Practical phenotyping of difficult asthma. Online supplement

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This online supplement contains longer summaries of the responses of the authors to the presented cases.

In addition, all specialists were asked how they phenotype asthma. Each specialist used different terminology (RG: clusters of pathological and clinical features; RN: inflammation or not, layers of clinical and pathological issues; LH: clinical problems of non-adherence followed by inflammatory patterns; IH, non-asthma pathologies, eosinophilic vs. non-eosinophilic disease). The commonest clinical theme was the problem of non-adherence to treatments, and the requirement to pay careful attention to the basics of inhaler technique and education.

**Case 1. An overweight ex smoker with airflow obstruction and moderately high treatment needs.**

AT: What should I do with a 40 year old woman, BMI 32, ex-smoker with 10 pack-year history, asthma as a child, with a 4 year history of episodic breathlessness, cough and wheeze? Exercise tolerance has become progressively more limited. She has received several courses of oral prednisolone with only temporary improvement. Currently on combined inhaled corticosteroid (ICS) and long acting beta agonist (LABA). Spirometry shows FEV1 2.08 (65%), FVC 3.15 (80%), ratio 66%. Predicted values were 3.21/3.94. Her FeNO was 42 ppb.

Below are summaries of the responses of the panel, based on transcripts of an evolving conversation with AT.

RG: Many issues are presented here. The pattern of symptoms and spirometry suggest that there may be some COPD overlap, and fixed airflow obstruction. The persistent airflow obstruction despite partially steroid responsive symptoms suggests this is less likely to be eosinophilic asthma. My initial approach would be to determine whether she has an eosinophilic phenotype (historical blood counts with particular attention to eosinophil counts during exacerbations, induced sputum,
tests for atopy), then to consider a therapeutic trial of prednisolone for 2 weeks to determine whether the airway obstruction is fixed. Lung function during exacerbations may be helpful. Her presentation later in life would lead me to exclude occupational asthma or fungal allergy. Depending on these results, if a non-eosinophilic phenotype with fixed airflow obstruction was confirmed, I would move on to addressing her general fitness and weight, and for non-eosinophilic asthma might consider a trial of macrolides.

RN: This appears to be a patient who probably has fixed airflow obstruction. The smoking history probably is not long enough for a COPD component. I would determine if she is eosinophilic (blood tests and induced sputum), noting that the FeNO is unreliable but is raised. There may be a component of dysfunctional breathing as her obstruction is not severe but her symptoms are. If she was eosinophilic I might consider a trial of triamcinolone. I would culture sputum if she is producing it.

LH: I would review the original diagnosis of asthma and would look for evidence of eosinophilic disease in stable state and during exacerbations, and try to determine whether her previous oral steroid courses were associated with measurable clinical benefit and improvement in lung function. Her raised BMI may be contributing to her reduction in FEV1, in addition to asthma-related airways obstruction (my tests would include total lung capacity). I would consider issues of possible poor adherence given her exacerbation frequency, particularly if these were eosinophilic. Her smoking history may have contributed to the pathology and to some poorly characterised long term steroid resistance. I would probably progress to an exercise test to determine her degree of exercise limitation to make sure that the limiting factor was asthma, as she appears very limited despite only mildly obstructive lung function, and consider smoking-related non respiratory issues (e.g. cardiac disease). I probably would not initially undertake a steroid trial.

IH: I would phenotype for eosinophilic and atopic disease, and assess reversibility, and if needed I might include a bronchial hyperresponsiveness challenge to assess this. She is probably too young
to have a major COPD component, but her smoking and increased body mass are still probably contributing to her disease. I would supportively address her increased weight. I might consider an HRCT, would culture sputum if produced, and if she has recurrent Haemophilus infection I would test the relevant antibody titres. The FeNO is not particularly helpful in this patient. I would be likely to consider an oral steroid trial.

Case 2. A young eosinophilic atopic asthmatic with normal lung function and marked symptoms.

AT: I have another patient to discuss: a 25 year old woman with a history of atopy and poor asthma control over the past year. She has been on prednisolone 20 mg daily for the past 12 months, high dose ICS+LABA, a leukotriene receptor antagonist, and frequently using a short-acting beta agonist. Her exercise tolerance is limited by breathlessness and wheeze. She has frequent nocturnal symptoms. Her blood eosinophil level is 0.5 x10^9/l. Spirometry shows FEV₁ 3.0 (80%) / FVC 4.3 (97%), ratio 70%. Predicted values were 3.75/4.42.

The authors note that in general, an eosinophil count of ≥ 0.4 x10^9/l is probably perceived, in the context of asthma, to be a significant eosinophilia.

RG: The raised peripheral blood eosinophil count with marked symptoms suggests that she has poorly controlled eosinophilic airway inflammation. Were it assessed, her sputum eosinophil count would probably be raised, although since eosinophilic inflammation is already evident induced sputum would not be necessary here. Her oral prednisolone should have suppressed the eosinophilia, and I would be very concerned about her levels of treatment adherence. I would focus first on assessing and addressing her adherence by discussing this with the patient and if necessary performing prescription checks. If this did not give clear answers I would move onto a trial of i.m. triamcinolone. If this was successful, it would show the patient the benefits of good control to facilitate discussions about adherence and treatment goals. She may be a candidate for a SMART treatment regime. If she is truly adherent with particularly severe or partially steroid resistant
eosinophilic disease she would be a candidate for additional therapies (immunosuppression, biologicals).

RN: This fits with eosinophilic, poorly controlled asthma and the relatively normal current lung function does not contradict this. I would check a cortisol level and a prednisolone level to assess adherence and would be likely to progress to a trial of i.m. triamcinolone. The diagnosis of eosinophilic disease is already made, but I would sub-divide this into atopic or non-atopic by further testing to guide the next stage of management (e.g. considering the use of omalizumab). If she is steroid-resistant without suppression of her eosinophil count by triamcinolone (rare, but can occur) I might progress to immunosuppression or consider her inclusion in drug trials of newer agents. The inflammation-dominant phenotype makes her less suitable for thermoplasty.

LH: This case of persistently eosinophilic asthma despite high doses of therapy is highly likely to be associated with non-adherence. I would seek corroborative GP and pharmacy evidence regarding treatment adherence. I would check her prednisolone and cortisol level, and then have a discussion with her about why she is not taking her treatment. In many cases, this will allow a way forward, particularly if a specific reason can be identified for not taking steroid therapy. I would rarely progress to a trial of i.m. triamcinolone as this is not addressing the fundamental problem, and is not a sustainable long-term maintenance strategy. If she was adherent with this level of treatment and persistently eosinophilic, which I doubt, she might be a candidate for escalation to other treatments like anti-IgE.

IH: Very few patients fail to show a suppression of eosinophils with oral steroids. Poor treatment adherence is likely to be an issue here. I would seek further information from her GP, and measure theophylline levels (if she is on this). It might be that a small subgroup of people fail to adequately absorb oral steroids, and I might consider i.m. triamcinolone trials as a mechanism to explore this, and possibly facilitate discussions about adherence. I am uncomfortable about using triamcinolone to test adherence without clear and open discussions with the patient ahead of the test. In her age
group steroid-sparing immunosuppression seems less desirable, and depending on the clinical picture, I might consider cautious supervised reductions in oral steroids with clinical reassessment as doses are reduced. I would address psychological issues if present.