N-ACETYLCYSTEINE in Management of COPD

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Chronic obstructive pulmonary disease (COPD), which includes chronic bronchitis and chronic emphysema, is a rapidly growing problem with global impact.

The prevalence of COPD in Bangladesh is more than 11% among subjects at 35 years or older.

NAC has been used in conventional medicine for more than 30 years, primarily as a mucolytic agent.

With its ability to reduce oxidative stress and simultaneously quash chronic inflammatory changes, NAC is can be a game-changing therapy in COPD.

"Excessive viscous mucus" in the airway is one of the major symptoms in **acute or chronic respiratory diseases.**

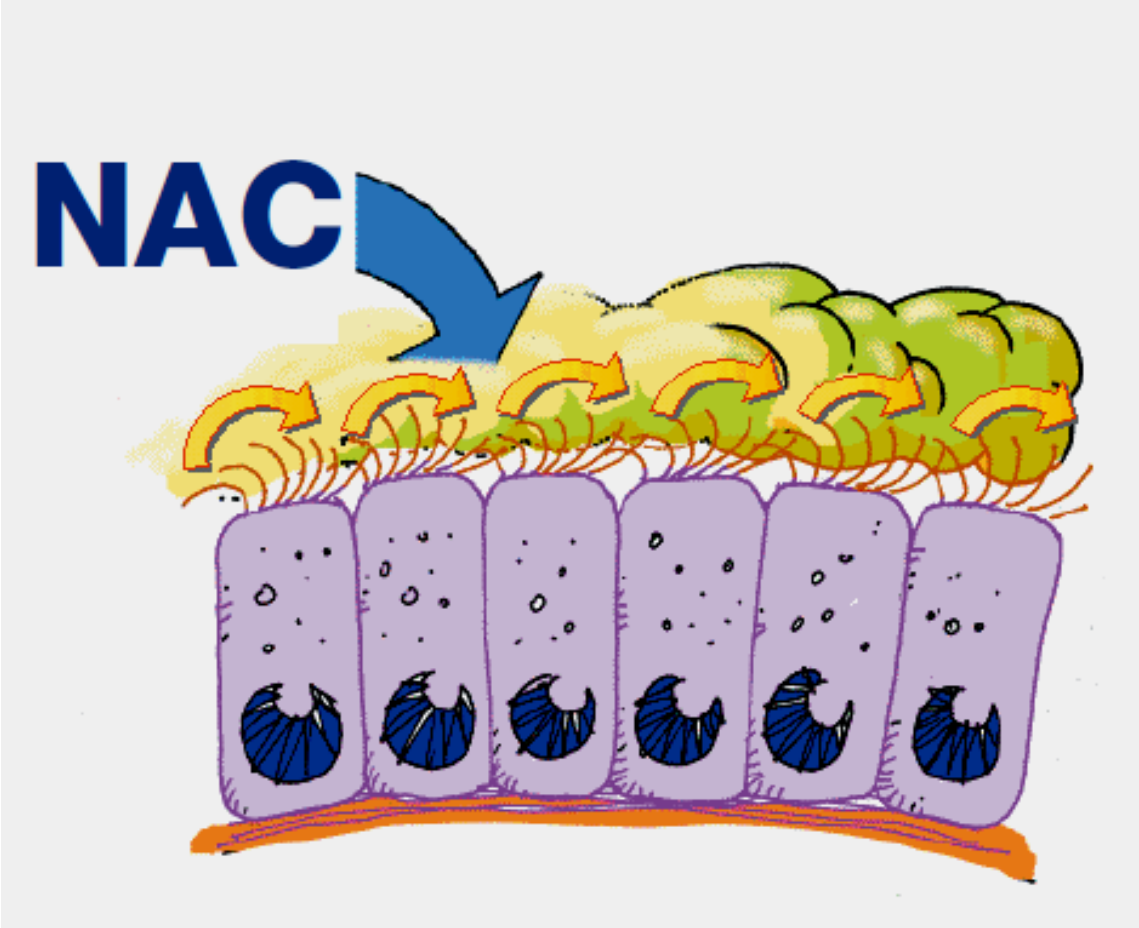
AND clearing airways is an important part in the management of those **diseases.**

