DM-Seminar

Steroid Resistant Asthma-Definitions, Mechanisms and Approach to Therapy

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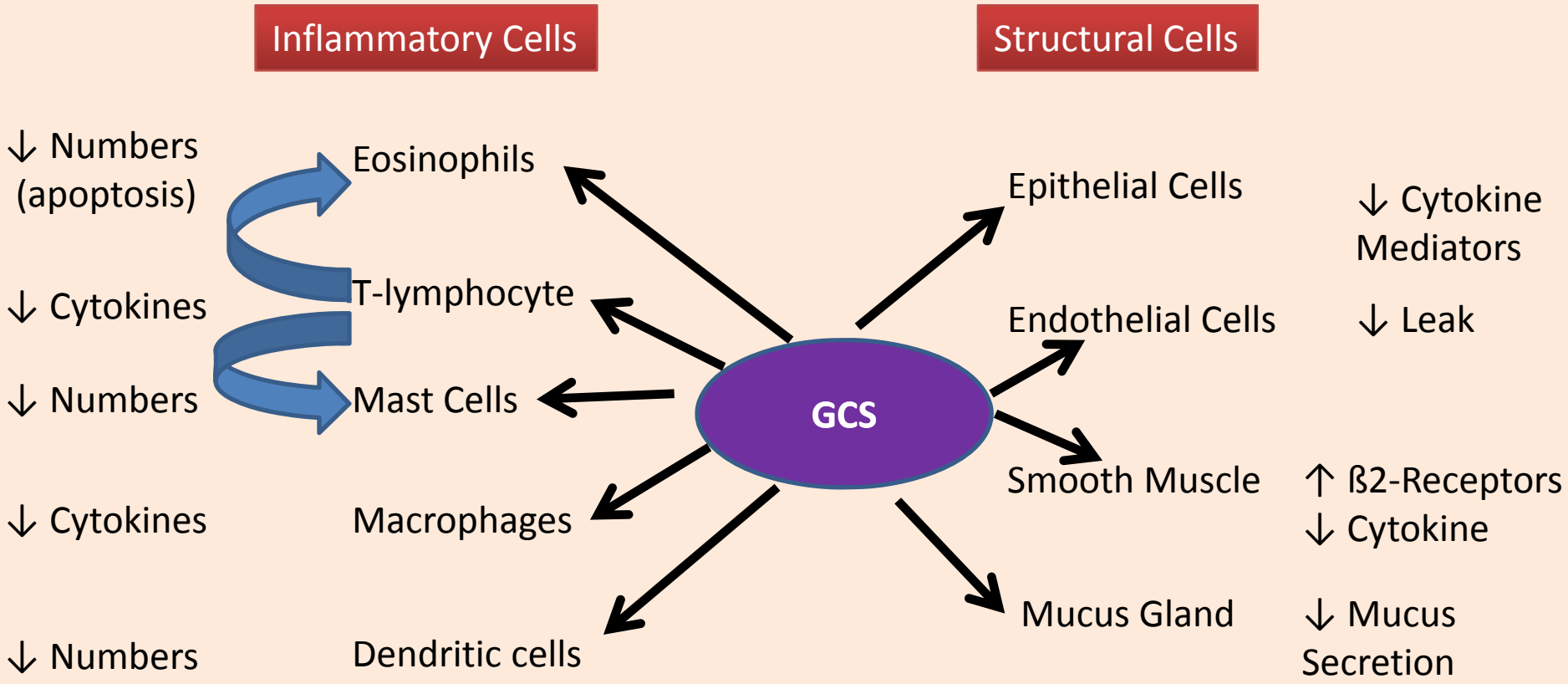
Introduction....

- Asthma- specific pattern of inflammation in airways
  - Degranulated mast cells
  - Infiltration of eosinophils
  - Increased number of activated TH2 cells
- Current guidelines -Anti-inflammatory therapy with glucocorticoids
- Majority responds to inhaled corticosteroids
- Subsets - Poorly responsive high doses of oral prednisone

Glucocorticoid actions....



