



Management & Chemotherapy of Asthma-A Review

Uttam Borah*, Biswajit Dash, Jashabir Chakraborty, Juman Deka, Lawrence Kalita,

*Girijananda Chowdhury Institute of Pharmaceutical Science,
Azara, Guwahati-781017*

Abstract:

Asthma is yet interminable malady that spots substantial monetary weight on patients, their families, and the human services framework. Asthma can impact personal satisfaction by bringing about missed daily activities, therapeutic costs, and unexpected passing.

Asthma is the most widely recognized respiratory issue in India. Regardless of the huge change in the analysis and administration of this issue, the lion's share of Indians with asthma remain inadequately controlled. In many patients, be that as it may, control can be accomplished using evasion measures and suitable pharmacological intercessions. Breathed in corticosteroids speak to the standard of tending to the greater part of patients. Blend Inhaled corticosteroids with long-acting beta-agonists inhalers are favoured for most grown-ups who neglect to accomplish control with Inhaled corticosteroids treatment. Allergen-particular immunotherapy speaks to a possible sickness changing treatment for some patients with asthma, yet ought to just be recommended by doctors with suitable preparing in hypersensitivity. General observing of asthma control, adherence to treatment and inhaler strategy are likewise fundamental segments of asthma administration.

So this article gives an audit of current writing and rules for the suitable chemotherapy and administration of asthma.

Keywords: Asthma, Corticosteroids, Long acting beta-agonist, antibodies.

ABBREVIATIONS:

COPD	chronic obstructive pulmonary disease
ICS	inhaled corticosteroid
IgE	Immunoglobulin E
LABA	long-acting beta2 -adrenergic receptor agonist
pMDI	pressurized metered-dose inhaler or 'puffer'
SABA	short-acting beta2 -adrenergic receptor agonist

INTRODUCTION :

Asthma is characterized as an incessant incendiary illness of the aviation routes. The endless aggravation is related with aviation route hyper responsiveness (an overstated aviation route narrowing reaction to triggers, for example, allergens and exercise), that prompts intermittent indications, for example, wheezing, dyspnea (shortness of breath), trunk snugness and hacking. Side effect scenes are for the most part connected with far reaching, however, factor, wind current block inside the lungs that is typically reversible either suddenly or with fitting asthma treatment. [1]

Bronchial asthma is a typical malady, of which most patients are satisfactorily treated by standard treatment. Be that as it may, a little yet stressing gathering of patients with asthma has extreme, the unremitting sickness that can't be controlled by traditional techniques, including theophylline, maximal bronchodilator treatment, and high measurements of breathed in corticosteroids [2].

Administration of patients with troublesome asthma ought to incorporate assessment of solution consistency, ID of components that hasten intensifications, and in addition early appraisal of the dynamic weakening of the malady. Regardless, these patients frequently require long haul systemic corticosteroid treatment bringing about undesirable and potential genuine symptoms, for example, osteoporosis, skin diminishing, diabetes, hypertension and waterfall development [3].

Asthma is a typical, perpetual respiratory sickness influencing 1–18% of the populace in various nations. Asthma is portrayed by factor indications of wheeze,

shortness of breath, trunk snugness as well as hack, and by factor expiratory wind stream impediment. Both indications and wind stream impediment naturally change after some time and in power. These varieties are frequently activated by elements, for example, exercise, allergen or aggravation presentation, change in climate, or viral respiratory diseases. Indications and the wind current restriction may resolve suddenly or in light of drug, and may some of the time be missing for a considerable length of time or months on end. Then again, patients can encounter long winded flare-ups (intensifications) of asthma that might be life-undermining and convey a critical weight to patients and the group [4]. Asthma is typically connected with aviation route hyper responsiveness to immediate or backhanded jolts, and with interminable aviation route aggravation. These components typically hold on, notwithstanding when side effects are missing or lung capacity is ordinary, yet may standardize with treatment [5].

