



Control and prevention of asthma exacerbations

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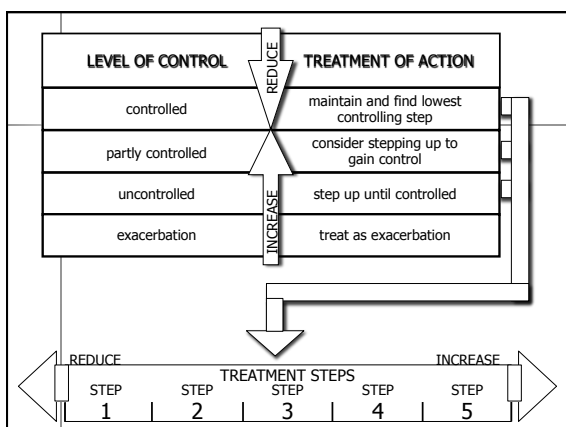
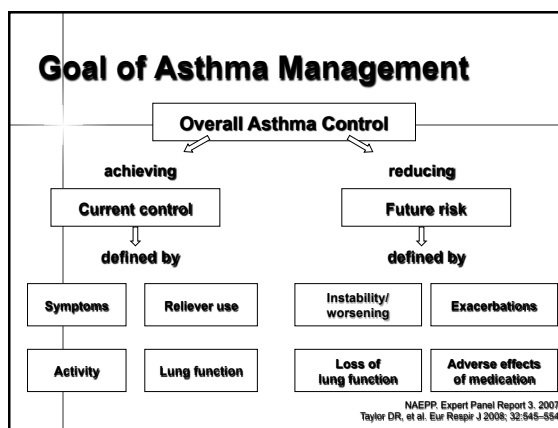



Synopsis

- Definition of asthma control
- Main causes of asthma exacerbations
- Physiopathology & treatment targets
- How to prevent/manage exacerbations

Levels of Asthma Control

Characteristic	Controlled (All of the following)	Partly controlled (Any present in any week)	Uncontrolled
Daytime symptoms	None (2 or less / week)	More than twice / week	3 or more features of partly controlled asthma present in any week
Limitations of activities	None	Any	
Nocturnal symptoms / awakening	None	Any	
Need for rescue / "reliever" treatment	None (2 or less / week)	More than twice / week	
Lung function (PEF or FEV ₁)	Normal	< 80% predicted or personal best (if known) on any day	
Exacerbation	None	One or more / year	1 in any week