Definition.....

- Failure to improve baseline FEV_1 by more than 15% after treatment with high doses of prednisolone (30–40 mg daily) for 2 weeks
- Afflicts ~5% of asthma population
- Complete steroid resistance in asthma is rare -1:1000
- Reduced responsiveness to steroids - corticosteroid-dependent (CD) asthma, where large inhaled or oral doses of steroids are needed to control asthma adequately

Features….

- Increased levels of T cell activation
- Failure of GCs to:
  - Inhibit PHA-induced T cell proliferation in vitro
  - Decrease production of airway IL-2, IL-4, & IL-5 after GC therapy
  - Reduce eosinophilia
  - Suppress monocyte/macrophage secretion of IL-8
  - Inhibit cutaneous tuberculin delayed skin responses
- Increased IL-2 and IL-4 gene expression in the airways
- Enhanced AP-1 transcriptional activity in PBMC
- Increased GR expression in PBMC and airway cells

Types....

- **Type I Steroid Resistant Asthma**
  - Reduction in glucocorticoid receptor-binding affinity
  - Cytokine induced, reversible with deprivation of cytokines
  - Mimicked by incubation of cells with high concentrations of IL-2 and IL-4 or by IL-13 alone

J Allergy Clin Immunol 2002;109:649-57

J Allergy Clin Immunol 2003;111:3-22

J Clin Invest 1994;93:33-9

  - Develop severe side effects, including adrenal gland suppression and cushingoid features from pharmacological doses

Types....

- **Type I Steroid Resistant Asthma**
  - Further divided into
  - Cytokine induced:
    - Associated with genetic polymorphisms -overproduction of cytokines (e.g., IL-4) or various key molecules involved in alteration of GC action
  - Acquired:
    - Allergen- or infection-induced cell activation or chronic exposure to medications such as beta-agonists or corticosteroids

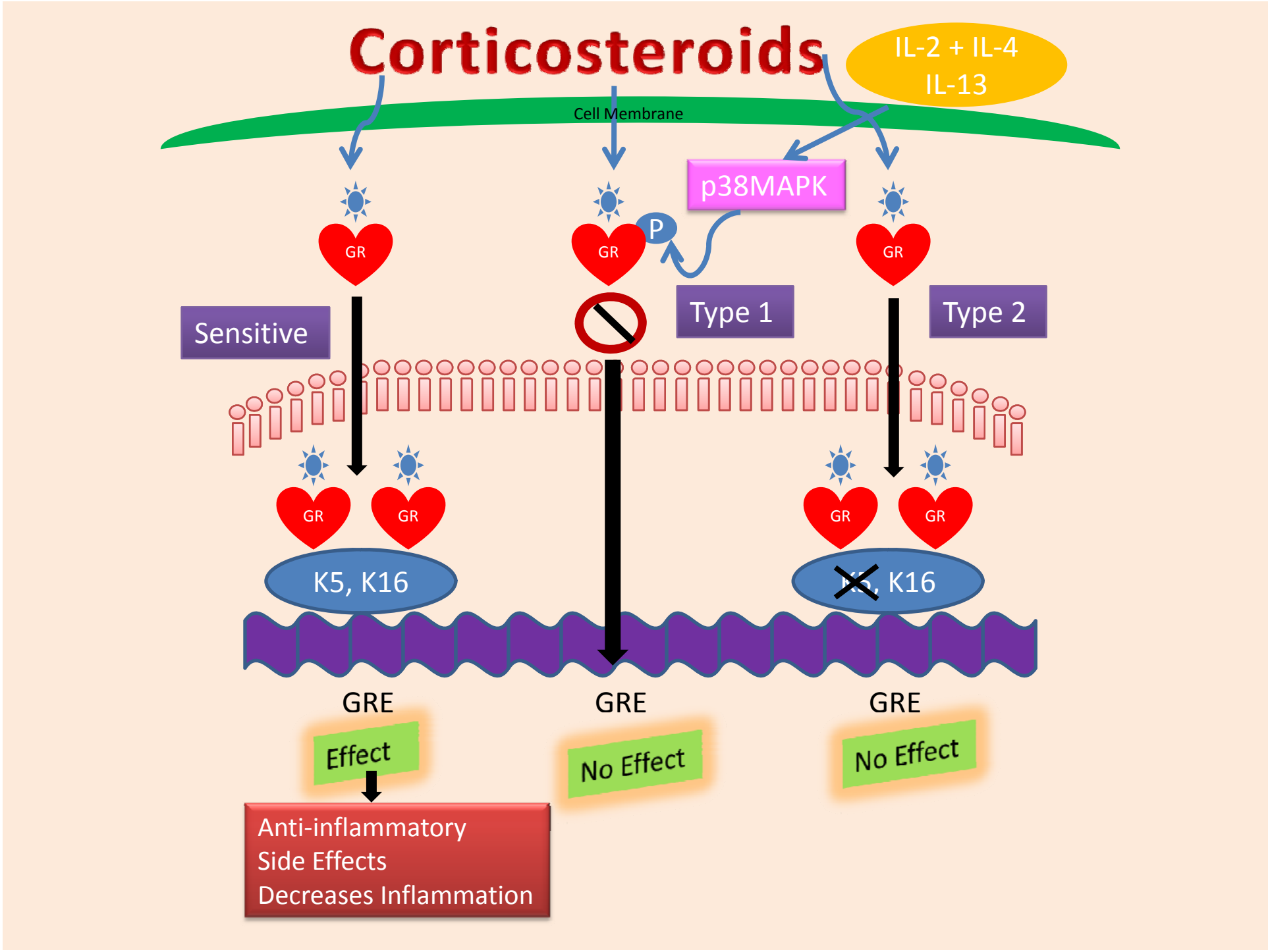
Types….

