Attenuation of influenza-like symptomatology and improvement of cell-mediated immunity with long-term N-acetylcysteine treatment.

S. De Flora, C. Grassi, L. Carati.

ABSTRACT: N-acetylcysteine (NAC), an analogue and precursor of reduced glutathione, has been in clinical use for more than 30 yrs as a mucolytic drug. It has also been proposed for and/or used in the therapy and/or prevention of several respiratory diseases and of diseases involving an oxidative stress, in general. The objective of the present study was to evaluate the effect of long-term treatment with NAC on influenza and influenza-like episodes.

A total of 262 subjects of both sexes (78% ≥65 yrs, and 62% suffering from non- respiratory chronic degenerative diseases) were enrolled in a randomized, double- blind trial involving 20 Italian Centres. They were randomized to receive either placebo or NAC tablets (600 mg) twice daily for 6 months. Patients suffering from chronic respiratory diseases were not eligible, to avoid possible confounding by an effect of NAC on respiratory symptoms.

NAC treatment was well tolerated and resulted in a significant decrease in the frequency of influenza-like episodes, severity, and length of time confined to bed. Both local and systemic symptoms were sharply and significantly reduced in the NAC group. Frequency of seroconversion towards A/H1N1 Singapore 6/86 influenza virus was similar in the two groups, but only 25% of virus-infected subjects under NAC treatment developed a symptomatic form, versus 79% in the placebo group. Evaluation of cell-mediated immunity showed a progressive, significant shift from anergy to normoergy following NAC treatment.

Administration of N-acetylcysteine during the winter, thus, appears to provide a significant attenuation of influenza and influenza-like episodes, especially in elderly high-risk individuals. N-acetylcysteine did not prevent A/H1N1 virus influenza infection but significantly reduced the incidence of clinically apparent disease. Eur Respir J 1997; 10: 1535–1541.

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"The present multicentric study, referred to as the NACIS study (acronym for N-acetylcysteine in Immune System), was designed in order to evaluate the efficacy of NAC, administered orally throughout the cold season, in preventing the occurrence and reducing the severity of influenza-like episodes in general, and specifically those caused by the influenza A/H1N1 virus. Another goal of this study was to assess the effect of NAC treatment on cell-mediated immunity."

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Table 2. – Compliance with treatment, adverse effects, and frequency of influenza-like episodes as related to treatments

Variable	Treatment	
	Placebo	NAC
Compliance with treatment* n	120 (93)	125 (94)
Adverse events n		
Total	7 (5)	12 (9)
Dysuria	0	2 (2)
Epigastralgia	3 (2)	4 (3)
Nausea/vomiting	1 (1)	1 (1)
Constipation	0	1 (1)
Diarrhoea	3 (2)	2 (2)
Flushing	0	2 (2)
Nonevaluable patients n		
Adverse events before first control	1 (1)	1 (1)
Lost to follow-up	6 (5)	6 (5)
Patients evaluable for efficacy n	122 (95)	126 (95)
Duration of treatment days	167±34 (32–199)	166±35 (33–206)
Treatment ≥5 months n	116 (90)	108 (81)
Influenza-like symptomatic cases n		
Total cases	62 (51)	37 (29)†
Patients suffering from 1 episode	36 (30)	24 (19)
Patients suffering from 2–3 episodes	18 (15)	11 (9)
Patients suffering from ≥4 episodes	8 (7)	2 (2)

Data are presented as mean±SD and range in parenthesis, or as absolute value and percentage in parenthesis. *: drug or placebo intake ≥80%. NAC: N-acetylcysteine. †: significantly lower than in the placebo group (p=0.0006), as assessed by Chi-squared analysis.

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Effect of N-acetylcysteine (NAC) treatment on the frequency of influenza-like episodes during the 6 months of treatment.

