CASE BASED DISCUSSIONS

Practical phenotyping of difficult asthma

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Asthma comprises multiple but incompletely understood and characterised clinical phenotypes. We created two imaginary but typical cases and presented them to asthma specialists. This text summarises responses, which are presented in greater length in the online supplement.

Key messages

- The basics are important: in the poorly controlled asthmatic, examine and readdress adherence and inhaler technique.
- In the poorly controlled asthmatic or a well-controlled patient on high levels of treatment, address other comorbidities or causes of lung disease, including smoking and obesity.
- The number of specific asthma phenotypes remains uncertain, but divides reasonably clearly into eosinophilic and non-eosinophilic disease.
- Historical data on blood eosinophilia, variability in lung function and airways pressure/$PaCO_2$ during episodes of ventilation are important in the guidance of management and for providing for onward referral.

AN OVERWEIGHT EX-SMOKER WITH AIRFLOW OBSTRUCTION AND MODERATELY HIGH TREATMENT NEEDS

AT: What should I do with a 40-year-old woman, body mass index (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 and currently on combined inhaled corticosteroid (ICS) and long-acting β-agonist (LABA). Spirometry shows forced expiratory volume in the first second (FEV_1) 2.08 (65%), forced vital capacity (FVC) 3.15 (80%), ratio 66%. Predicted values were 3.21/3.94. Her FeNO was 42 ppb.

RG, RN, LH, IH: The most important thing to determine is if this is eosinophilic or non-eosinophilic asthma. These asthma phenotypes are discussed in the Commentary section below. To determine if eosinophilic disease is or has been present, we would look at historical blood counts in stable state and during exacerbations, induced sputum where available, and perhaps gain support from tests for atopy. We all suspect this first case is probably one of non-eosinophilic asthma. The measurement of FeNO is probably not helpful here. We would all revisit the basics of education and inhaler technique.

RG: Symptoms and spirometry suggest some chronic obstructive pulmonary disease (COPD) overlap and possible fixed airflow obstruction. The persistent airflow obstruction suggests this is less likely to be eosinophilic asthma. I would consider a trial of prednisolone for 2 weeks to determine whether the airway obstruction is fixed. I would exclude occupational asthma or fungal allergy. If a non-eosinophilic phenotype with fixed airflow obstruction was confirmed I would address her general fitness and weight, and might consider a trial of macrolides.

RN: The patient probably has fixed airflow obstruction. The smoking history is probably not long enough for a COPD component. 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: Her raised BMI may be contributing to reduced lung function. I would consider issues of possible poor adherence given her exacerbation frequency, particularly if these were eosinophilic. Her smoking may have contributed to the pathology. I would test her degree of exercise limitation to make sure that the limiting factor was asthma. I probably would not initially undertake a steroid trial.

IH: I would assess reversibility, and might include bronchial hyper-responsiveness testing. She is probably too young to have a major COPD component, but her smoking and increased BMI are relevant. I might consider an high resolution computerised tomography, would culture sputum if produced and if she has recurrent *Haemophilus* infection I would test the relevant antibody titres. I would be likely to consider an oral steroid trial.

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 β-agonist. Her exercise tolerance is limited by breathlessness and wheeze. She has frequent nocturnal symptoms. Her blood

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eosinophil level is 0.5×10^9/l. Spirometry shows FEV_1 3.0 (80%), FVC 4.3 (97%), ratio 70%. Predicted values were 3.75/4.42.

RG, RN, LH, IH: In general, an eosinophil count of $\geq0.4\times10^9$/l in the context of asthma is significant. We all recognise this as a case of poorly controlled eosinophilic asthma and are all concerned about adherence to therapy since her steroids should have suppressed her eosinophilia.

RG: The raised peripheral blood eosinophil count with marked symptoms shows poorly controlled eosinophilic airway inflammation. Her sputum eosinophil count would probably also be raised, but eosinophilic inflammation is already evident and induced sputum would not be necessary here. I would focus on assessing and addressing 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 intramuscular triamcinolone. If successful, it would show the patient the benefits of good control and facilitate discussions about adherence and treatment goals. She may be a candidate for a SMART treatment regime.[1] 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 intramuscular triamcinolone. The diagnosis of eosinophilic disease is already made, but I would investigate for atopy to guide further management (eg, 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: Persistently eosinophilic asthma despite substantial therapy is highly likely to be associated with non-adherence. I would seek general practitioner (GP) and pharmacy evidence regarding treatment adherence, check her prednisolone and cortisol level, and discuss with her why she is not taking her treatment. This will usually allow a way forward. I would rarely progress to a trial of intramuscular 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 omalizumab.