- **Type II Steroid Resistant Asthma**
  - Much less frequently identified defect
  - Due to low numbers of glucocorticoid receptors
  - Irreversible abnormality that affects all cell types
  - Fail to derive any benefit from glucocorticoids
  - Involves generalized primary cortisol resistance, which affects all tissues

Types....

Features	Type I	Type II
AM Cortisol	Suppressed	No
Cushingoid Side Effects	Yes	No
Cause	Cytokine-induced (may be genetic) Acquired (allergies, microbes)	Genetic
GCR ligand and DNA binding affinity	Reduced	Normal
GCR number	Normal or High	Low
Reversibility of GCR defect	Yes	No

Clinical and Laboratory Features of Steroid-Resistant Asthma


Corticosteroids
IL-2 + IL-4
IL-13
Cell Membrane
p38MAPK
P
GR
GR
GR
Sensitive
Type 1
Type 2
GR
GR
GR
GR
K5, K16
K5, K16
GRE
GRE
GRE
Effect
No Effect
No Effect
Anti-inflammatory
Side Effects
Decreases Inflammation

Mechanisms….

- Genetic abnormalities in glucocorticoid receptors
- Effects of Th2 cytokines (IL-2+IL-4, IL-13)
- Increased GR-β
- p38 MAP kinase activation
- Reduced IL-10 secretion
- ↑ activation of AP-1 (activation of Jun-*N terminal kinase)*
- Abnormalities in histone acetylation
- Oxidative stress and cigarette smoking
- Latent viral infections

Mechanisms….

Genetic abnormalities in glucocorticoid receptors

- Extremely rare familial glucocorticoid resistance
- Point mutations of the GR gene - abnormal GR structure-reduced corticosteroid binding affinity
- Sher et al. described two types of corticosteroid resistance
  - Reduced affinity of GR binding confined to T-lymphocytes which reverted to normal after 48 hours in culture
  - Reduction in GR density which did not normalize with prolonged incubation

J Clin Invest 1994;93:33–39

Mechanisms….

