ASTHMA MANAGEMENT IN CHILDREN

Cristian Gheonea ¹, Vasile Valeriu Lupu ²

1 University of Medicine and Pharmacy of Craiova, Romania
2 „Gr. T. Popa” University of Medicine and Pharmacy, Iasi, Romania
According to Robinson, 85% of the National Institutes of Health database is being upgraded every 5 years, available medical information is doubling every 5 years, and 90% of information learned will be obsolete in 15 years (Robinson, 1993).
Global Initiative for Asthma

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GINA Global Initiative for Asthma (GINA) Teaching slide set 2016 update

GINA Global Strategy for Asthma Management and Prevention 2016

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Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation.

It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation.
Prevalence of asthma in children aged 13-14 years

GINA 2016 Appendix Box A1-1; figure provided by R Beasley
Prevalence of asthma in children aged 13-14 years
Development of the “allergic” (Th2) or “tolerant” phenotype (Th1)

• At birth, the immune system is not fully developed: it tends to be directed towards the predominance of the T-helper (Th)2 phenotype in order to prevent the rejection of the in utero product of conception.

• Instead, the Th2 phenotype leads to the stimulation of IgE production by the B-lymphocytes, thus increasing the risk of allergic reactions through the activation of mastocytes.
Development of the “allergic” (Th2) or “tolerant” phenotype (Th1)

• The epigenetic stimulation, even from the early stages of life, inverts the paradoxal reaction of Th2 and determines the predominance of Th1 phenotype, with simultaneous stimulation of the Th3 cells.

Figure 3. Asthma can be divided into $T_{H2}$-low and $T_{H2}$-high subgroups. Levels of gene expression for T helper 2 ($T_{H2}$) cell cytokines$^{76}$ or for the activation of epithelial cells by $T_{H2}$ cell cytokines$^{77}$ show a continuum in the airways of patients with asthma (rather than a bimodal distribution). Individuals with asthma who have expression levels higher than the range found in healthy controls have specific clinical, pathological and treatment-response characteristics. This suggests a threshold effect of $T_{H2}$ cell cytokines in the airways above which type 2 inflammation influences the clinical features of asthma and the responsiveness to specific treatments. Biomarkers of type 2 inflammation in blood and
<table>
<thead>
<tr>
<th>Known or suspected determining factors</th>
<th>Strength/direction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wheezing viral infection</td>
<td>++++</td>
</tr>
<tr>
<td>Febrile viral infection</td>
<td>++++</td>
</tr>
<tr>
<td>Sensitization to perennial aeroallergens</td>
<td>++++</td>
</tr>
<tr>
<td>Sensitization to other classes of allergens</td>
<td>++</td>
</tr>
<tr>
<td>Age of infection and type of virus</td>
<td>++</td>
</tr>
<tr>
<td>Genetic predisposition to Th2 immune bias</td>
<td>++</td>
</tr>
<tr>
<td>Daycare</td>
<td>+</td>
</tr>
<tr>
<td>Sex</td>
<td>+</td>
</tr>
<tr>
<td>Maternal smoking</td>
<td>+</td>
</tr>
<tr>
<td>Postnatal tobacco smoke exposure</td>
<td>+</td>
</tr>
<tr>
<td>Maternal and antenatal infection (and antibiotic use)</td>
<td>+</td>
</tr>
<tr>
<td>Bronchial hyperresponsiveness</td>
<td>+</td>
</tr>
<tr>
<td>Low-lung function/lung growth</td>
<td>+</td>
</tr>
<tr>
<td>Mucosal inflammation</td>
<td>+</td>
</tr>
<tr>
<td>Obesity</td>
<td>+</td>
</tr>
<tr>
<td>Lung microbiota</td>
<td>+</td>
</tr>
<tr>
<td>Cesarean delivery</td>
<td>+</td>
</tr>
<tr>
<td>Maternal and antenatal environmental exposure</td>
<td>+++/-</td>
</tr>
<tr>
<td>Domestic animal exposure</td>
<td>+/-</td>
</tr>
<tr>
<td>Microbiota development in gut</td>
<td>+/-</td>
</tr>
<tr>
<td>Maternal and antenatal nutrition</td>
<td>+/-</td>
</tr>
<tr>
<td>Number of siblings</td>
<td>-</td>
</tr>
</tbody>
</table>