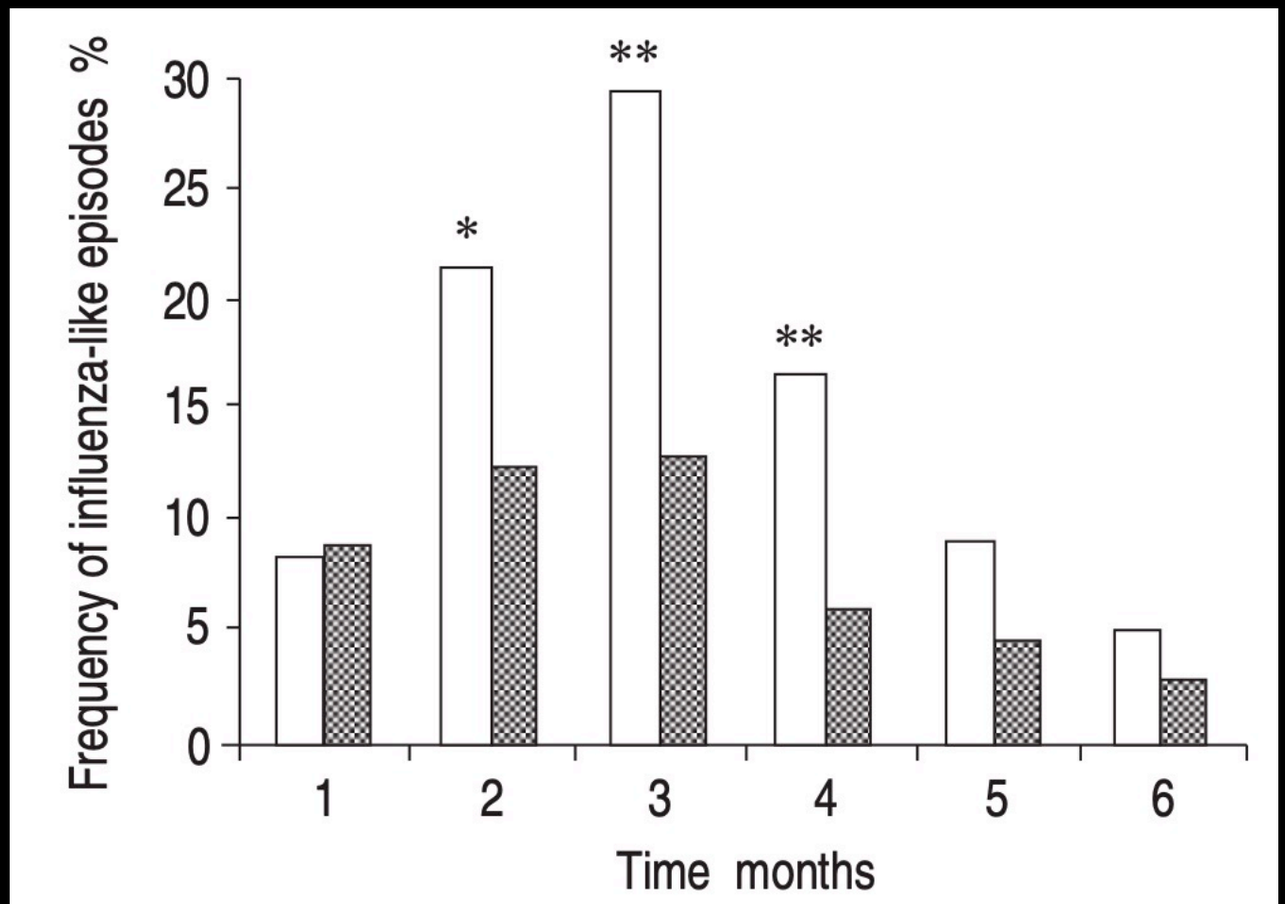

Fig. 1. – Effect of N-acetylcysteine (NAC) treatment on the frequency of influenza-like episodes during the 6 months of treatment. ▭ : placebo; ▩ : NAC. *: $p<0.05$; **; $p<0.01$, significance of difference between the frequency of episodes occurring in the NAC group and in the placebo group, as assessed by Chi-squared analysis.

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Effect of N-acetylcysteine (NAC) treatment on cell-mediated immunity