Inflammatory cytokines

- IL-2, IL-4, and IL-13, show ↑ expression in bronchial biopsies in CR asthma induce a reduction in affinity of GR in inflammatory cells-T-lymphocytes & monocytes, resulting in local resistance to the anti-inflammatory actions of corticosteroids
- IL-2 and IL-4 activates p38MAPK- phosphorylates GR and reduces corticosteroid binding affinity and steroid-induced nuclear translocation of GR
- p38 MAP kinase inhibitors might reduce this steroid resistance

Mechanisms….

Glucocorticoid receptor beta

- ↑ expression of an alternatively spliced form of GR-β, which binds to DNA but not to corticosteroids
- Dominant negative inhibitor by competing with GR-β for binding to GRE sites
- Overexpression of GR- has no effect on the inhibition by corticosteroids of inflammatory transcription factors by *trans-repression,* this mechanism is unlikely to interfere with their anti-inflammatory actions

Mol Cell Endocrinol 1999;157:95–104

Mechanisms….

Interaction with transcription factors

- Corticosteroids suppress the expression of inflammatory genes regulated by proinflammatory transcription factors AP-1 and NF- κB
- AP-1 activity is increased in PBMC in CR asthma that may counteract the anti-inflammatory action of corticosteroids

J Exp Med 1995;182:1951–1958
J Immunol 1995;154:3000–3005

- Increased activity of Jun *N-terminal kinase, the MAP kinase that* activates AP-1

J Allergy Clin Immunol 1999; 104:565–574

Mechanisms….

Abnormal histone acetylation pattern

- Defect in acetylation of histone-4-mechanism by which corticosteroids activate steroid-responsive gene

- Specific acetylation of lysine 5 of histone-4 is defective-corticosteroids are not able to activate genes that are critical to the anti-inflammatory action of high doses of corticosteroids

Am J Respir Crit Care Med 2000;161:A189

Mol Cell Biol 2000;20:6891–6903

Mechanisms….

Interleukin 10

- Secretion is defective from alveolar macrophages and circulating monocytes of patients with asthma
- Corticosteroids increase macrophage secretion of IL-10
- Reduction in T-lymphocyte secretion of IL-10 in patients with CR asthma - contribute to the reduced responsiveness

Am J Respir Crit Care Med 1998;157:256–262
J Allergy Clin Immunol 2002;109:369–370

Mechanisms….

Cigarette smoking

- Corticosteroids is less effective in reducing inflammatory cells in BAL or induced sputum in patients with asthma who are smokers

Am J Respir Crit Care Med 1996; 153:1519–1529

Thorax 2002;57:226–230

- Mechanisms for corticosteroid resistance in cigarette smokers - ? Oxidative stress related

Management….

- Steroid unresponsiveness poses a considerable challenge to the clinician for its management
- Chan et al.- 25% of severe asthma had SR asthma – 75% severe asthma can be approached by optimizing management

J Allergy Clin Immunol 1998;101:594–601

- A systematic, stepwise approach is important for a successful outcome

Management….

Considerations in Management of SR Asthma

- Rule out asthma mimics
- Consider medical problems affecting asthma care:
  - Vocal cord dysfunction
  - Gastroesophageal reflux
  - Chronic sinusitis or other respiratory infections
  - Allergic bronchopulmonary aspergillosis
- Consider psychosocial factors affecting self-care:
  - Poor adherence with medications
  - Depression

Management….

Considerations in Management of SR Asthma

- Inadequate technique of medication administration
- Persistent inflammation due to chronic:
  - Allergen exposure & Microbial colonization
  - Inadequate glucocorticoid dose/potency
  - Need for combination therapy
  - β-agonist overuse
- GCR binding abnormalities
- Alternative anti-inflammatory approach

Management….

First Step

- Obtain a thorough history
- Physical examination
- Appropriate laboratory tests to confirm the diagnosis of asthma
- Rule out concomitant medical disorders
  - Evaluation of vocal cord dysfunction – Indirect laryngoscopy
  - Evaluation for GERD & ABPA

Management….