Once identified, such factors can be measured and the data introduced into modeling systems to generate and test hypotheses on asthma development. “+” contributes to etiology/pathogenesis and “-” protective.
• The first report regarding the use of cortisone in bronchial asthma was published in 1950 (Carrer HM, J Allergy, 21:282-86).

• The clinical efficacy was obvious, but soon the adverse reactions reports started to gather: high blood pressure, diabetes mellitus, osteoporosis, obesity, acne, moon facies, glaucoma and height growth retardation (occurring especially in children).
Cellular effects

- The exact mechanism of action of corticosteroids (CS) in pulmonary diseases are not well defined.
- CS exert direct inhibiting effects on many inflammatory cells.
- CS accelerate eosinophil apoptosis and they reciprocally inhibit neutrophils apoptosis, thus prolonging their life duration at the level of the airways.
Cellular effects

- Although CS do not inhibit the release of mastocyte mediators, the inhaled corticosteroids (ICS) therapy reduces the number of mastocytes from the airways.
- CS may reduce microvascular permeability
- CS may reduce mucus production.
The ideal inhaled corticosteroid

• Lipid conjugation, with the extension of pulmonary residence time (one daily administration) and the reduction of systemic side effects.
The ideal inhaled corticosteroid

Conjugation with serum proteins – this way the systemically absorbed fraction is not active

<table>
<thead>
<tr>
<th>Protein-binding</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>BDP</td>
<td>87</td>
</tr>
<tr>
<td>BMP</td>
<td>NA</td>
</tr>
<tr>
<td>BUD</td>
<td>88</td>
</tr>
<tr>
<td>CIC</td>
<td>99</td>
</tr>
<tr>
<td>des-CIC</td>
<td>99</td>
</tr>
<tr>
<td>FLU</td>
<td>80</td>
</tr>
<tr>
<td>FP</td>
<td>90</td>
</tr>
<tr>
<td>MF</td>
<td>98</td>
</tr>
<tr>
<td>TAA</td>
<td>71</td>
</tr>
</tbody>
</table>
The equivalent daily dose of ICS

<table>
<thead>
<tr>
<th>Drug</th>
<th>Low Daily Dose (µg)</th>
<th>Medium Daily Dose (µg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beclomethasone dipropionate</td>
<td>100 - 200</td>
<td>&gt;200 - 400</td>
</tr>
<tr>
<td>Budesonide*</td>
<td>100 - 200</td>
<td>&gt;200 - 400</td>
</tr>
<tr>
<td>Budesonide-Neb</td>
<td>250 - 500</td>
<td>&gt;500 - 1000</td>
</tr>
<tr>
<td>Ciclesonide*</td>
<td>80 - 160</td>
<td>&gt;160 - 320</td>
</tr>
<tr>
<td>Flunisolide</td>
<td>500 - 750</td>
<td>&gt;750 - 1250</td>
</tr>
<tr>
<td>Fluticasone propionate</td>
<td>100 - 200</td>
<td>&gt;200 - 500</td>
</tr>
<tr>
<td>Mometasone furoate*</td>
<td>100 - 200</td>
<td>&gt;200 - 400</td>
</tr>
<tr>
<td>Triamcinolone acetonide</td>
<td>400 - 800</td>
<td>&gt;800 - 1200</td>
</tr>
</tbody>
</table>
Therapeutic efficacy

Therapeutic efficacy = Efficacy x Adherence

Efficacy: Oral vs. inhaled
Adherence: Number of administrations, Side-effects, Costs, Patient education, Inhalation technique, Duration until the effect is present

