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Drugs for Asthma.................................................................p 11

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INHALATION DEVICES

Inhalation is the preferred route of delivery for most asthma drugs. Chlorofluorocarbons (CFCs), which have ozone-depleting properties, are being phased out as propellants in metered-dose inhalers. Non-chlorinated hydrofluoroalkane (HFA) propellants, which do not deplete the ozone layer, are being used instead.

Metered-dose inhalers (MDIs) require coordination of inhalation with hand-actuation of the device. Valved holding chambers (VHCs) or spacers can help young children or elderly patients use MDIs effectively. VHCs have one-way valves that prevent the patient from exhaling into the device, eliminating the need for coordinated actuation and inhalation. Spacers are open tubes placed on the mouthpiece of an MDI. Both VHCs and spacers retain the large particles emitted from the MDI, preventing their deposition in the oropharynx and leading to a higher proportion of small respirable particles being inhaled.

Dry powder inhalers (DPIs), which are breath-actuated, can be used in patients who are capable of performing a rapid deep inhalation.

Delivery of inhaled asthma medications through a nebulizer with a face mask or mouthpiece is less dependent on the patient’s coordination and cooperation, but more time-consuming than delivery through an MDI or DPI.

SHORT-ACTING BETA-2 AGONISTS

Inhaled short-acting beta-2 agonists (SABAs), such as albuterol, are used for rapid relief of asthma symptoms. Their onset of action occurs within 5 minutes; their peak effect occurs within 30-60 minutes and they have a duration of action of 4-6 hours. SABAs do not decrease the inflammation of the airways that occurs in asthma. They should only be used as needed for relief of symptoms or for prevention of exercise-induced bronchoconstriction (EIB). In patients whose asthma is under control, SABAs should be needed infrequently (<2 days/week).

Adverse Effects – Inhaled SABAs can cause tachycardia, QTc interval prolongation, tremor, anxiety, hyperglycemia, hypokalemia and hypomagnesemia, especially if used in high doses. Tolerance (some loss of effectiveness) can occur with daily use.

RECOMMENDATIONS: Use of a short-acting bronchodilator as needed for relief of symptoms may be sufficient for asthma patients whose symptoms are infrequent, mild and transient. In patients with more frequent or more severe cough, wheeze, chest tightness or shortness of breath, regular use of a controller medication is recommended. Low daily doses of an inhaled corticosteroid suppress airway inflammation and reduce the risk of exacerbations. Higher inhaled corticosteroid doses may be needed in patients with more severe disease. In patients who remain symptomatic despite compliance with inhaled corticosteroid treatment and good inhalational technique, addition of a long-acting beta-2 agonist is recommended. In patients ≥12 years old with uncontrolled allergic asthma, omalizumab can be added. For patients of any age with allergic asthma, allergen immunotherapy may provide long-lasting benefits.

Failure of pharmacologic treatment can usually be attributed to lack of adherence to prescribed medications, uncontrolled co-morbid conditions, or continued exposure to tobacco smoke or other airborne pollutants, allergens or irritants.
CORTICOSTEROIDS

Inhaled – In all age groups with persistent asthma, whether it is mild, moderate or severe, inhaled corticosteroids (ICSs) are the most effective long-term treatment for control of symptoms. In randomized controlled trials, they have been significantly more effective than long-acting beta-2 agonists, leukotriene modifiers, cromolyn or theophylline in improving pulmonary function, preventing symptoms and exacerbations, reducing the need for emergency department treatment, and decreasing deaths due to asthma. ICSs are most effective when used daily, and their efficacy does not persist after they are stopped.

Most of the beneficial effects of ICSs are achieved at relatively low doses. The ideal dose for a given patient is the lowest dose that maintains asthma control; this dose may change seasonally and over time. Current evidence suggests that, at usual doses, all ICSs are similar in efficacy and safety; they are not interchangeable on a per-microgram or per-puff basis because the dose varies with the drug, the formulation and the delivery device.