Asthma is a heterogeneous gathering of malady portrayed by provocative changes in the aviation route, prompting bronchial impediment, which brings about respiratory side effects and indications of shifting character and seriousness. Asthma is regularly however not all around repeating in nature, and is affected by hereditary, immunologic and ecological variables that are not all known right now. Asthma is a standout amongst the most well-known, whether not the most widely recognized, endless malady in youngsters. It is evaluated that more than 5% of the worldwide populace has asthma, which means a stunning 350 million individuals around the world. It is more typical in created nations, where occurrence rates can

keep running as high as 20%. The frequency has likewise been expanding, first in created nations, and now in creating countries. Death rates of asthma demonstrate no critical change in spite of the improvement of new medications and systems to treat asthma. However for an ailment that influences such a large number of individuals, there is no single indicative test accessible, and the capacity to make a finding depends exclusively on the clinical aptitudes of the current doctor. It is a colossal test. Presently asthma is not one ailment, but rather a heterogeneous gathering of clusters. Making an analysis of asthma includes a reasoning procedure that consolidates such a large number of components, both hereditary and natural, that patients are often misdiagnosed [6].

So this survey basically centers upon the pharmacological administration and chemotherapy and in addition analysis elements of Asthma.

PATHOPHYSIOLOGY:

Little aviation route check inside lungs prompts expanded aviation route resistance, diminished expiratory stream, air catching with every breath and lung hyperinflation. The lapse turns into a dynamic procedure. Diaphragmatic leveling from hyperinflation causes extra mechanical drawbacks. Both constrained expiratory volume and constrained essential limit are diminished and add up to lung volumes are expanded. Dynamic hyperinflation (air catching with each breath) in serious asthma can extend the aspiratory vasculature, expanding pneumonic vascular resistance and right ventricular afterload. Because of expansive negative intrathoracic weight amid motivation, left ventricular afterload is expanded, and systolic circulatory strain diminishes. Overstated variety in systolic circulatory strain amid motivation is named as pulsus paradoxus [7].

Airflow limitation in asthma is intermittent and brought on by an assortment of changes in the aviation route. These incorporate

Bronchoconstriction:- In asthma, the prevailing physiological occasion prompting clinical manifestations is aviation route narrowing and a resulting obstruction with wind current. In intense intensifications of asthma, bronchial smooth muscle compression (bronchoconstriction) happens rapidly to limit the aviation routes because of introduction to an assortment of boosts including allergens or aggravations. Allergen-induced acute bronchoconstriction results from an IgE-dependent release of mediators from mast cells that includes histamine, tryptase, leukotrienes, and prostaglandins that directly contract airway smooth muscle. Headache medicine and other nonsteroidal mitigating drugs can likewise bring about intense wind stream deterrent in a few patients, and confirmation demonstrates that this non-IgE-subordinate reaction additionally includes going between discharge from aviation route cells. Likewise, other boosts (counting exercise, frosty air, and aggravations) can bring about intense wind stream hindrance. The instruments managing the aviation route reaction to these variables are less all around characterized, however, the power of the reaction

seems identified with fundamental aviation route irritation. Stress may likewise assume a part in accelerating asthma intensifications. The instruments included presently can't seem to be set up and may incorporate improved era of expert fiery cytokines.

Airway edema:- As the disease becomes more persistent and inflammation more progressive, other factors further limit airflow. These include edema, inflammation, mucus hypersecretion and the formation of inspissated mucus plugs, as well as structural changes including hypertrophy and hyperplasia of the airway smooth muscle. These latter changes may not respond to usual treatment.

Airway hyper responsiveness:- Different components additionally constrain stream as the sickness turns out to be more industrious and irritation more dynamic. These incorporate edema, aggravation, bodily fluid hypersecretion and the development of inspissated bodily fluid attachments, and auxiliary changes including hypertrophy and hyperplasia of the aviation route smooth muscle. These last changes may not react to common treatment.

Airway remodeling:- In a few people who have asthma, wind current impediment might be just incompletely reversible. Lasting basic changes can happen in the aviation route these are relate a dynamic loss of lung capacity that is not averted by or completely reversible by current treatment. Aviation route redesigning includes an initiation of huge numbers of the auxiliary cells, with subsequent perpetual changes in the aviation route that expansion wind current hindrance and aviation route responsiveness and render the patient less receptive to treatment. These auxiliary changes can incorporate thickening of the substorm cellar layer, subepithelial fibrosis, aviation route smooth muscle hypertrophy and hyperplasia, vein multiplication and widening, and mucous organ hyperplasia and hypersecretion. Control of the repair and redesigning procedure is not settled, but rather both the procedure of repair and its direction are probably going to enter occasions in clarifying the constant way of the malady and confinements to a remedial reaction.