“Does it help the patient?”
Choosing the inhaler device for children with bronchial asthma

The choice should be based on: drug administration efficacy, costs, safety, usability and patient compliance.
Choosing the inhaler device for children with bronchial asthma

<table>
<thead>
<tr>
<th>Age</th>
<th>Device of choice</th>
<th>Alternative device</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 4 years of age</td>
<td>Pressurized container + spacer with face mask</td>
<td>Nebulizer with face mask</td>
</tr>
<tr>
<td>4-6 years of age</td>
<td>Pressurized container + spacer with mouthpiece</td>
<td>Nebulizer with mouthpiece</td>
</tr>
<tr>
<td>&gt; 6 years of age</td>
<td><strong>Dry powder container, or</strong> breath-activated pressurized container, or pressurized container + spacer with mouthpiece</td>
<td>Nebulizer with mouthpiece</td>
</tr>
</tbody>
</table>

Choice based on: drug administration efficacy, costs, safety, usability and patient compliance.
INHALED CORTICOSTEROIDS:

Drug of first choice, very strong

Unfavourable reputation: safety, tolerability, compliance
Control
Any exacerbation must lead to a reassessment of the maintenance treatment in order to make sure it is an adequate one.

The onset of an exacerbation in any of the weeks defines a week of uncontrolled asthma.

Testing the pulmonary function in children under 5 years of age is not reliable.

### Levels of Asthma Control

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Controlled (all of the following)</th>
<th>Partially controlled (any measure present in any week)</th>
<th>Uncontrolled</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Daytime symptoms</strong></td>
<td>None (≤ 2/week)</td>
<td>&gt; 2/week</td>
<td></td>
</tr>
<tr>
<td><strong>Limitations of activities</strong></td>
<td>None</td>
<td>Any</td>
<td>3 or more features of partially controlled asthma present in any week</td>
</tr>
<tr>
<td><strong>Nocturnal symptoms/awakenings</strong></td>
<td>None</td>
<td>Any</td>
<td></td>
</tr>
<tr>
<td><strong>Need for reliever/rescue treatment</strong></td>
<td>None (≤ 2/week)</td>
<td>&gt; 2/week</td>
<td></td>
</tr>
<tr>
<td><strong>Lung Function (PEF or MEVS)</strong></td>
<td>Normal</td>
<td>&lt; 80% of the predicted value or of the personal best value (if known)</td>
<td></td>
</tr>
<tr>
<td><strong>Exacerbations</strong></td>
<td>None</td>
<td>≥ 1/year*</td>
<td>1 in any week**</td>
</tr>
</tbody>
</table>

* - Any exacerbation must lead to a reassessment of the maintenance treatment in order to make sure it is an adequate one.

** - The onset of an exacerbation in any of the weeks defines a week of uncontrolled asthma.

*** - Testing the pulmonary function in children under 5 years of age is not reliable.
<table>
<thead>
<tr>
<th>← REDUCE</th>
<th>TREATMENT STEPS</th>
<th>→ INCREASE →</th>
</tr>
</thead>
<tbody>
<tr>
<td>STEP 1</td>
<td>STEP 2</td>
<td>STEP 3</td>
</tr>
</tbody>
</table>

**Patient education**  
**Environmental control**  

**WHAT PRODUCT?**  
Rapid-acting Beta2-agonist, as needed

<table>
<thead>
<tr>
<th>Options for maintenance drugs</th>
<th>Select one</th>
<th>Select one</th>
<th>Add one or more</th>
<th>Add one or more</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-dose ICS*</td>
<td>Low-dose ICS plus LABA</td>
<td>Medium or high dose ICS plus LABA</td>
<td>Systemic corticotherapy (lowest dose)</td>
<td></td>
</tr>
<tr>
<td>Antileukotriene **</td>
<td>Medium or high dose ICS</td>
<td>Antileukotriene</td>
<td>Anti-IgE treatment</td>
<td></td>
</tr>
<tr>
<td>Low-dose ICS plus antileukotriene</td>
<td>Sustained-release theophylline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low-dose ICS plus sustained-release theophylline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ICS = inhaled glucocorticosteroids  
LABA = long-acting Beta2-agonist
Definition