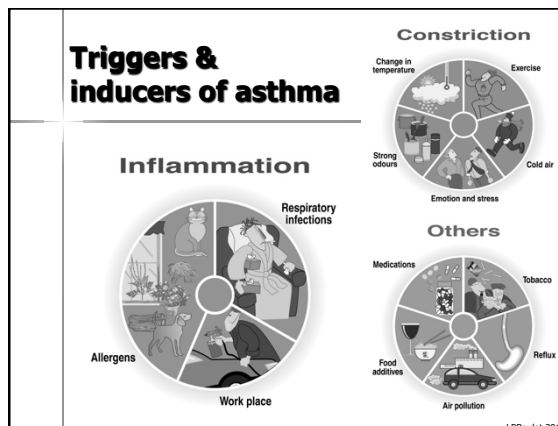


Exacerbations and poor control

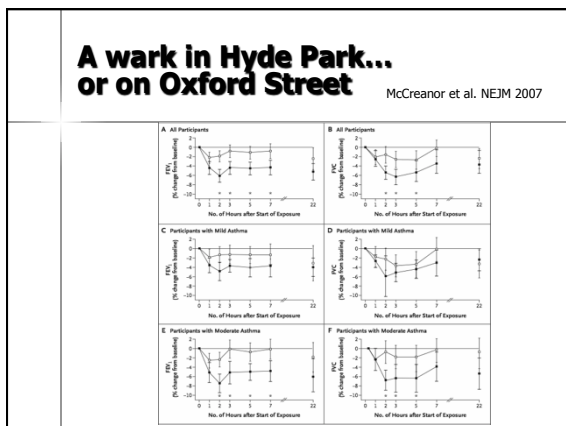
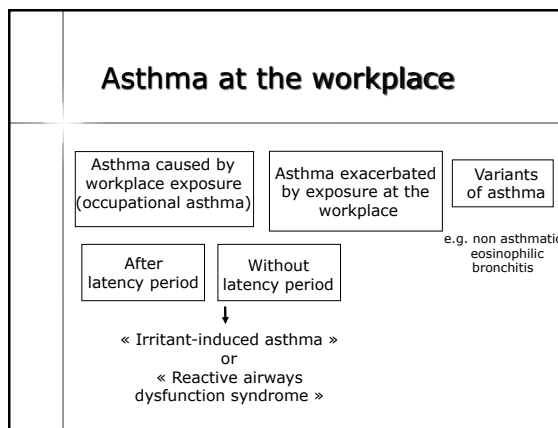
1. Exacerbations reflect poor control and severe asthma
 - Strong association between exacerbations and poor control (Vollmer 2002)
 - Exacerbations occur despite continuing ICS in patients with difficult-to-control asthma (in 't Veen, 1999)
 - Exacerbations are reduced when asthma control improves with Rx (Pauwels 1997, O' Byrne 2001, Bateman 2004)
 - Prevention: change usual Rx or dose, adherence, environment
2. Exacerbations may occur despite good control of asthma
 - Viral infections, *C. pneumoniae*, *M. pneumoniae*, ± allergen, ± pollution
 - Management: different from management of poor control
 - Short-term treatment of the acute event (perhaps with different agents e.g. telithromycin) → return to usual Rx

Adapted from H Reddel

<h2>Asthma exacerbations: some commonly reported causes</h2>
<p>Viral Infections</p> <ul style="list-style-type: none"> - Rhinovirus (RV) - Respiratory syncytial virus (RSV) - Human metapneumovirus (HMPV) - Influenza virus <p>Fungi</p> <p>Bacteria</p> <ul style="list-style-type: none"> - Mycoplasma pneumoniae - Chlamydia pneumoniae <p>Indoor & outdoors allergens</p> <ul style="list-style-type: none"> - Indoor: domestic mites, furred animals (dogs, cats, mice), cockroach allergen, fungi, molds, yeasts - Outdoor: pollens, fungi, molds, yeasts <p>Occupational exposures</p> <p>Irritants - Airway pollutants - Tobacco smoke (Passive/active smoking)</p>