Direct Mucolytic activity

NAC breaks the disulfide bond and rendering the mucous less Viscous and easier to expectorate

Current therapeutics;role of N-Acetylcysteine in the treatment of acuterespiratory disorder,ISBN 75561606

Activation of mucilliary clearence



NAC improves the physiological transport of mucous, facilitating its removal

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Acetylcysteine is not only **powerful mucolytic** in the treatment of chronic respiratory diseases, but also gives ***diversified biological action-***

N-acetylcysteine (NAC), a precursor of reduced glutathione (GSH)

GSH is

- Most abundant non-protein **thiol** in the cell;
- It serves antioxidant and cytoprotective functions in the cell;
- It is critical in maintaining the **redox** environment of the cell

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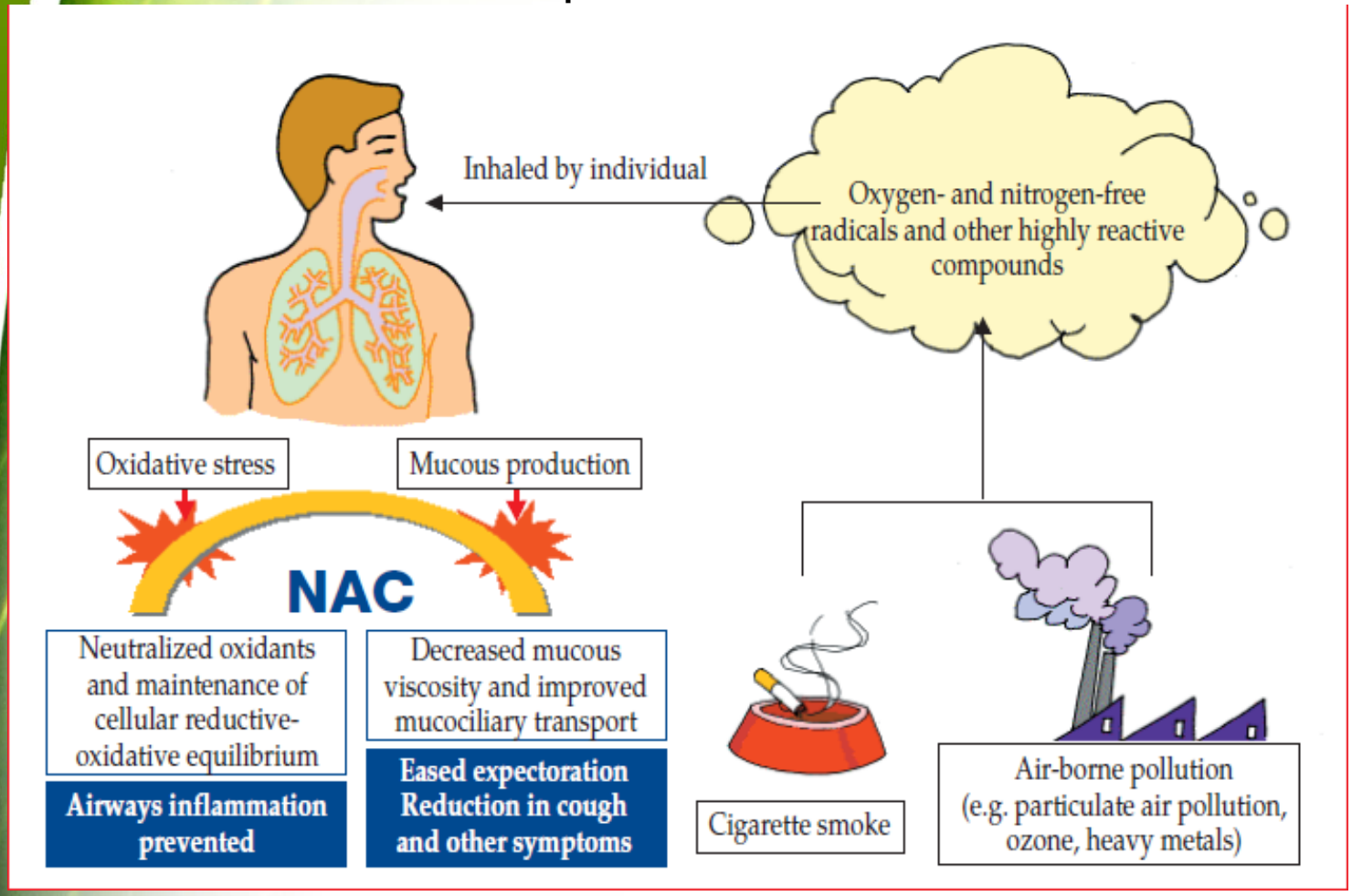
Benefits of N-acetylcysteine (NAC) on countering the airway effects of cigarette smoke or air-borne pollution.