- A defining element of exacerbation is the alteration of the pulmonary function, evidenced by the measurement of MEVS (maximum expiratory volume per second) or PEF (peak expiratory flow) values.
- The measurement of these parameters offers more reliability than clinical symptomatology, since patients usually underestimate their symptoms.
Causes of exacerbations

• The most frequent causes of asthma exacerbations are respiratory viral infections
Causes of exacerbations

• acute exposure to pneumo-allergens or irritant agents (sulphur dioxide, air pollutants);
• some drugs: nonsteroidal anti-inflammatory drugs or non-selective beta-blockers, sedatives;
• emotional stress;
• non-compliance with chronic treatment of asthma.
Recognizing exacerbations

• most of the times, the clinical manifestations of asthma exacerbations are characteristic and easily recognisable

• expiratory dyspnea, wheezing and sibilant rales are almost constantly present.

• these symptoms are not present in status asthmaticus!
Appreciating the severity of exacerbation

Performing the *anamnesis* of the patient and establishing:

- If asthma diagnosis is already known or not (*an inaugural exacerbation may be easier to treat*);
- If the patient was previously treated with inhaled or oral corticoids (*the onset of an exacerbation while under efficient treatment may be more severe and harder to control*);
- If the patient previously suffered from life-threatening asthma episodes or if he was admitted to an intensive care unit (*this indicating a greater risk for such an episode to repeat itself*).
Appreciating the severity of exacerbation

• Chest radiograph – is only useful for the diagnosis of pneumothorax.

• Purulent sputum – is often a pseudo purulence (degraded eosinophils), generated by intense bronchial inflammation and not by a bacterial suprainfection. The bacteriological examination of sputum is rarely necessary.
Appreciating the severity of exacerbation

- Excepting mild exacerbation, the *transcutaneous oxygen saturation of hemoglobin* (SaO2) *measurement* is compulsory.

- The initiation and maintenance of oxygen therapy depends on the SaO2 value.
Appreciating the severity of exacerbation

- *Arterial blood gas measurement* is important, especially in severe exacerbations. Most of the times, it indicates *mild hypoxemia* (PaO2 between 66 and 69 mmHg), *hypocapnia* (PaCO2 33-36 mmHg) and *respiratory alkalosis*.

- *Arterial blood gas measurement* is compulsory when a mild or severe exacerbation does not respond to the initial treatment, as the onset of acidosis requires intubation and mechanical ventilation.
Appreciating the severity of exacerbation

- *Ventilation parameters (MEVS or PEF)* measurement in asthma exacerbation is recommended by all national and international asthma guides.
- Ventilation parameters are expressed as a percentage of the predicted theoretical value or of the personal best value.

...............  