Second Step

- Psychosocial factors affecting the illness
- Poor adherence with recommended therapy
  - Simple forgetfulness
  - Inability to pay for the medications
- Depression - ability to function & adhere to therapy is impaired
- Psychosocial stress has been found to attenuate cortisol responses

Psychosom Med 1997;59:419–426

Management….

Third Step

- Review technique of medication administration
- Spacer devices - to optimize medication delivery and reduce adverse effects
- Mouth rinsing and expectoration of mouth rinse to further reduce the extent of systemic steroid absorption

Management….

Fourth Step

- Assure appropriate environmental control at home, in school, and at work
- Identify potential allergens triggering the disease
- Allergen exposure can induce GCR insensitivity

Am J Respir Crit Care Med 1997;155:87-93

Fifth Step

- Evaluation for potential microbial infection in the airways
- Atopic dermatitis – S.aureus can produce super-antigens that promote GC resistance

Management….

Sixth Step

- Maximize combination therapy for control of disease symptoms
- Combination of ICS & LABA
  - Improve symptom control
  - Facilitate adherence
- Inhaled salmeterol
  - Reduce corticosteroid requirements in asthma
  - Enhance nuclear translocation of the GR

BMJ 2000
J Allergy Clin Immunol2001
J Biol Chem 1999

- Leukotriene antagonists or theophylline-steroid-sparing effects

Management….

Seventh Step

- Evaluate systemic corticosteroid pharmacokinetics
  - Incomplete corticosteroid absorption
  - Failure to convert to an active form
  - Rapid elimination
- Poor absorption of prednisone
  - Oral liquid steroid preparations
  - Split-dosing regimen

Management….

Eighth Step

- Assess evidence for persistent tissue inflammation despite treatment with high-dose GCs
  - Markers of inflammation- exhaled NO
  - Plasma eosinophilic cationic protein
- FOB
  - Examine airways for evidence of airway inflammation in the BAL
  - Bronchial biopsy specimens
- Induced sputum

Management….

Final Step

- Consider alternative anti-inflammatory and immunomodulator approaches
- Type II SR asthma associated with a generalized primary GC resistance
- Poorly controlled type I SR asthma

Management….

Intravenous Immunoglobulin

- Inhibit lymphocyte activation and the production of IL-2 and IL-4 *in vivo*
- Haque et al. – IVIG provides a potentially important adjunctive therapy in severe steroid-dependent asthma, reducing steroid requirement and decreasing hospital admissions, but not improving lung function
- Used IVIg @ 1 g/kg each month for 6 months in 7 patients

Intern Med J. 2003 Aug;33(8):341-4

- Similar results in other studies

Chest 1998; 114:1349–1356
Clin Immunol 1999; 91: 126–133
J Allergy Clin Immunol 1999; 103:810–815

Management….

Nebulized lidocaine

- de Paz Arranz et al. used 2% nebulized lidocaine in a 52 years old women for SR asthma – improvement in symptom, steroid dose reduction
- Useful alternative

Allergol Immunopathol (Madr). 2005 Jul-Aug;33(4):231-4

- Similar findings in 18 patients by Hunt et al

Mayo Clin Proc. 1996 Apr;71(4):361-8

Management….

Methotrexate

- Marin et al- Metanalysis
  - Low-dose methotrexate - significant steroid-sparing effect

Chest. 1997 Jul;112(1):1-3

- Comet et al. in a RCT of 46 patients showed steroid sparing effect of methotrexate (54.8% vs 4.4% P<0.001)
- Methotrexate is an effective steroid-sparing agent

Respir Med. 2006 Mar;100(3):411-9

Management....