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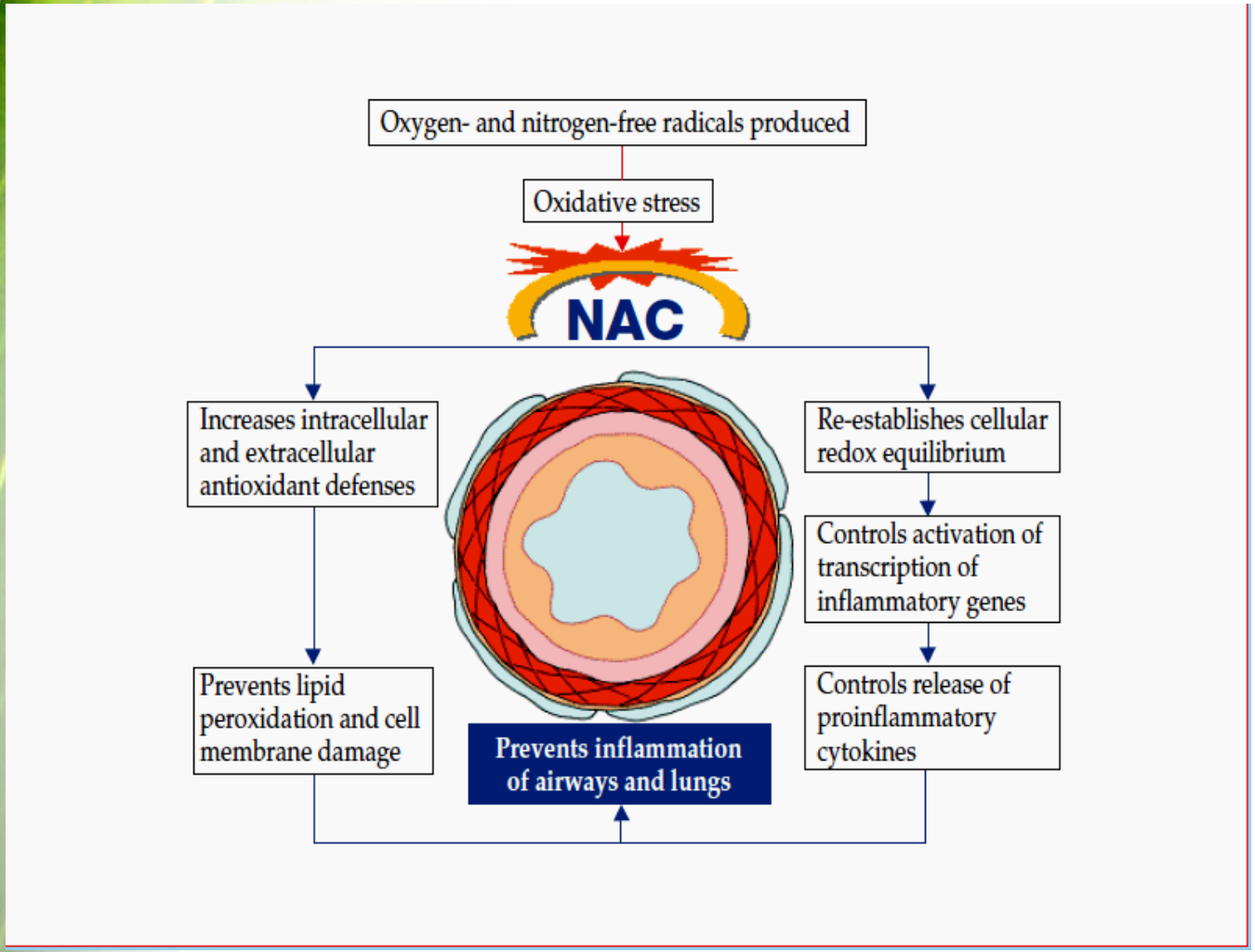
as an antioxidant and re establisher of reductive oxidative (redox)