- IgE, allergy testing, asthma scores, etc.
<table>
<thead>
<tr>
<th><strong>Symptom</strong></th>
<th><strong>Mild</strong></th>
<th><strong>Moderate</strong></th>
<th><strong>Severe</strong></th>
<th><strong>Imminent respiratory arrest</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnea</td>
<td>While walking</td>
<td>While talking</td>
<td>At rest</td>
<td></td>
</tr>
<tr>
<td>Position</td>
<td>Tolerates clinostatism</td>
<td>Prefers orthostatism</td>
<td>Hunched forward</td>
<td></td>
</tr>
<tr>
<td>Talks in</td>
<td>Complex Sentences</td>
<td>Sentences</td>
<td>Words</td>
<td></td>
</tr>
<tr>
<td>Alertness</td>
<td>May be agitated</td>
<td>Usually agitated</td>
<td>Usually agitated</td>
<td>Confused</td>
</tr>
<tr>
<td>Respiratory rate</td>
<td>Increased</td>
<td>Increased</td>
<td>&gt;30/min</td>
<td></td>
</tr>
<tr>
<td>Accessory muscle use</td>
<td>None</td>
<td>Present</td>
<td>Present</td>
<td>Paradoxical thoracoabdominal movement</td>
</tr>
<tr>
<td>Wheezing</td>
<td>Moderate, at the end of expiration</td>
<td>Intense</td>
<td>Intense</td>
<td>Absent</td>
</tr>
<tr>
<td>Pulse</td>
<td>&lt;100</td>
<td>100-120</td>
<td>&gt;120</td>
<td>Bradycardia</td>
</tr>
<tr>
<td>Pulsus paradoxus</td>
<td>Absent</td>
<td>May be present 10-25 mmHg</td>
<td>Often present &gt; 25 mmHg</td>
<td>Absence suggests respiratory muscle fatigue</td>
</tr>
<tr>
<td>PEF(^1) after initial BD(^2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% predicted value or % personal best value</td>
<td>&gt;80%</td>
<td>60-80%</td>
<td>&lt;60%</td>
<td></td>
</tr>
<tr>
<td>PaO(_2)</td>
<td>Normal</td>
<td>&gt;60 mmHg</td>
<td>&lt;60 mmHg (cyanosis)</td>
<td></td>
</tr>
<tr>
<td>PaCO(_2)</td>
<td>&lt;45 mmHg</td>
<td>&lt;45 mmHg</td>
<td>&gt;45 mmHg</td>
<td></td>
</tr>
<tr>
<td>SaO(_2)</td>
<td>&gt;95%</td>
<td>91-95%</td>
<td>&lt;90%</td>
<td></td>
</tr>
</tbody>
</table>

\(^1\) PEF - Peak expiratory flow  \(^2\) BD - Bronchodilator
Elements that suggest a life-threatening exacerbation

• sensitivity alteration,
• orthostatism,
• diaphoresis,
• difficulty while speaking, interruptions
• cyanosis,
• exhaustion,
• pulsus paradoxus (decrease in systolic blood pressure during inspiration of more than 15 mmHg),
• intercostal retraction,
• complete silence on auscultation,
• decrease of MEVS under 25% of the predicted value.
STATUS ASTHMATICUS

paroxysmal expiratory dyspnea: clinical severity
prolonged duration (> 24 hours)
lack of response to bronchodilators

**Fighting phase**—respiratory manifestations
- **intense expiratory dyspnea** (the patient adopts a typical attitude)
- cyanosis
- short inspiration, marked retraction, nasal flaring
- regular breathing with **tachypnea**, then progressively irregular, with short pauses
- hyperinflated thorax
- pulmonary hypersonority
- diminished vesicular murmur

**Bronchoplegia Phase** (coma or precoma)
1. Respiratory manifestations
   - bronchospasm replaced by bronchodilation
   - rare superficial breathing
2. Cardiovascular manifestations
   - tachycardia, other rhythm disorders
   - heart failure
   - initial high blood pressure (HBP), then low blood pressure (LBP) with the onset of collapse
3. Neuropsychic manifestations
   - agitation, anxiety
   - somnolence, progressive hyporeactivity, coma, convulsions, cardiac arrest
Short-acting beta-mimetics

- Produce the dilation of the bronchi and the relaxation of smooth muscles through the activation of adenyl cyclase and the increase of cellular cAMP (cyclic adenosine monophosphate) concentration
- Act via $\beta_2$ receptors producing bronchodilation
- Salbutamol
- Terbutaline
- Side effects: hypokalemia, tremor, nausea, vomiting, tachycardia
Salbutamol
• May be administered:
  – with a nebulizer: (also possible by means of the ventilator circuit)
    0.1-0.15 mg/kg/dose in infants and small children (without exceeding
    5 mg) every 20-30 minutes until the asthma crisis is resolved, then
    every 6 hours. In teenagers and adults the dosage is of 2.5 mg/dose
    3 or 4 times a day
  – with an inhaler (100 μg/puff) - according to recommendations