Epithelial damage :- In asthma, the epithelium (the layer of cells that line the aviation routes) can end up noticeably harmed and peel away. Epithelial shedding can add to aviation route hyper-responsiveness in a few ways; these incorporate loss of hindrance capacity, which may permit entrance of allergens; loss of enzymes that break down inflammatory mediators; exposure of sensory nerves, which may prompt reflex neural impacts on the aviation route. Changes can likewise happen in the subepithelial layer, for example, the setting down of collagen.

Mucus hypersecretion: Bodily fluid hypersecretion Asthma causes the bodily fluid discharging cells in the aviation routes to duplicate and the mucous organs to grow. Expanded bodily fluid emission adds to the development of viscid mucous fittings that can block the aviation routes [8-10].

CAUSES OF ASTHMA

Introduction to various aggravations and substances that trigger sensitivities (allergens) can trigger signs and signs of asthma. Asthma triggers are special in connection to the individual to individual and can include:

- Airborne substances, for instance, dust, clean vermin, form spores, pet dander or particles of cockroach waste
- Respiratory sicknesses, for example, the basic icy
- Physical development (work out initiated asthma)
- Cold air, Air poisons, and aggravations, for example, smoke
- Certain drugs, including beta blockers, headache medicine, ibuprofen and naproxen.
- Strong feelings and stress
- Preservatives added to a couple sorts of nourishments and drinks, including shrimp, dried organic product, handled potatoes, brew and wine
- Gastroesophageal reflux malady (GERD), a condition in which stomach acids go down into your throat [11].

SIGN AND SYMPTOMS:

- Recurrent scenes of wheezing
- Troublesome hack amid the night
- Cough or wheeze after exercise
- Cough, wheeze or trunk snugness after presentation to airborne allergens or poisons
- Colds "go to the trunk" or take over 10 days to clear [12].

DIAGNOSIS:

Diagnosing asthma in adults: There is no single solid test and no institutionalized indicative criteria for asthma. In a few patients, watching a reaction to treatment may help affirm the finding, yet absence of reaction to bronchodilators or to breathed in corticosteroids does not preclude asthma.

The analysis of asthma in grown-ups depends on:

- History
- Physical examination
- Considering other diagnoses
- Documenting variable airflow limitation.

Diagnosis of Asthma in Children:

The clinical finding of asthma in kids includes the thought of:

- History of repetitive or determined wheeze
- Presence of hypersensitivities or family history of asthma and sensitivities
- Absence of physical discoveries that recommend an option conclusion
- Tests that bolster the finding
- A reliable clinical reaction to a breathed in bronchodilator or preventer.

It can be hard to determine asthma to have assurance in kids matured 0–5 years, in light of the fact that:

- Episodic respiratory side effects, for example, wheezing and hack are extremely regular in kids, especially in youngsters under 3 years
- Objective lung work testing by spirometry is normally not plausible in this age gathering
- A high extent of youngsters who react to bronchodilator treatment don't go ahead to have asthma in later youth [13,14].

MANAGEMENT & PHARMACOTHERAPY OF ASTHMA:

There are vast number of synthetic, semi synthetic and antibodies are accessible to control asthma. Asthma is a ceaseless sickness and it must be controlled, yet unrealistic to cure it totally. The medications or antiasthma tic operators are utilized to enhance the prosperity of patients. The different hostile to asthmatic medications are outlined beneath.

Table-1. Classification of drug used in asthma

Drug	Example	Possible Mechanism of action
Beta-2 sympathomimetic	Salbutamol, Terbutaline, Salmeterol	Dilate the bronchial smooth muscle
Methylxanthines	Theophylline, Aminophylline	Dilate the bronchial smooth muscle
Anti cholinergic	Ipratropium bromide, Tiotropium Bromide	Dilate the bronchial smooth muscle
Leukotriene antagonist	Montelukast	Antagonise the <i>cysLT₁</i> receptor mediated bronchoconstriction
Mast cell stabilizer	Sodium cromoglicate	Inhibit degranulation of mast cell.
Steroids	Systemic- Hydrocortisone Inhalational- Beclomethasone Budesonide	Reduce the bronchial hypersensitivity
Anti-IgE antibody	Omalizumab	Neutralize the free IgE in blood.

APPROCHES TO TREATMENT:

- Prevention of AG:AB reaction
- Neutralization of IgE- Omalizumab
- Suppression of inflammation and bronchial Hypersensitivity- Steroids
- Prevention of release of release mediators- mast cell stabilizer
- Antagonism of released mediator- Leukotriene antagonist
- Blockade of constrictor neurotransmitter- sympathomimetics
- Directly acting bronchodilator- Methyl xanthines [16]

Table 2: Antiasthmatic plants and their mechanism of action [17].