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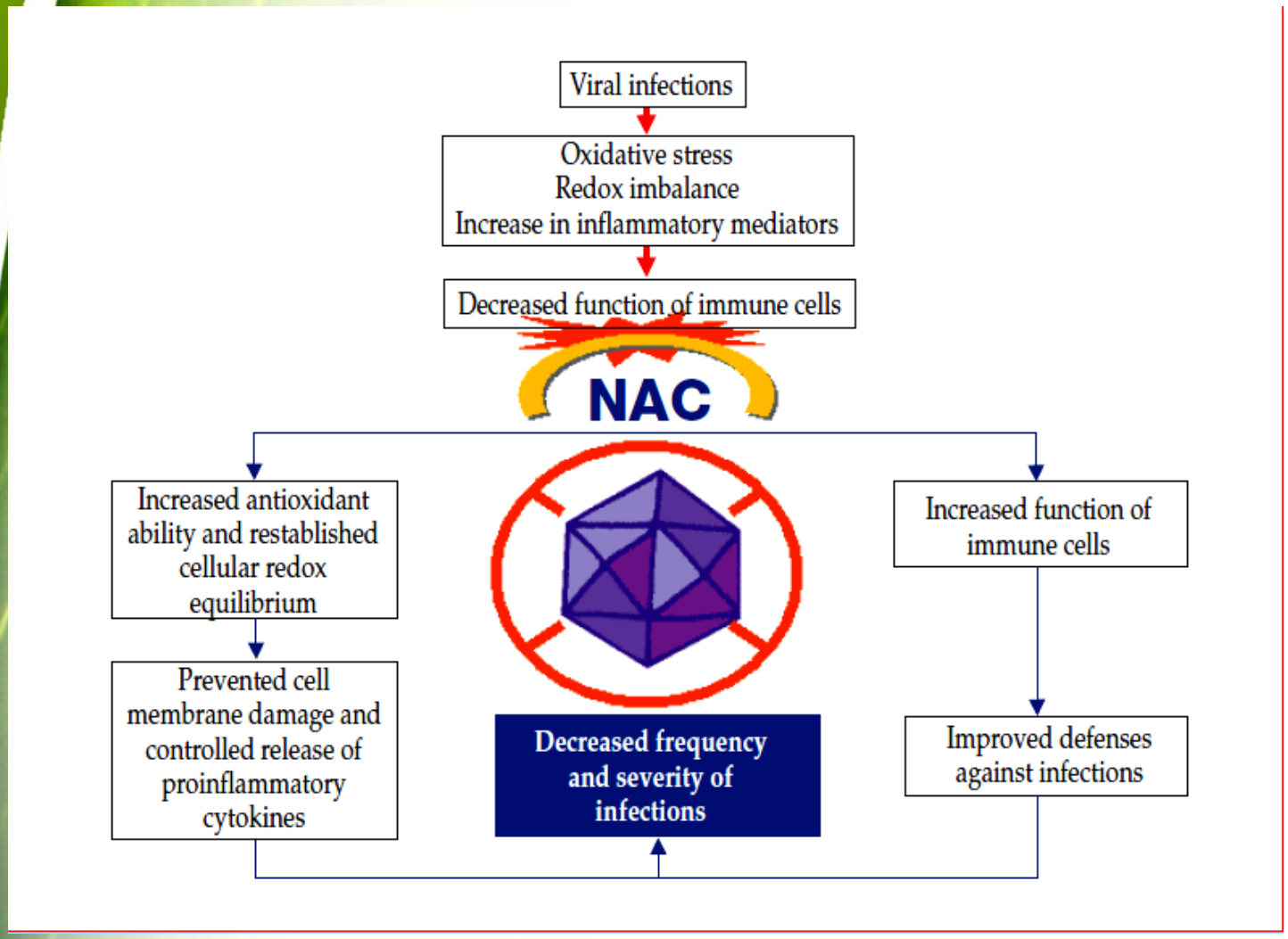
Immunomodulatory effects of N-acetylcysteine (NAC).