Adverse Effects – Local adverse effects of ICSs may include oral candidiasis (thrush), dysphonia, and reflex cough and bronchospasm. Their incidence can be reduced by use of a valved holding chamber (VHC) or a spacer, and by mouth-rinsing after inhalation.

Clinically relevant adverse effects on hypothalamic-pituitary-adrenal (HPA) axis function generally do not occur with low- or medium-dose ICSs. Regular administration of low- or medium-dose ICSs may reduce growth velocity slightly during the first year of treatment, but final adult height does not appear to be affected. Patients who require high-dose ICS treatment should be monitored for HPA axis suppression, changes in bone density, and development of cataracts or glaucoma. ICSs do not increase the risk of pneumonia in patients with asthma.

Oral – Oral systemic glucocorticoids are the most effective drugs available for exacerbations of asthma incompletely responsive to bronchodilators. Even when an acute exacerbation responds to bronchodilators, addition of a short course of an oral glucocorticoid can decrease symptoms and may prevent a relapse. For asthma exacerbations, daily systemic glucocorticoids are generally required for only 3-10 days, after which no tapering is needed.

Oral glucocorticoids should only rarely be used as long-term control medications and then only in that small minority of patients with uncontrolled severe persistent asthma. In this situation, an oral glucocorticoid should be given at the lowest effective dose, preferably on alternate mornings, in order to produce the least toxicity.

LONG-ACTING BETA-2 AGONISTS

Monotherapy with an inhaled long-acting beta-2 agonist (LABA), such as salmeterol or formoterol, is not recommended. If a LABA is required, it should be used in combination with an ICS, preferably in the same inhaler. The combination inhalers salmeterol/fluticasone (Advair), formoterol/budesonide (Symbicort) and formoterol/mometasone (Dulera) are FDA-approved for use in patients with persistent asthma that is not well-controlled on an ICS alone. The addition of a LABA improves lung function, decreases symptoms and exacerbations, and reduces rescue use of short-acting beta-2 agonists.

Adverse Effects – LABAs, especially if used in higher-than-recommended doses, can cause tremor, muscle cramps, tachycardia and other cardiac effects. Tolerance (some loss of efficacy) can occur with daily use of a LABA.

An FDA meta-analysis found that use of a LABA was associated with an increased risk of asthma-related hospitalization, intubation and death; the greatest risk was in children 4-11 years old. These results prompted the FDA to recommend that LABAs be discontinued once asthma is controlled. A secondary analysis of the original meta-analysis did not find a significant increase in risk in a subset of patients who were assigned to use an ICS with a LABA. The manufacturers of LABAs are conducting post-marketing trials to assess the safety of a LABA-ICS combination compared to that of an ICS alone.

LEUKOTRIENE MODIFIERS

Leukotriene modifiers are less-effective alternatives to low-dose ICS treatment for patients who are unable or unwilling to use an ICS. They are also generally less effective than an inhaled LABA as add-on therapy for patients not well controlled on an ICS alone. In one small study, some children with asthma uncontrolled on an ICS demonstrated a better response to step-up treatment with a leukotriene modifier than with a LABA.

Adverse Effects – Montelukast is considered safe for long-term use. Both zafirlukast and (especially) zileuton have been reported to cause life-threatening hepatic injury; liver function tests should be monitored and patients should be warned to discontinue the med-
ication immediately if abdominal pain, nausea, jaun-
dice, itching or lethargy occur. Rarely, Churg-Strauss
vasculitis has been reported with montelukast and zafir-
lukast; in most cases, this was likely a consequence of
corticosteroid withdrawal rather than a direct effect of
the drug.13 The FDA has received post-marketing
reports of psychiatric symptoms, including suicidality,
with leukotriene modifiers.