<h3>Risk factors for exacerbations and hospital admissions in asthma of early childhood Wever-Hess J 2000</h3>
<p>In young children:</p> <p>Predisposing risk factors for exacerbation were:</p> <ul style="list-style-type: none"> - damp housing (odds ratio (OR) 7.6 (2.0–28.6)) - colds (OR 3.6 (1.4–9.6)) <p>For recurrent exacerbations:</p> <ul style="list-style-type: none"> ■ sensitization to inhalant allergens (Phadiatop®) (OR 8.1 (1.6–40.5)) ■ damp housing (OR 3.8 (1.1–12.8)) <p>For older children, predisposing risk factors for exacerbation were mean age at initial presentation (OR 0.92 (0.88–0.97)) and level of total IgE (OR 2.3 (1.4–3.9)), whereas for recurrent exacerbations no predictor variables were found.</p>



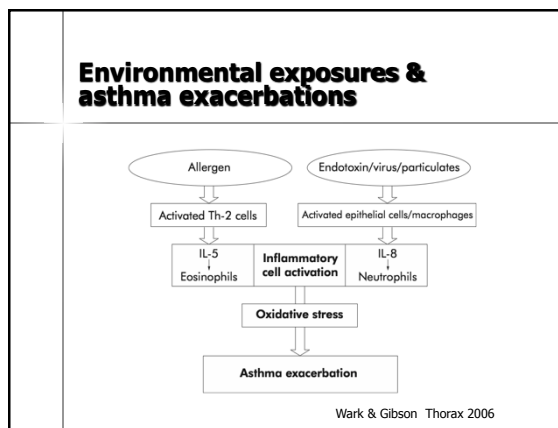
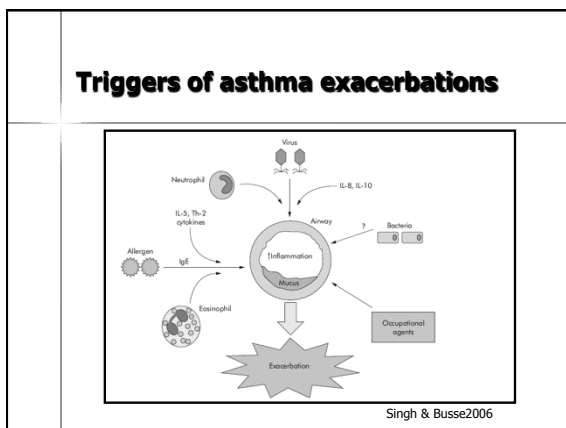
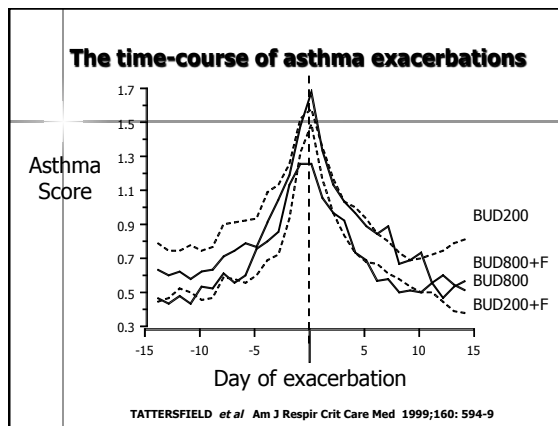
<h3>Does air pollution increase the effect of aeroallergens on hospitalization for asthma?</h3>
<ul style="list-style-type: none"> ■ Aeroallergens are risk factors for asthma severe enough to precipitate hospitalization ■ The presence of air pollution appears to increase the morbidity from aeroallergens ■ Decreasing air pollution levels might reduce the severity of allergic asthma exacerbations in the general population <p style="text-align: right;">Cakmak et al. JACI 2011</p>