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Proposed Mechanism in COPD

- Mucolytic effect
- Inhibit transmigration of neutrophil
- Decrease epithelial thickening
- Reduce lung hyperinflation
- Reduce lysozyme and lactoferrin
- Reduce activation of neutrophil and macrophages

Intentional journal of COPD.2014:9

Because of these various effects there is speculation that N-acetylcysteine could have a role in management of patients with COPD to prevent recurrent exacerbations and disease progression.

(Evidence B)

2014;Global Initiative for Chronic Obstructive Lung disease

Cochrane 2010 Analyze

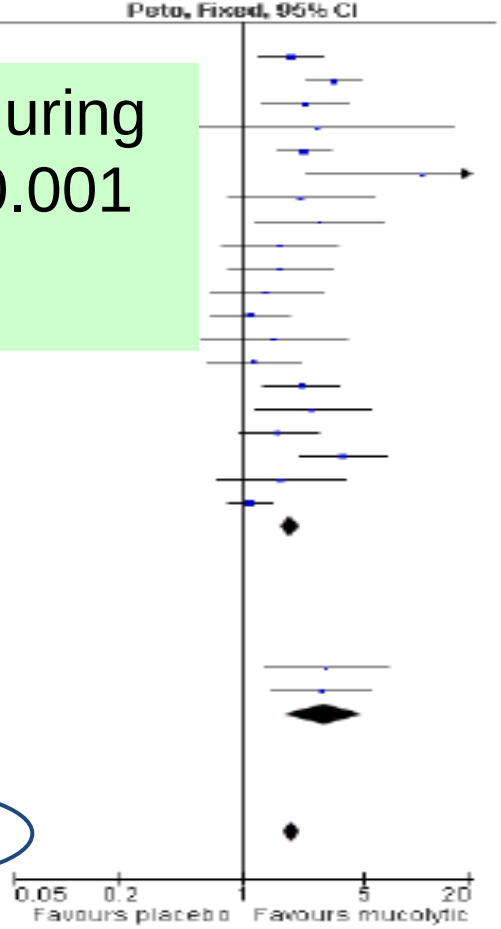
- COPD patients
- Oral mucolytics / Placebo
- 28 studies
- 7042 patients
- At least 2 months therapy

Exacerbation free patients during study

Figure 2. Forest plot of comparison: 1 Mucolytic versus Placebo, outcome: 1.3 Patients with no exacerbations in study period.