ANTICHOLINERGICS

Ipratropium bromide is an inhaled short-acting anti-
cholinergic bronchodilator FDA-approved to treat
chronic obstructive pulmonary disease (COPD). In
asthma, it is used off-label as an alternative reliever
medication in patients who cannot take a short-acting
beta-2 agonist.4 Tiotropium bromide, an inhaled long-
acting anticholinergic bronchodilator, is also approved
only for use in COPD. In patients with asthma uncon-
trolled on an ICS, addition of tiotropium has been as
effective as adding the LABA salmeterol in improving
lung function and symptoms.14 In one study, addition
of tiotropium to combination treatment with an ICS
and a LABA improved lung function in patients with
poorly controlled severe asthma.15

Adverse effects of anticholinergics include dry mouth,
pharyngeal irritation, increased intraocular pressure and
urinary retention. They should be used with caution in
patients with glaucoma, prostatic hypertrophy or blad-
der neck obstruction.

THEOPHYLLINE

Theophylline, taken alone or concurrently with an
ICS, is now used infrequently for persistent asthma.
Monitoring serum theophylline concentrations is rec-
commended to maintain peak levels between 10 and
15 mcg/mL.

Adverse effects of theophylline include nausea, vom-
iting, nervousness, headache and insomnia. At high
serum concentrations, hypokalemia, hyperglycemia,
tachycardia, cardiac arrhythmias, tremor, neuromuscu-
lar irritability, seizures and death can occur. Many
other drugs used concomitantly can interact with theo-
phylline, either by increasing its metabolism and
decreasing its serum concentrations and efficacy, or by
decreasing its metabolism, leading to higher concen-
trations and toxicity.

ANTI-IgE ANTIBODY (OMALIZUMAB)

Omalizumab (Xolair) is a recombinant humanized
monoclonal antibody that prevents IgE from binding to
mast cells and basophils, thereby preventing release of
inflammatory mediators after allergen exposure. It is
FDA-approved for use in patients ≥12 years old with
moderate to severe persistent asthma not well con-
trolled on an ICS who have well-documented specific
sensitization to a perennial airborne allergen, such as
mold or animal dander.

Subcutaneous injection of omalizumab every 2 or 4
weeks reduces asthma exacerbations and has a modest
ICS-sparing effect. In adults and adolescents, when
added to standard treatment, omalizumab improved
symptoms and reduced exacerbations.16,17 When added
to standard treatment in children with allergic asthma,
omalizumab improved asthma control, decreased exac-
erbations and reduced maintenance ICS doses.18 Use of
omalizumab does not preclude simultaneous use of
allergen immunotherapy.

Adverse Effects – Injection-site pain and bruising
occur in up to 20% of patients. Anaphylaxis has
occurred, but the incidence is extremely low (0.2% of
patients). A national task force monitoring these rare
cases of anaphylaxis continues to advise keeping
patients under observation for 2 hours after the first
two omalizumab injections, and for 30 minutes
after subsequent injections. Additionally, patients
receiving omalizumab should be instructed on how to

<table>
<thead>
<tr>
<th>Table 1. Treatment of Asthma</th>
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<tbody>
<tr>
<td><strong>Asthma Severity</strong></td>
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<tr>
<td></td>
</tr>
<tr>
<td>Mild Intermittent</td>
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<tr>
<td>Mild Persistent</td>
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<tr>
<td>Preferred</td>
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<tr>
<td>Alternatives</td>
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<tr>
<td>Moderate Persistent</td>
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<tr>
<td>Preferred</td>
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<tr>
<td>Alternatives</td>
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<tr>
<td>Severe Persistent</td>
</tr>
<tr>
<td>Preferred</td>
</tr>
<tr>
<td>Alternatives</td>
</tr>
</tbody>
</table>

SABA = inhaled short-acting beta-2 agonist; ICS = inhaled corticosteroid;
LABA = inhaled long-acting beta-2 agonist
1. For patients ≥12 years old. Treatment should be adjusted based on
   response.
2. The ideal dose of an ICS is the lowest dose that maintains asthma control.
3. The FDA recommends stopping a LABA once symptoms are controlled.
4. In patients who remain uncontrolled despite aggressive treatment with a
   high-dose ICS plus a LABA, oral glucocorticoids are sometimes added.

Addition of omalizumab can be considered in patients with allergic asthma.