Smoking and asthma: clinical consequences



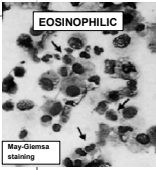
- Increased asthma morbidity and severity
- Reduced asthma control
- Increased health care use
- Increased rate of decline in pulmonary function
- Reduced response of asthma medications

Boulet LP, et al. Smoking and asthma: clinical/radiologic features, lung function, and airway inflammation. Chest. 2006
 Urick CS, Lange P. Cigarette smoking and asthma. Monaldi Arch Chest Dis. 2001
 Lange P, et al. A 15 year follow-up study of ventilatory function in adults with asthma. N Engl J Med 1998
 Stroux V, et al. Relationships of active smoking to asthma and asthma severity in the EGEA study. Eur Respir J 2000
 Chalmers GW, et al. Influence of cigarette smoking on inhaled corticosteroid treatment in mild asthma. Thorax 2002
 Thomson NC, et al. Corticosteroid insensitivity in smokers with asthma: clinical evidence, mechanisms, and management. Treat Respir Med. 2006



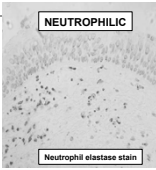
Asthma inflammatory responses/phenotypes

EOSINOPHILIC



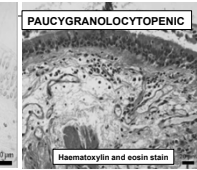
May-Giemsa staining

NEUTROPHILIC



Neutrophil elastase stain

PAUCYGRANULOCYTOPENIC



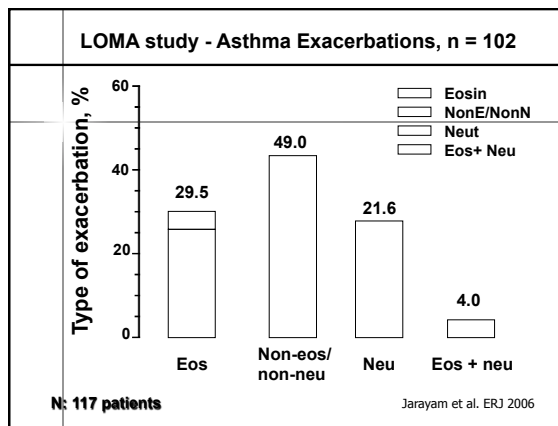
Haematoxylin and eosin stain

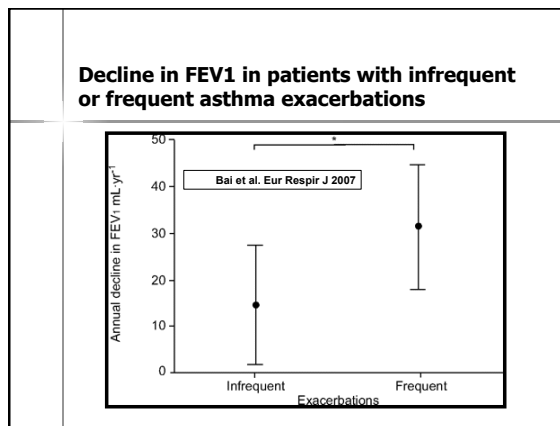
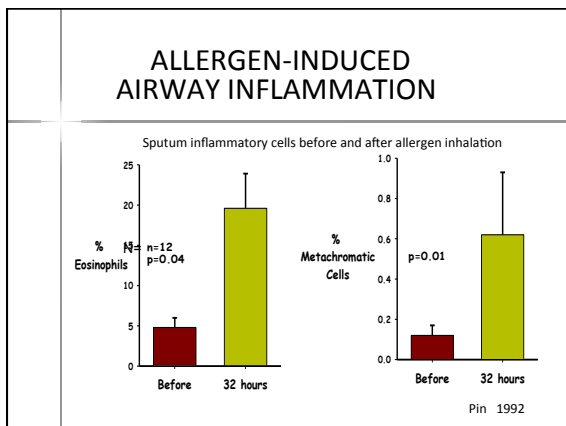
Allergens
Sensitizing agents
Steroid reduction
Others

Viral & bacterial infections
Cigarette Smoking
Pollutants
Occupational agents
Exercise
Obesity
Others

CS-resistant asthma ?
High-doses of CS ?
Others ?

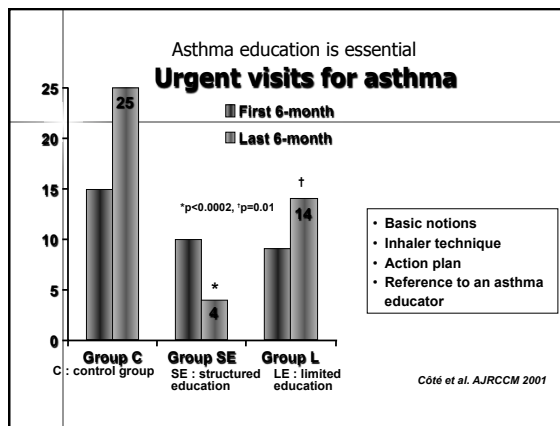
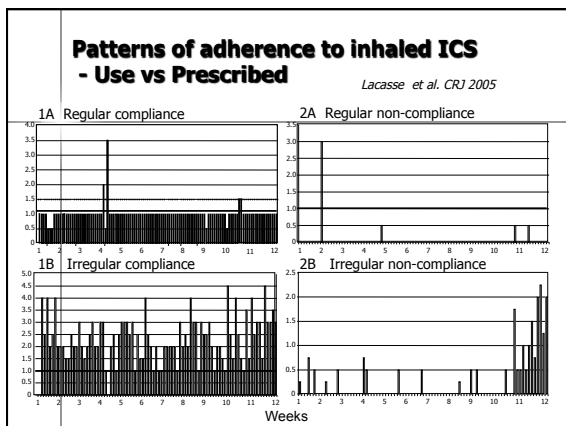
19Boulet 2010





- ### How to prevent asthma exacerbations ?
- 1) Preventative measures and patient education
 - 2) Ensure adequate baseline treatment of asthma
 - 3) « Fine-tuning » of asthma control ?
 - 4) Regular follow-up

- ### Environmental measures
- Tobacco smoke: Stop smoking (cessation programs). Avoidance of exposure
 - Drugs, foods, and additives: Avoid if they are known to cause symptoms
 - Animals with fur:
 - Use air filters. Remove animals from the home/reduce exposure
 - House dust mites:
 - Wash bed linens and blankets weekly in hot water and dry (hot dryer or sun)
 - Encase pillows and mattresses in air-tight covers.
 - Replace carpets with hard flooring, especially in sleeping rooms
 - Cockroaches: Clean the home thoroughly and often. Use pesticide spray but make sure the patient is not at home when spraying occurs
 - Outdoor pollens and mold: Close windows and doors and remain indoors when pollen and mold counts are highest
 - Indoor mold: Reduce dampness in the home; clean any damp areas frequently.



Outcomes of asthma self-management

	Overall effects	Effects of optimal self-management intervention	NNT
Hospital admission	0.64 (0.50 to 0.82)	0.58 (0.43 to 0.77)	21
Emergency visit	0.82 (0.73 to 0.94)	0.78 (0.67 to 0.91)	18
Unscheduled doctor visit	0.68 (0.56 to 0.81)	0.73 (0.58 to 0.91)	24
Days off work	0.79 (0.67 to 0.93)	0.81 (0.65 to 1.01)	12

Results are shown as relative risk (95% CI). All results $p < 0.05$.
NNT, number needed to treat.