• Dosage:
  – Depends on age, severity of disease, administration device
  – Concentration is determined depending on heart rate and
    therapeutic response
  – Usual doses for the nebulizer:
    • <10kg: 2.5mg/h
    • 10-20kg: 5mg/h
    • 20-30kg: 10mg/h
    • >30kg: 15mg/h
Terbutaline

• May be administered:
  – with a nebulizer
  
  – with an inhaler (1-2 puffs every 4 hours, maximum 4 administrations / day)
Systemic glucocorticoids

- are indispensable in all asthma exacerbation cases, except the milder ones.
- represent the only medication that addresses the physiopathological substratum

- must be used especially if:
  - the initial bronchodilators therapy does not have a lasting effect
  - exacerbation emerged despite a previous oral corticoid therapy
  - previous exacerbations required the administration of oral corticoids

- Solu-Medrol
  - 2mg/kg/day divided at 6h
  - Max 60mg/day in children and 180mg/day in adults
  - IV

- Prednisone or Prednisolone
  - Oral administration

- Oral administration is as efficient as intravenous one. The effects of the drug start to appear approximately 4 hours after administration. It is advisable to be intravenously administered in intensive care units, as polypnea and nausea increase aspiration risk.
Corticosteroids

• Complications
  – High blood pressure
  – Hyperglycemia
  – Hypokalemia
  – Gastritis
Anticholinergics

- Atropine
- Bronchodilator, reduces mucus production
- Additive effect when combined with beta-agonists
- Used for beta-blocker induced asthma
- Complications: dryness of mucous membrane, aggravation of wheezing (rarely)
- Dosage (Atrovent): 250-500mcg/dose, every 20 minutes or so, for 2 to 4 hours.
Methylxanthines

- Theophylline and miophylline
- Theoretical benefits:
  - Phosphodiesterase inhibitor (increases cAMP)
  - Stimulates the release of catecholamines
  - Stimulates diuresis
  - Stimulates diaphragm contractility
  - Prostaglandin antagonist

HIGH RISK OF SIDE EFFECTS (tachycardia, arrhythmia, low blood pressure, convulsions, death)
Other options (unconfirmed)

- Antileukotrienes IV
- magnesium sulfate – a better option!
Contraindicated or useless drugs in asthma exacerbations

- **Sedatives** *(strictly contraindicated)*
- **Mucolytics** *(accentuate coughing)*
- **Kinetotherapy** *(accentuates discomfort)*
- **Hydration with large quantities of liquids** *(possible exceptions: infants, small children)*
- **Antibiotics** *(excepting simultaneous bacterial infections)*
Patient and family education program

– The education program comprises information regarding:
- the disease;
- the recognition of exacerbation and severity signs (knowing hospitalization criteria);
- the immediate drug measures for asthma crisis and the necessity to call the doctor in case of failure;
Patient and family education program

Controlling the evolution of the disease at home, while following the pre-established, individualised chronic treatment:

- Understanding and respecting the therapeutic scheme recommended by the specialized pediatrician and cooperating with the family doctor in regard to any treatment adjustment;
- Observing the onset of complications (infections, drug or nutrition related problems, etc.);
- Respecting the method of administration for oral and inhaled drugs;
- Using correctly the drug administration devices;
- Supervising treatment efficacy via PEF measuring;
- Regularly contacting the family doctor to ensure the intercritical treatment is properly administered.
Periodic monitoring

• Seeing the specialized physician for re-evaluation every 3 months or anytime it is needed

• Adjusting the treatment in accordance with the evolution of disease
  – aggravation → moving to a superior severity step ("step-up")
  – improvement → moving to an inferior severity step ("step-down")
Treatment adherence in pediatric asthma: Ideal world vs. real world