Novel views on endotyping asthma, its remission, and COPD

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Chapter 6

Applying the CAMP trial asthma remission prediction model to the Dutch asthma remission studies

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Introduction

A small subset of patients with asthma can go into spontaneous remission later in life [1, 2]. Predicting this clinical trajectory would be of great interest, because these asthma remission subjects are not burdened by symptoms anymore and no longer require any medication. Wang *et al.* [3] created a prediction model that could predict asthma remission outcome. They showed that the combination of normal FEV_1/forced vital capacity (FVC) ratio, less severe bronchial hyperresponsiveness, and blood eosinophil counts of less than 500 cells/μL at age 8 years yields more than 80% probability to achieve asthma remission by adulthood.

Methods

We were interested in the generalizability of predicting remission in childhood and applied this prediction model on our Dutch asthma remission cohorts. Children included in these cohorts described by Vonk et al (cohort 1, n = 94) and Carpaij et al (cohort 2, n = 157) had doctor-diagnosed asthma and were bronchial hyperresponsive (i.e. substance provocative concentration causing a 20% drop in FEV_1 [PC_{20}] ≤16 mg/mL histamine)[1,2]. Similar to the definition used by the *Childhood Asthma Management Program* (CAMP), we defined asthma remission at follow-up as no wheeze or asthma attacks in the last year, having an FEV_1/inspiratory vital capacity (IVC) ratio of greater than or equal to 80%, and no use of asthma-related medication. We used a different measure for airway obstruction, that is, FEV_1/IVC, because no data on FVC were available. Subjects with missing data were excluded. Normally and non-normally distributed variables were compared with t test and Mann-Whitney U test, respectively. We constructed 6 groups on the basis of baseline criteria provided in Wang et al and calculated the prevalence of subjects in remission for each group.

Results and discussion

After combining cohorts 1 and 2, the clinical and complete remission rate was 10.0% compared with 26.1% in CAMP (table 1). Like Wang et al, we observe an increase if the prevalence of remission as baseline FEV_1/IVC% is higher. In subjects with an FEV_1/IVC ratio of greater than or equal to 85%, PC_{20} value of greater than or equal to 1 mg/mL, and an eosinophil level of less than 500 cells/μL has additional value to predict asthma remission (table 2). In this group, the prevalence of remission was 40%, whereas those with greater than or equal to 500 eosinophils/μL had a 10% prevalence of remission. In accordance to the CAMP study, children in cohorts 1 + 2 had a significantly higher FEV_1, FEV_1/IVC%, and PC_{20} threshold and significantly lower blood eosinophils in the asthma remission group compared with the persistent asthma group. These are known clinical features associated with asthma remission [4-6]. The FEV_1/FVC% measured in CAMP was higher than in cohorts 1 + 2, resulting in a higher proportion of subjects subdivided in group 2. The definition for airway obstruction is not expected to be the cause, because the difference between FEV_1/FVC% and FEV_1/IVC% is marginal in children and young adults with mild to moderate asthma [7].

Conclusion

Taking this into account, we show that the model proposed by Wang et al can correctly predict future development of asthma remission in up to 40% of cases. Although usable, more research is needed to disentangle the pathophysiology of asthma remission, which is a highly relevant yet poorly understood outcome of childhood asthma.

Table 1: baseline clinical characteristics of three prospective childhood cohorts and application of the prediction model

	Persistent asthma			Asthma remission		
	Cohort 1 Vonk *et al.* 2004 (n = 79)	**Cohort 2** Carpaij *et al.* 2017 (n = 147)	**CAMP** Wang *et al.* 2018 (n = 650)	**Cohort 1** Vonk *et al.* 2004 (n = 15) (15%)	**Cohort 2** Carpaij *et al.* 2017 (n = 10) (6.4%)	**CAMP** Wang *et al.* 2018 (n = 229) (26.1%)
Enrollment year range	1966 - 1969	1972 – 1976	1993 - 1995	1966 - 1969	1972 – 1976	1993 - 1995
Mean age at baseline (SD)	9.9 (2.0)	9.7 (1.4)	8.8 (2.1)	9.6 (2.0)	10.2 (1.2)	8.6 (1.9)
Mean follow-up (years)	16	15	12	16	15	12
Male sex (N, %)	58 (73.4%)	105 (71.4%)	407 (62.6%)	9 (60.0%)	7 (70.0%)	115 (50.2%)
Mean FEV_1 % pred. (SD)	82.1% (16.5)*	75.4% (14.3)*	92.2% (14.1)*	85.7% (17.2)*	82.0% (10.6)*	99.0% (12.7) *
Mean FEV_1/VC % (SD)#	75.0% (12.2)*	72.3% (7.9)*	77.9% (7.9)*	78.1% (12.0)*	79.7% (7.1)*	85.6% (6.3) *
Median PC_{20} threshold in mg/ml [IQR] #	2.0 [7.0]*	4.0 [6.0]*	0.9 [1.6]*	8.0 [30.0]*	8.0 [4.0]*	1.7 [3.6] *
Median blood eosinophil count in cells/μL [IQR]	462.0 [495.0]*	385.0 [396.0]*	422.0 [493.5]*	220.0 [297.0]*	286.0 [236.5]*	320.5 [327.3] *

*NA: not applicable, #: FEV_1/IVC and PC_{20} histamine threshold on cohort 1 and 2, FEV_1/FVC and PC_{20} methacholine threshold in CAMP. *: either significant difference (P<0.05) between asthma remission and persistent asthma within cohort 1+2 or CAMP.*

Table 2: implementing the prediction model

	Group 1 FEV_1/FVC% ≤75%	**Group 2** FEV_1/FVC% 75-79%	**Group 3** FEV_1/FVC% 80-84%	**Group 4** FEV_1/FVC% ≥85% PC_{20} <1mg/ml	**Group 5** FEV_1/FVC% ≥85% PC_{20} ≥1mg/ml blood eosinophils ≥500 cell/μL	**Group 6** FEV_1/FVC% ≥85% PC_{20} ≥1mg/ml blood eosinophils <500 cell/μL
CAMP* (n = 876)	9.5% (n = 199)	27.6% (n = 190)	53.8% (n = 228)	58.3% (n = 71)	65.4% (n = 49)	82.6% (n = 139)
Cohort 1+2 (n = 251)	5.5% (n = 3/55)	5.6% (n = 7/126)	15.4% (n = 6/39)	0.0% (n = 0/1)	10.0% (n = 1/10)	40.0% (n = 8/20)

**: predicted probability*

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