predicted	FEV_1 <30% Predicted or Chronic Respiratory Failure or Right-Sided Heart Failure
				Consider transplantation or other surgical treatment
			Add pulmonary rehabilitation Add long-term oxygen to correct arterial hypoxemia	
		Add long-acting bronchodilator(s) for relief of persistent dyspnea Add inhaled corticosteroids for persistent dyspnea on bronchodilator(s) or repeated exacerbations Consider pulmonary rehabilitation for patients who are persistently dyspneic despite therapy with long-acting bronchodilators and inhaled corticosteroids		
	Add short-acting bronchodilator for relief of intermittent dyspnea			
Smoking cessation for all smokers Vaccinations against influenza and pneumoccocal infection for those older than 65 years				

Do inhaled steroids prevent COPD exacerbations?

- Patients: 244 pts, 64 yo with stable moderate to severe COPD, no asthma
- Design: 6 month single site, blinded, placebo controlled RCT
- Intervention: 4 months run–in on steroids and ipatropium then randomize to continued steroid vs placebo

Outcomes	EER Inhaled Steroids	CER Usual care no steroids	RRR	NNT
COPD Exacerbation	48%	58%	24%	8

- *Steroids delayed 1st exacerbation, reduced recurrent exacerbations (NNT 7), better QOL.*
- *Most clear benefit in FEV1 <50%*

Am J Respir Crit Care Med 2002: 166:1358

AR Question #8

Which of the following have been shown to delay progression of COPD (loss of FEV1)?
(May choose more than 1)

1. Smoking cessation
2. Inhaled Steroids
3. B2 Inhalers
4. Ipatropium

Do inhaled steroids slow progression of COPD?

- Patients: 3715 stable COPD pts. No asthma.
- Design: Meta-analysis 8 RCTs w/ >2 yr f/u
- Intervention: Inhaled corticosteroids

Outcomes	Steroids	No steroids	Rate difference	Rel. Diff.
Rate of FEV1 decline	46 ml/yr	54 ml/yr	8 ml/yr	15%

- *Steroids: 15%"slower decline in FEV1*
- *Smoking Cessation: 50% slower decline in FEV1*

Thorax 2003;58:937

AR question #9

- What long term management intervention has the greatest impact on symptoms in patients with COPD? (choose 1)
  1. Inhaled steroids
  2. B2 agonist Inhalers
  3. Smoking cessation
  4. Ipatropium

Do inhaled B2 agonist improve function in COPD?

- Patients: 237 COPD pts. 56-70 yo
- Design: Cochrane Meta-analysis of 13 placebo RCTs
- Intervention: Short acting B2 agonist inhalers >7d

Outcomes	EER Salbutemol, Terbutaline., Isoprot.	CER Placebo	RRR	NNT
Treatment failure rate	22%	46%	51%	4

- *Better symptom scores with short acting B2 inhalers.*
- *Improved FEV1, FVC, PEFR, and Sx scores.*

Thorax 2003:58:580

Is Tiotropium more effective than Salmeterol in COPD?

- Patients:1207 pts. 64 yo stable COPD. no asthma, O2.
- Design: 6 mo. multi-center/multi-national, blinded, placebo RCT
- Intervention: Tiotropium, Salmeterol, Placebo

Outcomes	EER Tiotropium	CER Salmeterol	RRR	P value
# COPD Exacerbations	1.07	1.23	.14	NS

No difference between Tiotropium and Salmeterol in #, duration of exacerbations, hospitalizations, FEV1, symptom scores.

Thorax 2003;58:399

Are self management programs effective in COPD?

- Patients: 191 pts with stable COPD FEV1 25-75% predicted. No major co-morbidities.
- Design:12 mo multi-center blinded, RCT. F/u 86%
- Intervention: Self Management program.

Outcomes	EER SMP	CER Usual Care	RRR	NNT
Hospitalizations	71	118	40%	2

Self management program resulted in impressive reduction in hospitalizations, ED visits

Arch Int Med 2003;163:585


SPEED
LIMIT
50
YOUR SPEED
167
POLICE

COPD flare: Diagnostic tests

- CXR changes therapy in 16-21% cases
- FEV1 of <40% predicted => sensitivity 96% in predicting relapse or hospitalization
- Hypercapnia is unlikely if FEV1 >35% predicted .

Ann Emerg Med 1993;22:680

COPD flare: Are MDIs more or less effective than Nebulizers?

- Bottom line:

  Meta-analysis of 12 high quality study in 2002 and a subsequent excellent trial showed no difference between MDI (w/ or w/o spacers) and nebulizers

Arch of Intern Med 1997;157:1737

COPD flares: What is the optimal duration of Steroids?

- Patients: 271 hospitalized VA pts w/ COPD flare
- Design:6 mo. multi-center blinded RCT
- Intervention: 3 d IV steroids + 2 or 8 wks oral compared to placebo

Outcomes	EER Steroids	CER Placebo	RRR	NNT
Treatment Failure	23%	33%	30%	10

- *Treatment with steroids resulted in fewer treatment failures, 1 d shorter hospital stay*
- *8 wks steroid rx is not better than 2wks!*

NEJM 1999;340 (35):1941

COPD flares: Are Inhaled steroids as effective as oral?

- Patients: 199 hospitalized pts w/ COPD flare
- Design:20 mo. multi-center, blinded, placebo controlled RCT
- Intervention: Inhaled vs IV steroids vs Placebo

- *Inhaled vs IV steroids – no significant clinical outcome differences.*

- *Minimal advantage of steroids (IV or Inhaled) over placebo in physiologic measures (FEV1)*

Am J Respir Crit Care Med 2002:165:698

COPD flares: Does Ipatropium improve outcomes?

- 5 RCTs have compared Anticholinergic vs. B2 Agonist monotherapy
  - No substantial physiologic or patient outcome difference.

- 7 RCTs have compared adding an anticholinergic bronchodilator to B agonist.
  - No significant differences in physiologic or patient outcomes

Ann Int Med 2001 134(7):600

COPD flares: Does Theophylline improve outcomes?

-
- No. It increases side effects.

On that Note….

Thank you.

Questions?