Study/Year	Design	Patients†	MTX Dose, mg/wk	Duration of Therapy, wk	OCS Reduction	MTX Response	Adverse Events
Mullarkey et al[21]/1988	Crossover	22 (14)	15 PO	2 × 12	Yes	Yes ($p = 0.01$)	G, R, L
Shiner et al[22]/1990	Parallel	69 (60)	15 PO	24	Yes	Yes ($p < 0.005$)	L, G
Erzurum et al[23]/1991	Parallel	19 (17)	15 IM	12	Yes ($p < 0.003$)	No	G, D
Dyer et al[24]/1991	Crossover	12 (10)	15 PO	2 × 12	Yes	Yes ($p < 0.01$)	Minimal
Trigg and Davies[25]/1993	Crossover	18 (12)	30 PO	2 × 12	NR	No	H, G, I, C
Taylor et al[26]/1993	Crossover	11 (9)	15 PO	2 × 24	Yes	No	G, L, O
Stewart et al[27]/1994	Crossover	24 (21)	15 PO	2 × 12	No	Yes ($p = 0.045$)	Minimal
Coffey et al[28]/1994	Crossover	14 (11)	7.5–15 PO	2 × 12	Yes ($p < 0.01$)	No	G, A, R, H
Kanzow et al[29]/1995	Parallel	24 (21)	15 PO	16	Yes ($p < 0.01$)	Yes ($p < 0.01$)	G
Ogirala et al[30]/1995	Parallel	19 (19)	15 PO	24	NR	No	G, L, R, O
Hedman et al[31]/1996	Crossover	13 (12)	15 PO	2 × 12	Yes	Yes ($p < 0.05$)	G, N

Randomized Trials of Methotrexate in Patients With Severe Asthma

Management….

Cyclosporine

- Blocks the late asthmatic reaction and inhibit production of eosinophil-related cytokines after allergen challenge
- Alexander et al — Lancet 1992; 339:324–328
  - 12% increase in PEFR ($p<0.004$)
  - 17.6% increase in FEV1 ($p<0.001$)
  - 48% reduction in exacerbations requiring increased steroid dosing
- Lock et al in 16 patients — Am J Respir Crit Care Med 1996; 153:509–514
  - Significant reduction in the median daily prednisolone dosage (62% vs 25%, respectively; p 0.043)
- Nizankowska — Eur Respir J 1995; 8:1091–1099
  - No statistically significant effects of cyclosporine using the objective markers of pulmonary function and steroid-sparing effects