Plant	Part used	Extract/Active principle	Probable mechanism of action
<i>A. aspera</i>	Roots	Oily preparation	Decreased ESR, Decreased total Eosinophil count.
<i>A. vasica</i>	Leaves Roots	Alkaloids	Bronchodilator, Anti- anaphylactic
<i>A. lebbec</i>	Stem bark	Aqueous. Extract	Mast cell stabilizing activity
<i>B. serrata</i>	Root	Boswellin, boswellic acids	Inhibit LT biosynthesis and block synthesis of 5-HETE & LTB4
<i>C. gigantea</i> , <i>C. procera</i>	Flower	α & β calotropeol, β -amyrin, calotropin, giganteol	Bronchodilator, anti-inflammatory
<i>C. deodara</i>	Wood	Himacholol	Mast cell stabilizing activity
<i>C. minima</i>	Whole plant	lactones, flavonoids	Inhibits passive cutaneous anaphylaxis in rats
<i>C. serratum</i>	Leaves	Aqueous extract.	Bronchodilator
<i>C. longa</i>	Rhizome	Tumerones, curcuminoids	Inhibits histamine release from rat peritoneal mast cells
<i>I. racemosa</i>	Roots	Aqueous, alcoholic extract	Anti-histaminic, Anti-serotonergic
<i>P. kurroa</i>	Roots	Picrorrhizin	Inhibits release of histamine and SRS-A
<i>S. xanthocarpum</i>	Herb	Salasodin	Bronchodilator
<i>S. brevistigma</i>	Twigs	Alkaloid fraction	Inhibits passive cutaneous anaphylaxis in rates
<i>T. purpurea</i>	Whole plant	Ethanollic extract	Bronchodilatory, antianaphylactic
<i>T. cardoifofia</i>	Stem	Aqueous extract.	Mast cell stabilizing activity
<i>T. indica</i>	Whole plant	Indolizidine alkaloid.	Bronchodilatory, membrane stabilizing
<i>V. negundo</i>	Leaves	Alcoholic extract	Bronchodilatory, membrane stabilizing

Management of asthma in adult:

Asthma administration in grown-ups depends on:

- Confirming the analysis
 - Assessing asthma control (late asthma indication control and hazard elements).
 - Identifying administration objectives in a joint effort with the patient .
 - Choosing introductory treatment fitting to late asthma manifestation control, hazard components and patient inclination .
 - Reviewing and changing medication treatment intermittently .
- Providing data, abilities and apparatuses for self-administration, including:
 - Training in right inhaler method .
 - Information and support to boost adherence .
 - A composed asthma activity arrange .
 - Information about maintaining a strategic distance from triggers, where suitable.
 - Managing flare-ups when they happen.
 - Managing comorbid conditions that influence asthma or add to respiratory indications.
 - Providing counsel about smoking, good dieting, physical action, solid weight and inoculation [18].

Table -3. Guide to selecting and adjusting asthma medication for adults and older adolescents [23]

Clinical situation	Action
Newly diagnosed asthma	Consider low-dose ICS (plus SABA as needed) If symptoms severe at initial presentation, consider one of: <ul style="list-style-type: none"> • ICS plus a short course of oral corticosteroids • a short initial period of high-dose ICS then step down • (private prescription) combination ICS/LABA†
Good recent asthma symptom control	If maintained 2–3 months, no flare-up in previous 12 months and low risk for flare-ups, step down where possible (unless already on low-dose ICS).
Partial recent asthma symptom control	Review inhaler technique and adherence – correct if suboptimal If no improvement, consider increasing treatment by one step and reviewing (if still no improvement, return to previous step, review diagnosis and consider referral)
Poor recent asthma symptom control	Review inhaler technique and adherence – correct if suboptimal Confirm that symptoms are likely to be due to asthma Consider increasing treatment until good asthma control is achieved, then step down again when possible
Difficult-to-treat asthma	Consider referral for assessment or add-on options
Patient with risk factors	Tailor treatment to reduce individual risk factors

Table -4. Options for adjusting medicines in a written asthma action plan for adults [23].