IH: I would seek further information from her GP regarding adherence, 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 intramuscular 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 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.

COMMENTARY

Asthma comprises multiple incompletely characterised clinical and scientific phenotypes.[2 3] Specific management of these is now feasible with the advent of therapies targeting IgE, IL-5, IL-13 and smooth muscle (thermoplasty). Difficult asthma is complicated by issues of marked inter-individual variations in symptomatology for any given level of airways dysfunction, and the poorly understood problems of dysfunctional breathing and vocal cord dysfunction.

The key message of our cases was the need to distinguish eosinophilic from non-eosinophilic inflammation. Eosinophilic disease is supported by blood eosinophilia currently, in the past or during acute flares. Sputum eosinophilia, where the test is available, is diagnostic.[4] Eosinophilic asthma divides into atopic and non-atopic variants; thus, atopy is supportive but not critical to the diagnosis of eosinophilic disease. In the specific context of difficult asthma, FeNO was felt to be of limited utility and a relatively poor predictive of eosinophilic inflammation. However, measurements of FeNO combined with directly observed ICS therapy can identify non-adherence in difficult asthma.[5] Ongoing eosinophilic disease in the face of significant treatment has always raised the issues of non-adherence, a major and common problem.[6 7] Prescription histories from GPs and pharmacists are valuable in understanding a patient's medication usage. Attention to adherence is critical, and requires sensitive and sometimes multi-disciplinary approaches to overcome problems.

Adherence of patients on long-term oral steroids may be further probed in a specialist clinic with a trial of triamcinolone.[8] A further benefit is that in troublesome disease this sometimes results in sustained clinical benefit. If triamcinolone therapy suppresses eosinophilia and improves disease where oral prednisolone did not, we suspect poor adherence with oral steroids. However, rare patients also exist who fail to show a good response to oral steroids even if adherent, and a small number of patients may be truly steroid resistant.[5]

Non-eosinophilic asthma raises other management issues. Previous eosinophilia may identify those with controlled inflammation. In consistently non-eosinophilic patients, consider screening for recurrent infection and overlap with bronchiectasis-like syndromes. Additional complicating features of smoking, fixed airways obstruction and obesity may be relevant. Persistent non-eosinophilic asthma is less likely to respond to escalation of systemic steroids,[4] but still requires treatment with ICS in stable state, and systemic steroids in exacerbations. Where symptoms dominate in the absence of clinical signs and airflow obstruction, bronchial hyper-reactivity challenge and exercise testing can be used to explore the correlation of symptoms and signs, and a combined multi-disciplinary assessment with physiotherapy may be useful. Patients in whom marked exertional limitation is evident in the absence of significant bronchospasm, airways obstruction or other limiting pathologies (eg, heart disease) may have dysfunctional breathing syndromes or basic problems with fitness.

In any asthmatic, particularly where treatment response is suboptimal, it is always important to check basics of education, inhaler technique and adherence. Subsequently, practical disease phenotyping is feasible and is likely to result in improved outcomes. An initial approach should identify if any of the confounders and complicating issues in severe asthma are present (including occupational disease, smoking, obesity, allergic bronchopulmonary aspergillosis, exertional asthma, perimenstrual disease, airways infection and possibly reflux). Subsequently, determination of the likelihood of eosinophilic versus neutrophilic asthma is helpful and will guide further management.

Where poor control is present, particularly with requirement for frequent rescue or continuous oral steroids, or a history of life-threatening or near-fatal exacerbations, onward referral to specialised asthma clinics should be considered. Referring physicians will be able to make a very informed assessment of asthma phenotype using the above guide. Additional valuable information in referrals includes historical blood eosinophil trends, and where ITU care has been required information on ventilation

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pressures and duration of intubation, and $PaCO_2$ during admissions. Specialist management of the difficult asthmatic will focus on accurate phenotyping, further review of adherence, and where required the subsequent consideration of biologicals, immunosuppressants and thermoplasty.

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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 FEV_1 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 FEV_1, 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 FEV_1 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.