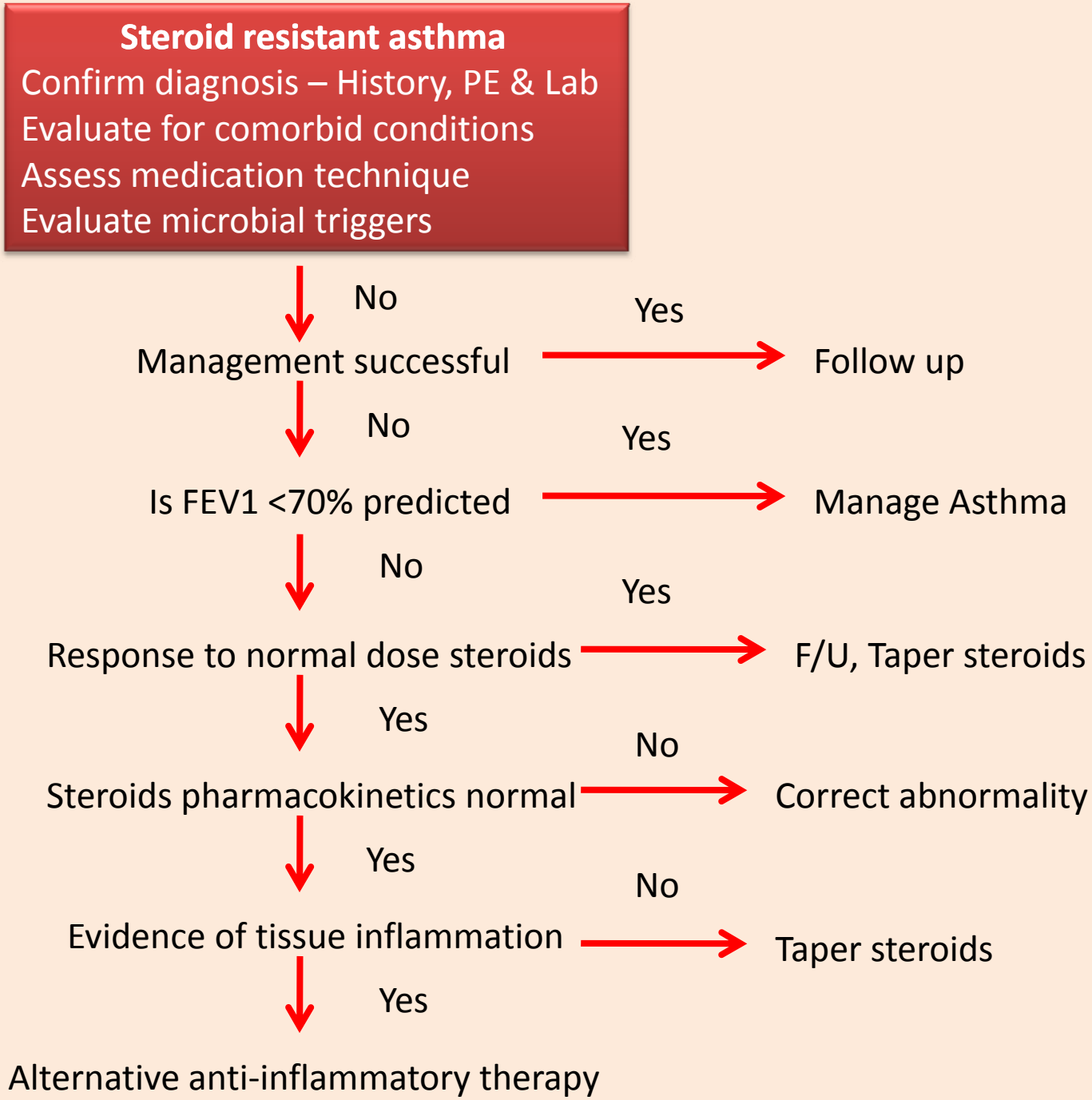
Management….

- Randhwa et al. – 30 yrs review
  - High-dose inhaled corticosteroids are the first-line option
  - Omalizumab is effective in reducing oral corticosteroid requirements in allergic asthma
  - Methotrexate, gold, and cyclosporine have corticosteroid-sparing effects clinically that must be weighed against a serious adverse effect profile
  - Nebulized diuretics and lidocaine, with a low adverse effect profile, offer promising results but require further study

Management….

Miscellaneous therapies

- Anti- CD4+ T-cell antibody (keliximab) showed beneficial effects in a group of patients with CD asthma Eur Respir J 2001;18:45-52
- Anti-IgE therapy (Omalizumab) in a small cohort I of CR asthma has also shown clinical effectiveness Clin Exp Allergy 2004;34:632-8
- Thompson et al in 3 patients showed steroid and cyclosporin sparing effect Respirology (2007) 12 (Suppl. 3), S29–S34
- Vitamin D3, which may inhibit the production of IL-2 and IL-4
- Gene therapy


Steroid resistant asthma
Confirm diagnosis – History, PE & Lab
Evaluate for comorbid conditions
Assess medication technique
Evaluate microbial triggers
No
Yes
Management successful
Follow up
No
Yes
Is FEV1 <70% predicted
Manage Asthma
No
Yes
Response to normal dose steroids
F/U, Taper steroids
Yes
No
Steroids pharmacokinetics normal
Correct abnormality
Yes
No
Evidence of tissue inflammation
Taper steroids
Yes
Alternative anti-inflammatory therapy

Conclusions….

- Correct diagnostic work up
- SR asthmatics do respond to bronchodilator therapy and that such medications should be instituted early as rescue therapy
- Presence of persistent airway inflammation predisposes them to airway remodeling and long-term irreversible airways diseases. Thus it is of paramount importance to treat their inflammation early and effectively