Usual treatment		Options for adjustments when asthma worsening	
		Option	Option 2
Any treatment		Increase reliever as needed in response to symptoms	N/A
Short-acting beta2 agonist reliever only (no preventer)		If symptoms continue to worsen, start short course prednisone	Start regular ICS-containing preventer treatment, and continue for at least 2–4 weeks
ICS-only preventer		Increase dose early for 7–14 days	Start short course prednisone in addition to usual dose of ICS
ICS/LABA combination	Budesonide/formoterol maintenance-and-reliever regimen	Take extra doses of budesonide/formoterol as needed to relieve symptoms No more than 6 actuations at one time	Start short course in addition to usual budesonide/formoterol regimen
	Budesonide/formoterol regimen	Increase dose of budesonide/formoterol up to a maximum of 72 mcg formoterol daily for 7–14 days	Start short course prednisone in addition to usual dose of budesonide/formoterol
	Fluticasone furoate/vilanterol	If using medium dose (100/25 mcg): Replace with highest strength formulation of same medicine (fluticasone furoate/vilanterol 200/25 mcg one inhalation once daily) for 7–14 days	Start short course prednisone in addition to usual dose of fluticasone furoate/vilanterol
	Fluticasone propionate/formoterol	If using 50/5 mcg: Replace with highest strength formulation of same medicine for 7–14 days If using 125/5 mcg: Increase dose for 7–14 days If using 250/10 mcg: Increase ICS dose by adding a separate fluticasone propionate inhaler for 7–14 days	Start short course prednisone in addition to usual dose of fluticasone propionate/formoterol
	Fluticasone propionate/salmeterol	Increase ICS dose by adding a separate fluticasone propionate inhaler for 7–14 days Increase fluticasone propionate/salmeterol if necessary to achieve total daily dose of salmeterol 100 mcg	Start short course in addition to usual dose of fluticasone propionate/salmeterol

MANAGING ASTHMA IN CHILDREN:

The administration of asthma and wheezing issue in youngsters depends on:

- Confirming the finding
- Assessing the example of side effects (counting recurrence of scenes and example of indications between scenes)
- Assessing triggers
- Discussing the objectives of administration with the youngster's folks and the kid • picking beginning treatment in light of the kid's age and example of side effects
- Reviewing and modifying treatment intermittently in view of late asthma side effect control and hazard components
- Managing comorbid conditions that influence asthma (e.g. unfavorably susceptible rhinitis)
- Providing guardians and youngsters with data and abilities to deal with their asthma, including:
 - A composed asthma activity arrange
 - Information about staying away from triggers, where suitable
 - Training in right utilization of solutions, including inhaler procedure
 - Information and support to amplify adherence
 - Managing flare-ups when they happen

- Providing counsel about evasion of tobacco smoke, adhering to a good diet, physical movement, sound weight and inoculation.

In kids, beginning treatment in the wake of making the determination of asthma is guided by the example and seriousness of asthma side effects. The points of asthma administration are to guarantee that the kid's asthma has been effectively analyzed, and to empower the youngster to keep up a typical personal satisfaction without impedance from asthma or the symptoms of asthma treatment.

For kids officially taking customary preventer treatment, acclimations to the treatment regimen depend on finding the least measurements of solutions that will keep up great control of side effects and avert flare-ups [24].

INHALER DEVICES AND TECHNIQUE:

There are three main types of inhalers for asthma medicines:

- Standard pressurised metered-dose inhalers
- Breath-activated pressurised metered-dose inhalers
- Dry powder inhalers [25]

Table- 5: Treatment for children [23].

Age	Pattern of symptoms	Management options and notes
0–12 months	Intermittent asthma OR Viral-induced wheeze	Regular preventer treatment is not recommended
	Multiple-trigger wheeze	Refer for specialist assessment or obtain specialist advice before prescribing
1–2 years	Intermittent asthma OR Viral-induced wheeze	Regular preventer treatment is not recommended
	Persistent asthma OR Multiple-trigger wheeze	Consider a treatment trial with sodium cromoglycate 10 mg three times daily and review response in 2–4 weeks† Consider a treatment trial of low-dose inhaled corticosteroids only if wheezing symptoms are disrupting child’s sleeping or play; review response in 4 weeks
2–5 years	Infrequent intermittent asthma OR Viral-induced wheeze	Regular preventer treatment is not recommended
	Frequent intermittent asthma OR Mild persistent asthma OR Episodic (viral) wheeze with frequent symptoms OR Multiple-trigger wheeze	Consider regular treatment with montelukast 4 mg once daily and review response in 2–4 weeks If symptoms do not respond, consider regular treatment with a low dose of an inhaled corticosteroid and review response in 4 weeks
	Moderate–severe persistent asthma OR Moderate–severe multiple-trigger wheeze	Consider regular treatment with a low dose of an inhaled corticosteroid and review response in 4 weeks

Table -6. Types of inhaler devices for delivering asthma medicines [23].