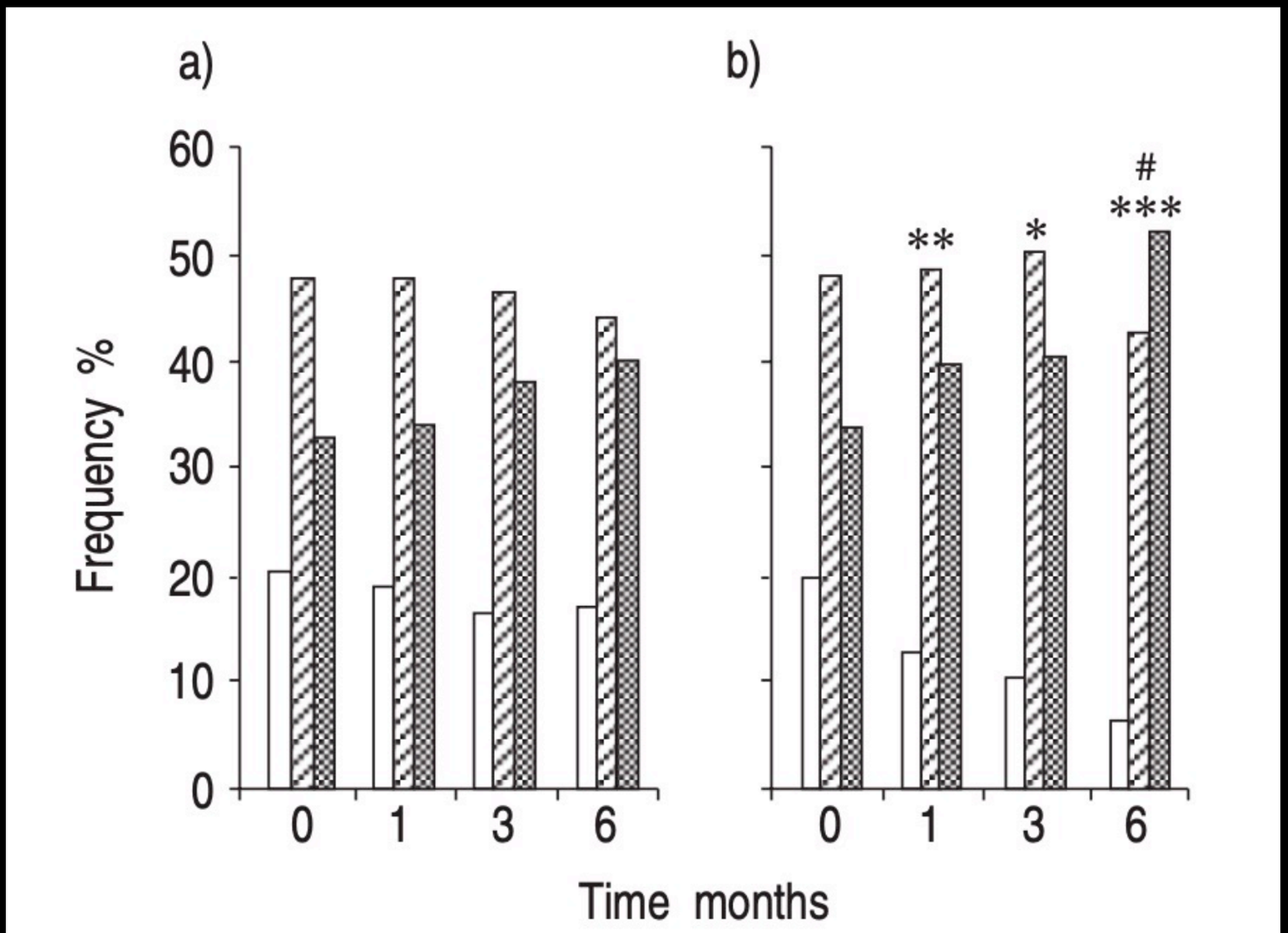

Fig. 3. – Effect of N-acetylcysteine (NAC) treatment on cell-mediated immunity. a) Placebo group; b) NAC-treated group. ▭ : anergy; ▨ : hypoergy; ▩ : normoergy. *:p <0.05; **: p<0.01; ***: p<0.001, significance of difference in the frequency of anergy, within the NAC group, after 1, 3 and 6 months, compared to the start of the study (time 0); #: p<0.05, significance of difference in the frequency of anergy between the NAC group and the placebo group, as assessed by Chi-squared analysis.