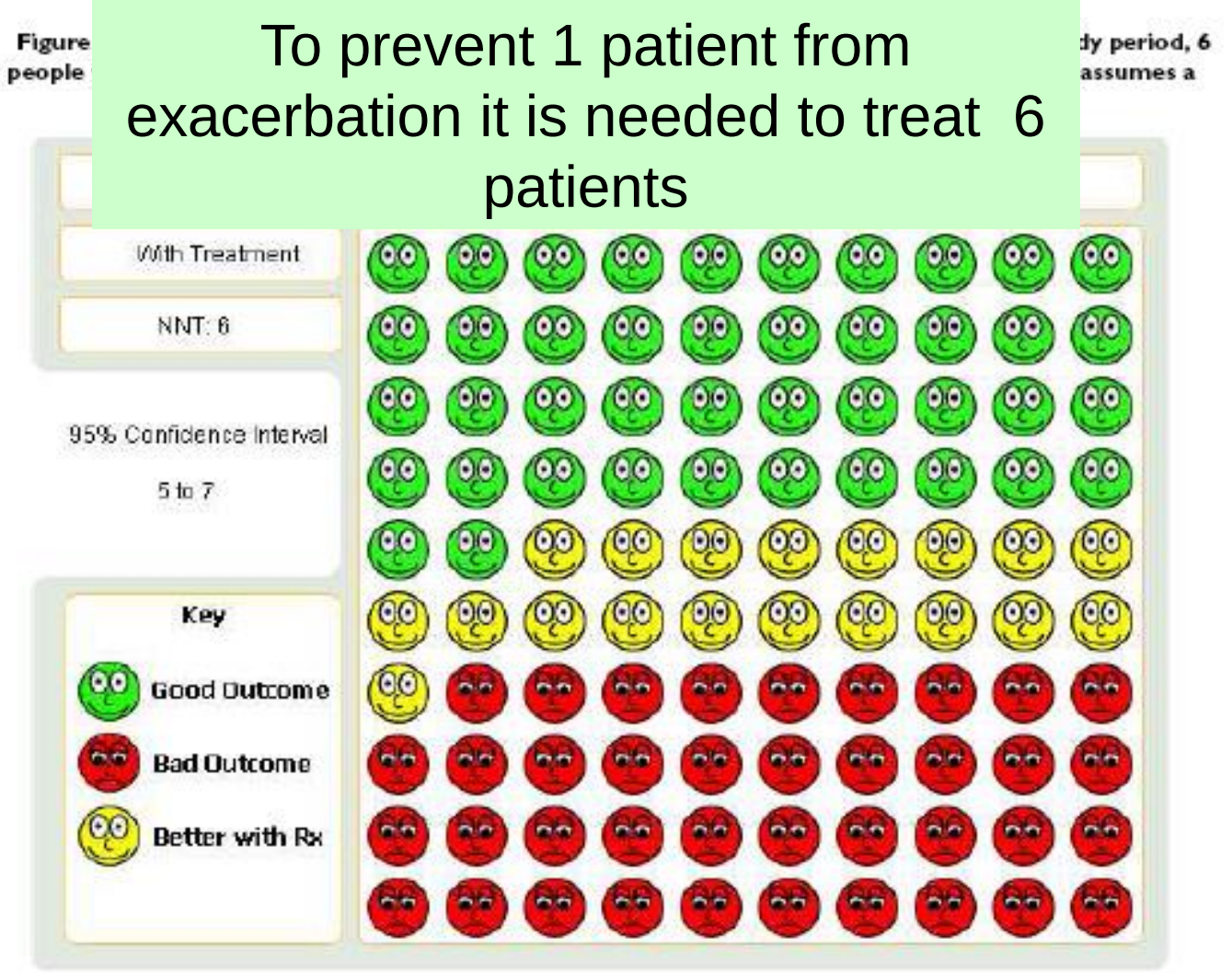
Study or Subgroup	Mucolytic Events	Mucolytic Total	Placebo Events	Placebo Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.3.1 Double Blind						
Allegra 1996	111	171	99	181	7.9%	1.90 [1.24, 2.99]
Babolini 199[illegible]						
Boman 1993						
Borgia 1991						
Castiglioni 1[illegible]						
Cremonini 1[illegible]						
Grassi 1976						
Grassi 1994						
Grillage 1985						
Hansen 1994						
Jackson 198[illegible]						
Malerba 2004						
McGavin 198[illegible]						
Meister 1986	37	90	34	91	4.0%	1.17 [0.64, 2.12]
Meister 1999	79	122	56	124	5.6%	2.20 [1.33, 3.63]
Moretti 2004	26	63	13	61	2.5%	2.50 [1.18, 5.33]
Nowak 1999	114	147	101	148	5.4%	1.60 [0.96, 2.67]
Olivieri 1987	56	110	21	104	4.5%	3.77 [2.16, 6.58]
Rasmussen 1988	28	44	24	47	2.1%	1.66 [0.73, 3.80]
Zheng 2008	159	353	151	354	16.0%	1.10 [0.82, 1.48]
Subtotal (95% CI)		**2232**		**2242**	**94.5%**	**1.88 [1.67, 2.13]**
Total events	1275		954			
Heterogeneity: Chi² = 44.82, df = 19 (P = 0.0007); I² = 58%						
Test for overall effect: Z = 10.17 (P < 0.00001)						
1.3.2 Single Blind/OpenSingle blind						
Bachh 2007	25	50	12	50	2.2%	3.02 [1.35, 6.77]
Pela 1999	37	83	17	80	3.3%	2.85 [1.49, 5.46]
Subtotal (95% CI)		**133**		**130**	**5.5%**	**2.91 [1.76, 4.83]**
Total events	62		29			
Heterogeneity: Chi² = 0.01, df = 1 (P = 0.91); I² = 0%						
Test for overall effect: Z = 4.14 (P = 0.0001)						
Total (95% CI)		**2365**		**2372**	**100.0%**	**1.93 [1.71, 2.17]**
Total events	1337		983			
Heterogeneity: Chi² = 47.52, df = 21 (P = 0.0008); I² = 56%						
Test for overall effect: Z = 10.85 (P < 0.00001)						
Test for subgroup differences: Chi² = 2.69, df = 1 (P = 0.10), I² = 62.9%						