Gibson P, Powell H, Coughlin J, et al. Self-management education and regular practitioner review for adults with asthma (Cochrane review). The Cochrane Library. Issue 4. Chichester, UK: John Wiley & Sons, 2004.

Action plans and asthma

Action plan component	RR (95% CI fixed)	Total (95% CI fixed)
% predicted PEF	0.46 (0.26, 0.81)	0.46 (0.26, 0.81)
Personal best PEF	0.66 (0.48, 0.91)	0.66 (0.48, 0.91)
4 action points	0.65 (0.48, 0.88)	0.65 (0.48, 0.88)
<4 action points	0.23 (0.07, 0.71)	0.23 (0.07, 0.71)
ICS and OCS	0.59 (0.44, 0.78)	0.59 (0.44, 0.78)

Figure 1 Comparison of the effects of action plan components on hospital admissions for asthma. ICS, inhaled corticosteroid; OCS, oral corticosteroid.

Fitzgerald and Gibson Thorax 2006

Prevention of asthma exacerbations: the role of inhaled corticosteroids

Pauwels et al. Lancet 2003

- 7241 patients randomised to receive budesonide 400 mg or 200 mg vs placebo
- 198 severe exacerbations in the placebo arm
- 117 in the active treatment arm (HR 0.56, 95% CI 0.45 to 0.71, $p < 0.0001$).

Sin et al. JAMA 2004

- overall relative risk (RR) of 0.46 (95% CI 0.34 to 0.62), $p < 0.001$, in subjects treated with ICS compared with placebo

Hawkins G, et al. BMJ 2003

- Once controlled is achieved, ICS can be tapered down

ICS vs LTRAs on asthma exacerbations

Ducharme FM. Inhaled glucocorticoids versus leukotriene receptor antagonists as single agent asthma treatment: systematic review of clinical evidence. BMJ 2003;326:621-5.

Study	Anti-leukotrienes	Inhaled glucocorticoids	Relative risk (95% CI)	Weight (%)	Relative risk (95% CI, random effect)
Montelukast 5 mg once daily					
McIntosh 2001 ¹⁷	1183	741	0.8	9	0.8 (0.3 to 1.9)
Subtotal					
Montelukast 10 mg once daily					
Baumgartner 1999 ¹⁵	15008	9308	1.0	10	
Busse 2000 ¹⁶	16032	10271	0.8	11	
Higgins 1998 (BDD) ¹⁸	913	923	0.9	0	
Higgins 1998 (FP) ¹⁸	912	923	0.9	0	
Lavigne 1999 ¹⁹	61001	22000	1.0	17	
Skelly 1999 ²⁰	9337	12329	0.8	9	
Williams 2001 A ¹⁴	85089	42167	1.0	20	
Subtotal	1861402	951321	0.8		1.5 (1.3 to 1.8)
Heterogeneity: χ^2 test=11.2, df=4, $P < 0.02$					
Zafirlukast 20 mg twice daily					
Bleeker 2000 ¹¹	14220	8231	1.0	10	
Busse 2000 ¹⁶	13111	5113	1.0	8	
Kim 2000 ¹²	13216	4221	1.0	7	
Subtotal	39547	17565	1.0		2.4 (1.3 to 4.1)
Heterogeneity: χ^2 test=0.0, df=2, $P = 0.7$					
Total	2260332	1191927	0.8		1.6 (1.2 to 2.2)
Heterogeneity: χ^2 test=16.4, df=8, $P < 0.04$					