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   response.
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4. In patients who remain uncontrolled despite aggressive treatment with a
   high-dose ICS plus a LABA, oral glucocorticoids are sometimes added.

Addition of omalizumab can be considered in patients with allergic asthma.
### Drugs for Asthma

#### Inhaled Beta-2 Agonists, Short-Acting

<table>
<thead>
<tr>
<th>Drug</th>
<th>Some Available Formulations</th>
<th>Adult Dosage</th>
<th>Pediatric Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Albuterol – generic</strong>&lt;br&gt;single-dose vials</td>
<td>0.63, 1.25, 2.5 mg/3 mL</td>
<td>1.25-5 mg q4-8h PRN</td>
<td>2-4 yrs: 0.63-2.5 mg q4-6h PRN</td>
</tr>
<tr>
<td>multi-dose vials</td>
<td>100 mg/20 mL</td>
<td></td>
<td>5-11 yrs: 1.25-5 mg q4-8h PRN</td>
</tr>
<tr>
<td><strong>AccuNeb (Dey)</strong>&lt;br&gt;single-dose vials</td>
<td>0.63, 1.25 mg/3 mL</td>
<td></td>
<td>2-12 yrs: 0.63 or 1.25 mg tdd-qid PRN</td>
</tr>
<tr>
<td><strong>ProAir HFA (Teva)</strong>&lt;br&gt;Proventil HFA (Schering)&lt;br&gt;Ventonil HFA (GSK)</td>
<td>HFA MDI (200 inh/unit)&lt;br&gt;90 mcg/inhalation</td>
<td>90-180 mcg q4-6h PRN</td>
<td>≥4 yrs: 90-180 mcg q4-6h PRN</td>
</tr>
<tr>
<td><strong>Levalbuterol – generic</strong>&lt;br&gt;Xopenex (Sepracor)</td>
<td>Solution for nebulization&lt;br&gt;0.31, 0.63, 1.25 mg/3 mL</td>
<td>0.63-1.25 mg q6-8h PRN</td>
<td>6-11 yrs: 0.31-0.63 mg tid q6-8h PRN</td>
</tr>
<tr>
<td></td>
<td></td>
<td>tid q6-8h PRN</td>
<td>≥12 yrs: 0.63-1.25 mg tid q6-8h PRN</td>
</tr>
<tr>
<td><strong>Proventil HFA (Schering)</strong></td>
<td>90 mcg q6-8h PRN</td>
<td></td>
<td>≥4 yrs: 90 mcg q4-6h PRN</td>
</tr>
<tr>
<td><strong>Ventolin HFA (GSK)</strong></td>
<td>200 mcg q6-8h PRN</td>
<td></td>
<td>12 yrs: 200-400 mcg q4-6h PRN</td>
</tr>
</tbody>
</table>