Exacerbation free patients during study odds ration 1.93 , p<0.001



NNT : 6
Number Needed to Treat

To prevent 1 patient from exacerbation it is needed to treat 6 patients



Cont….

- If studies of 8 months of treatment in winter months are considered, odds ratio for exacerbation free patients number is 2.23.

Result

- They are not effective on the decrease of FEV_1 decline rate.
- The decrease on FRC was significant
- Their effects on quality of life are variable

BRONCUS Study

- Double blind, placebo controlled, randomized
- 523 patient
- 3 year N-acetylcysteine 600 mg/day

RESULTS:

- FEV_1 decline rate per year is not different.
- No decrease in exacerbations.
- Decrease in exacerbation rates in a subgroup of patients not using inhaled steroid
- No effect on quality of life.
- Significant decrease in FRC(374 ml, $p < 0.001$)

HIACE Study

- Double-blind, Randomized, Placebo-controlled Trial on Chinese COPD patients
- NAC at a daily dose of 1200mg improves small airway disease ($FEF_{25\%-75\%}$)

Chest. 2013;144(1):106-118

PANTHEON Study

- A large, multi-centered, one year trial on Chinese patients with moderate to severe disease.
- High dose NAC reduce frequency of exacerbations.
- NAC significantly prolongs time to the second and third exacerbations.

Lancet Respir Med. 2014;2(3):187-194

Effect of high/low dose N-acetylcysteine on chronic obstructive pulmonary disease: a systematic review and meta-analysis.

This review yielded 11 studies.

CONCLUSION:

Long-term high-dose NAC treatment may lead to a lower rate of exacerbations. But the effect of low-dose NAC treatment remains uncertain. Further researches are needed to confirm this outcome and to clarify its mechanisms.

COPD. 2014 Jun;11(3):351-8. doi: 10.3109/15412555.2013.858315. Epub 2013 Dec 30.

GOLD Recommendation on Mucolytics

- The regular use of mucolytics in long-term studies are controversial.
- Patients with viscous sputum may benefit from mucolytics. The overall benefit seems to be very small. The widespread use of these agents can not be recommended at present (Evidence D)

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GOLD Cont…..

- They are not effective on FEV_1 decline.
- In patients not treated with inhaled steroids N-acetylcysteine may reduce exacerbations (Evidence B)
- They may have some effects on frequent exacerbations requiring hospitalization.

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Conclusion

- Even though NAC has a long history of use in humans and its safety and pharmacokinetics are well established, its role in disease progression is under further evaluation.
- As far as exacerbation rate, number of sick leave days and quality of life concerned; the use of NAC seems to be promising especially at high dose.

THANK YOU