Effect of N-acetylcysteine (NAC) treatment on the cumulative occurrence of individual influenza-like signs and symptoms throughout the duration of the study

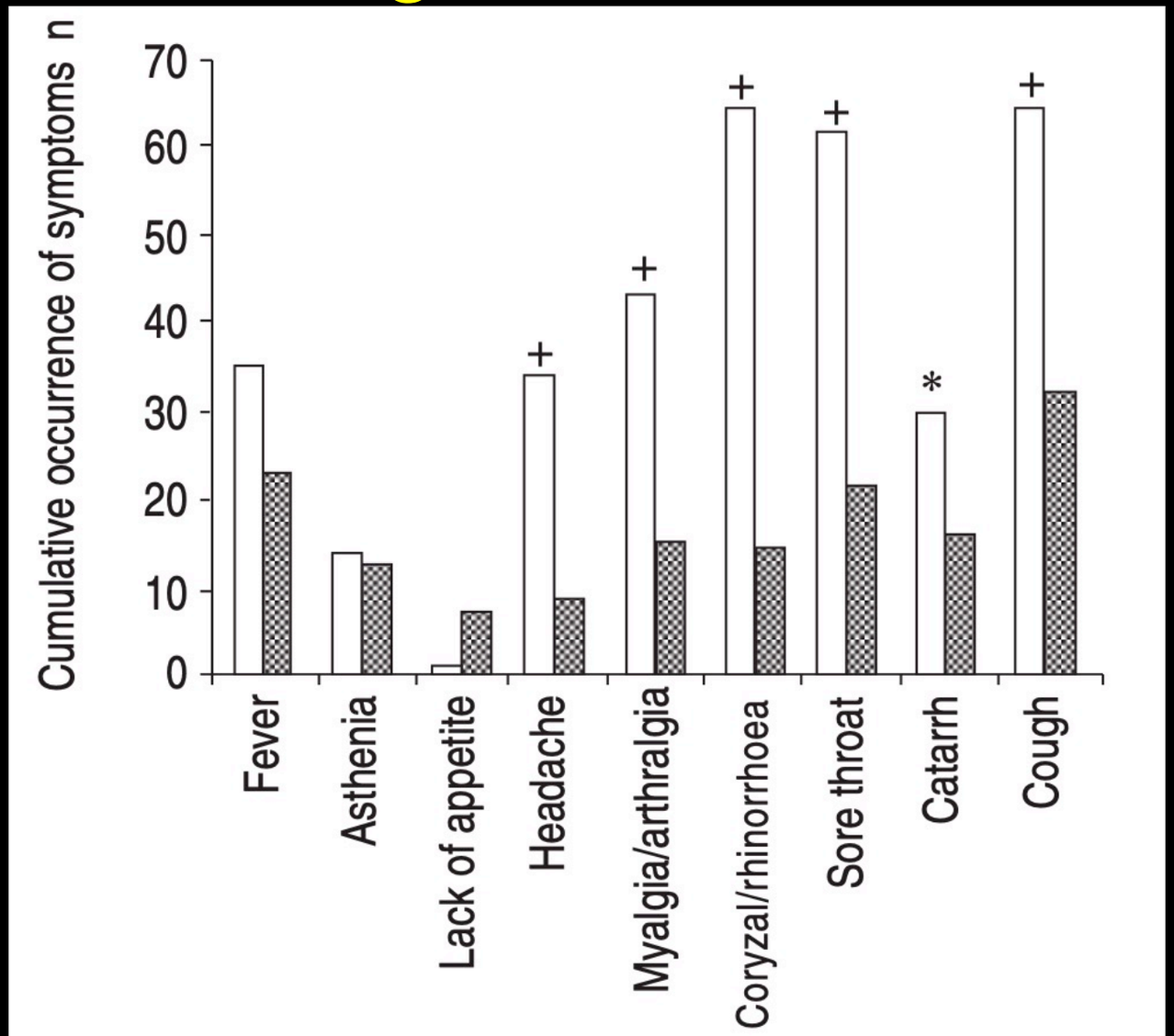

Fig. 2. – Effect of N-acetylcysteine (NAC) treatment on the cumulative occurrence of individual influenza-like signs and symptoms throughout the duration of the study. ▭ : placebo; ▩ : NAC. *: $p<0.05$; +: $p<0.0001$, significance of difference between the frequency of symptoms in the NAC group and the placebo group, as assessed by Chi-squared analysis. Note that the data reported in this figure also include isolated signs and/or symptoms whereas, as indicated in "Materials and methods", episodes are assessed based on the presence of at least two signs and/or symptoms.

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NAC tablets (600 mg) twice daily for 6 months.

600x2=1200mg/day x 180days=216,000mg

260gm @ $15/kg=$3.9/person/180days

283 million Americans x 3.9=$1.1billion