Design type	Brand name	Common medicines used with this type of inhaler
Standard pMDI	Generic inhaler used alone or with a spacer	Relievers Airomir (salbutamol) Symbicort (budesonide plus formoterol) via Rapihaler when used in a maintenance-and-reliever regimen
		Preventers Alvesco (ciclesonide) Flixotide (fluticasone propionate) Flutiform (fluticasone propionate plus formoterol) Intal (sodium cromoglycate)
Breath-activated pMDI	Autohaler	Relievers Airomir (salbutamol) Preventers Qvar (beclomethasone)
Dry-powder inhaler (capsule)	Aerolizer	Other Foradile (formoterol)
Dry-powder inhaler (breath-actuated)	Accuhaler	Preventers Flixotide (fluticasone) Seretide (salmeterol plus fluticasone)
		Other Serevent (salmeterol)
	Ellipta	Preventers Breo (fluticasone furoate plus vilanterol)
	Turbuhaler	Relievers Bricanyl (terbutaline sulfate) Symbicort (budesonide plus formoterol) when used in a maintenance- and-reliever regimen
Preventers Pulmicort (budesonide) Symbicort (budesonide plus formoterol)		

CONCLUSION:

Asthma is a malady of the aviation routes, described by aggravation and related with aviation route hyper-responsiveness, which can bring about scenes of shortness of breath, trunk snugness, wheezing and hack. Hereditary elements, natural impacts and particular trigger variables are involved in the advancement of the illness. A careful clinical history and target estimation of lung capacity are essential in setting up a sensibly certain finding of asthma. A scope of medications is utilized as a part of the administration of the sickness, and clinical rules advocate a stepwise way to deal with medication treatment, where treatment is ventured up when required and ventured down when control is great. Close by pharmacological administration of the malady, organization working amongst patients and social insurance experts, customized composed asthma activity arrangements, data and training are vital to enhancing the personal satisfaction of patients with asthma.

Asthma is the most widely recognized respiratory issue and it adds to critical horribleness and mortality. A determination of asthma ought to be suspected in patients with repetitive hack, wheeze, trunk snugness and dyspnea, and ought to be affirmed utilizing target measures of lung capacity (spirometry favored). Hypersensitivity testing is additionally prescribed to distinguish conceivable triggers of asthma indications. In many patients, asthma control can be accomplished using shirking measures and fitting pharmacological intercessions. ICSs speak to the standard of tend to the greater part of asthma patients. For the individuals who neglect to accomplish control with low-to-direct ICS measurements, blend treatment with a LABA and ICS is the favored treatment decision in many grown-ups. LTRAs can likewise be utilized as extra treatment if asthma is uncontrolled in spite of the utilization of low-to-direct measurements ICS treatment, especially in patients with simultaneous unfavorably susceptible rhinitis. Against IgE treatment might be helpful in select instances of hard to control asthma. Allergen-particular immunotherapy is a possibly sickness adjusting treatment, yet ought to just be recommended by doctors with proper preparing in sensitivity. All patients with asthma ought to have customary follow-up visits amid which criteria for asthma control, adherence to treatment and legitimate inhaler strategy ought to be audited

REFERENCES:

1. Global Initiative for Asthma (GINA): Global strategy for asthma management and prevention. 2009, Available at: <http://www.ginasthma.com> Accessed April 15, 2017.
2. Barnes PJ, Woolcock AJ. Difficult asthma. *Eur Respir J* 1998; 12:1209-11.
3. Barnes PJ, Pedersen S, Busse WW. Efficacy and safety of inhaled corticosteroids. *Am J Respir Crit Care Med* 1998; 157:51-7.
4. Pedersen SE, Hurd SS, Lemanske RF Jr, Becker A, Zar HJ, Sly PD, Soto-Quiroz M, Wong G, Bateman ED. Global strategy for the diagnosis and management of asthma in children 5 years and younger. *Pediatr Pulmonol* 2011;46: 1-17.
5. Reddel HK, Hurd SS, FitzGerald JM. World Asthma Day, GINA 2014: a global asthma strategy for a global problem. *Int J Tuberc Lung Dis* 2014;18:505-6.
6. DeFrances CJ, Lucas CA, Buie VC, Golosinskiy A. 2006 National Hospital Discharge Survey. National Health Statistics Reports No. 5, July 30, 2008
7. Becker AB, Nelson NA, Simons FE. The pulmonary index: assessment of a clinical score for asthma. *Am J Dis Child*.1984;138:574-6.
8. Busse W, Corren J, Lanier BQ, McAlary M, Fowler-Taylor A, Cioppa GD, van As A, Gupta N. Omalizumab, anti-IgE recombinant humanized monoclonal antibody, for the treatment of severe allergic asthma. *J Allergy Clin Immunol*. 2001;108(2):184-90.
9. Barnes PJ. Pathophysiology of asthma. *Br. J. Clin. Pharmacol*. 1996. 42, 1, 3-10
10. Rees J, Kanabar D, Pattani S. ABC of Asthma. Sixth Edition, John Wiley & Sons, Chichester, 1-54.
11. Diseases and Conditions, Asthma. Available at <http://www.mayoclinic.org/diseases-conditions/asthma/basics/risk-factors/con-20026992>. Accessed April 21, 2017.
12. Eder W, Ege MJ, Von M. E. The asthma epidemic. *N Engl J Med*. 2006;355(21):2226-35.
13. Respiratory Expert Group, Therapeutic Guidelines Limited. Therapeutic Guidelines: Respiratory, Version 4. Therapeutic Guidelines Limited, Melbourne, 2009.
14. British Thoracic Society (BTS) Scottish Intercollegiate Guidelines Network (SIGN). British Guideline on the Management of Asthma. A national clinical guideline. BTS, SIGN, Edinburgh; 2012.
15. Weinberger M, Abu-Hasan M. Pseudo-asthma: when cough, wheezing, and dyspnea are not asthma. *Pediatrics*, 2007; 120: 855-64.
16. Trpathi KD. Essentials of Medical Pharmacology. 6th ed. Jaypee brothers medical publishers; 2006. P. 213-30
17. ISMAIL M.Y.M . Antiasthmatic herbal drugs - a review. *Int J Pharmacy Pharm Sci* 2010; 2(3): 28-30
18. Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention. GINA; 2012. Available from: <http://www.ginasthma.org/>. Accessed April 21, 2017.
19. Camargo CA, Rachelefsky G, Schatz M. Managing asthma exacerbations in the emergency department: summary of the National Asthma Education And Prevention Program Expert Panel Report 3 guidelines for the management of asthma exacerbations. *Proc Am Thorac Soc* 2009 ; 6 : 357 - 66.Available from: <http://www.atsjournals.org/doi/full/10.1513/pats.P09ST2> Accessed April 21, 2017.
20. Goeman DP, Abramson MJ, McCarthy EA et al. Asthma mortality in Australia in the 21st century: a case series analysis. *BMJ Open* 2013; 3: e002539. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3657652> Accessed April 21, 2017.
21. Osborne ML, Pedula KL, O'Hollaren M et al. Assessing future need for acute care in adult asthmatics: the profile of asthma risk study: a prospective health maintenance organization-based study. *Chest* 2007; 132: 1151-61. Available from: <http://chestjournal.chestpubs.org/content/132/4/1151.long> Accessed April 21, 2017.
22. Thomas M, Kay S, Pike J et al. The Asthma Control Test (ACT) as a predictor of GINA guideline-defined asthma control: analysis of a multinational cross-sectional survey. *Prim Care Respir J* 2009; 18: 41-9. Available from: http://www.thepcrj.org/journ/view_article.php?article_id=615 Accessed April 21, 2017.
23. National Asthma Council Australia. Australian Asthma Handbook – Quick Reference Guide, Version 1.1. National Asthma Council Australia, Melbourne, 2015. Available from: <http://www.astmahandbook.org.au> Accessed April 21, 2017.
24. Global Initiative for Asthma (GINA), Global strategy for the diagnosis and management of asthma in children 5 years and younger. GINA; 2009. Available from: <http://www.ginasthma.org/>. Accessed April 21, 2017.
25. National Asthma Council Australia. Inhaler technique in adults with asthma or COPD. An information paper for health professionals. Melbourne: NAC; 2008. Available from: <http://www.astmahandbook.org.au> Accessed April 21, 2017.