The GOAL Study

Bateman et al. AJRCCM 2004

Open-label phase

For patients not achieving TOTAL CONTROL

Legend:
 Phase I: 8-week control assessment
 Phase II: 4-week control assessment

GOAL Study

STAY: Severe Exacerbations

Total exacerbations $p < 0.001$

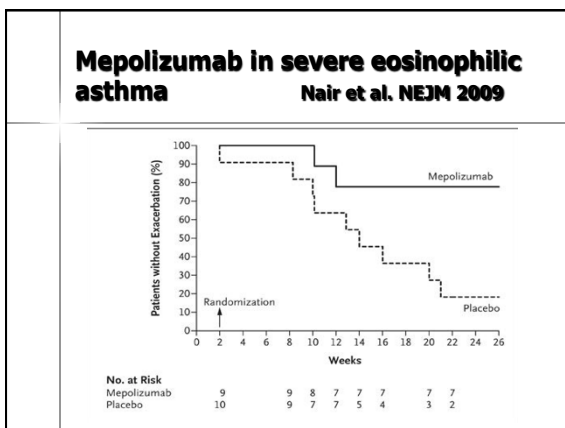
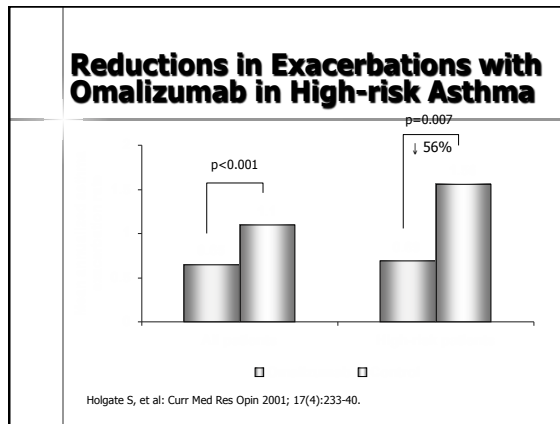
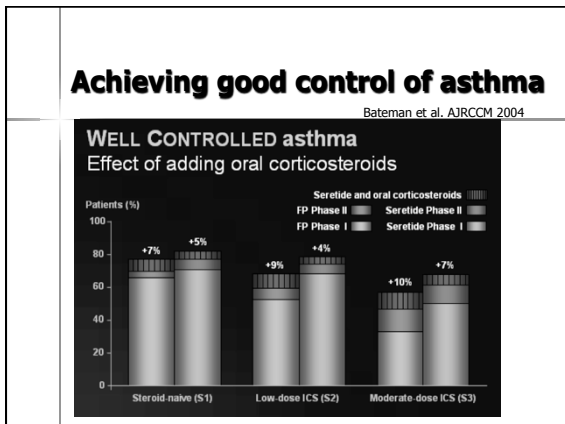
>80% identified post-hoc

Exacerbation subtypes:

- PEF falls
- Steroid courses
- Hospitalisations/ER treatment

Legend:
 4 x BUD + SABA
 Bud/Form + SABA
 Bud/Form SIT

O'Byrne PM et al. Am J Respir Crit Care Med 2005; 171:129-13



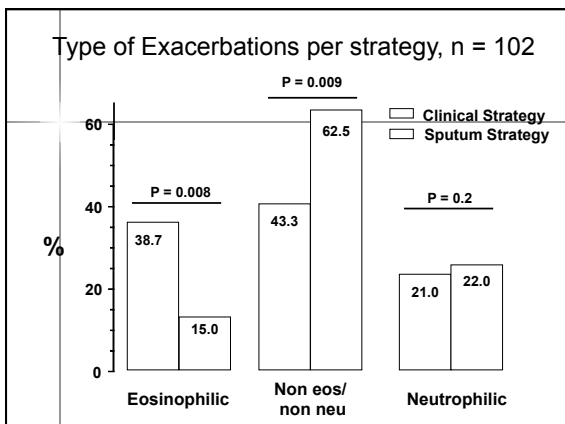
Evaluation of asthma control with induced sputum eosinophilia

Green et al Lancet 2002; 360: 1715-1721.

Does a strategy that minimized airway eosinophilia reduce asthma exacerbations compared to a standard management strategy ?

- 74 patients with moderate to severe asthma
- BTS Guidelines vs eosinophils control
- Assessment over a 12 months period

	Severe exacerbations	Hospital admissions
- BTS	109	6
- Sputum eosinophils	35	1
	(p= 0.01)	(p= 0.047)



Facebook asthma

- The sight of her ex-girlfriend profile on Facebook induced dyspnoea repeatedly in an 18 years old man
- After internet login “post-Facebook” PEF values were reduced by more than 20%
- In collaboration with a psychiatrist, the patient decided not to login to Facebook any longer and the asthma attacks stopped

D’ Amato. The Lancet 2010

	Conclusions
	<ul style="list-style-type: none">■ Asthma exacerbations are a frequent indicator of insufficient asthma control and lead to increase health care use and accelerated decline in lung function■ Viral infections and allergen exposure are the most common causes of asthma exacerbations■ Asthma exacerbations can be prevented by asthma education, preventative measures and adequate treatment■ Frequent exacerbations require a reassessment of the main causes of uncontrol