#### Inhaled Corticosteroids

<table>
<thead>
<tr>
<th>Drug</th>
<th>Some Available Formulations</th>
<th>Adult Dosage</th>
<th>Pediatric Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Beclomethasone dipropionate – QVAR (Teva)</strong>&lt;br&gt;HFA MDI (100 inh/unit)</td>
<td>40-320 mcg bid&lt;sup&gt;3&lt;/sup&gt;</td>
<td>5-11 yrs: 40-80 mcg bid&lt;sup&gt;3&lt;/sup&gt;</td>
<td></td>
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<tr>
<td></td>
<td>40, 80 mcg/inhalation</td>
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<tr>
<td><strong>Budesonide – Pulmicort Flexhaler</strong>&lt;br&gt;(AstraZeneca)&lt;br&gt;Pulmicort Turbuhaler</td>
<td>DPI (60, 120 inh/unit)&lt;br&gt;90, 180 mcg/inhalation</td>
<td>360-720 mcg bid</td>
<td>6-17 yrs: 180-360 mcg bid</td>
</tr>
<tr>
<td></td>
<td>DPI (200 inh/unit)&lt;br&gt;200 mcg/inhalation</td>
<td>200-800 mcg bid&lt;sup&gt;3&lt;/sup&gt;</td>
<td>≥6 yrs: 200-400 mcg bid&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Ciclesonide – Alvesco</strong>&lt;br&gt;(Nycomed)&lt;br&gt;Pulmicort RESPULES (AstraZeneca)</td>
<td>HFA MDI (60 inh/unit)&lt;br&gt;0.25, 0.5 mg/2 mL</td>
<td>0.25, 0.5 mg, 1 mg/2 mL</td>
<td>1-8 yrs: 0.25-0.5 mg once/d or bid or 1 mg once/d&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Fluticasone propionate – Flovent Diskus</strong>&lt;br&gt;(GSK)&lt;br&gt;Flovent HFA (GSK)&lt;br&gt;Mometasone furoate – Asmanex Twisthaler**&lt;br&gt;(Schering-Plough)&lt;br&gt;Asmanex Pressair (Schering-Plough)&lt;br&gt;Ciclesonide – Alvesco**&lt;br&gt;Alvesco HFA (AstraZeneca)</td>
<td>DPI (60 inh/unit)&lt;br&gt;50, 100, 250 mcg/blister</td>
<td>100-1000 mcg bid&lt;sup&gt;3&lt;/sup&gt;</td>
<td>4-11 yrs: 50-100 mcg bid&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>HFA MDI (120 inh/unit)&lt;br&gt;44, 110, 220 mcg/inhalation</td>
<td>88-880 mcg bid&lt;sup&gt;3&lt;/sup&gt;</td>
<td>4-11 yrs: 88 mcg bid</td>
</tr>
<tr>
<td></td>
<td>DPI (30, 60, 120 inh/unit)&lt;br&gt;110, 220 mcg/inhalation</td>
<td>220-440 mcg 1x/day in evening or 220 mcg bid</td>
<td>4-11 yrs: 110 mcg 1x/d in evening</td>
</tr>
</tbody>
</table>

#### Oral Glucocorticoids

<table>
<thead>
<tr>
<th>Drug</th>
<th>Some Available Formulations</th>
<th>Adult Dosage</th>
<th>Pediatric Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Methylprednisolone – generic</strong>&lt;br&gt;Medrol (Pfizer)</td>
<td>4, 8, 16, 32 mg tabs</td>
<td>5-60 mg once/d or every other day</td>
<td>0-11 yrs: 0.25-2 mg/kg once/d or every other day (max 60 mg/d)</td>
</tr>
<tr>
<td><strong>Prednisolone – generic</strong>&lt;br&gt;Prelox (Teva)</td>
<td>5, 15 mg/5 mL syrup</td>
<td></td>
<td>1-2 mg/kg x 3-10 days for an acute exacerbation (max 60 mg/d)</td>
</tr>
<tr>
<td></td>
<td>15 mg/5 mL syrup</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>OraPrad (Shionogi)</strong>&lt;br&gt;OraPrad OD&lt;br&gt;PediaPrad (UCB)</td>
<td>15 mg/5 mL PO solution</td>
<td>40-60 mg once/d or divided bid x 3-10 days for an acute exacerbation</td>
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<tr>
<td></td>
<td>10, 15, 30 mg disintegrating tabs</td>
<td></td>
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<tr>
<td></td>
<td>5 mg/5 mL PO solution</td>
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<td></td>
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<tr>
<td><strong>Prednisone – generic</strong>&lt;br&gt;Prednisone</td>
<td>1, 2.5, 5, 10, 20, 50 mg tabs; 5 mg/5 mL PO solution</td>
<td></td>
<td>1-2 mg/kg x 3-10 days for an acute exacerbation</td>
</tr>
</tbody>
</table>

CFC = Chlorofluorocarbon; DPI = Dry powder inhaler; HFA = Hydrofluoroalkane; MDI = Metered-dose inhaler

1. Nebulized solutions may be more convenient for very young, very old and other patients unable to use pressurized aerosols. More time is required to administer the drug, however, and the device is usually not portable.

2. CFC-containing MDIs will not be marketed after December 2013.

3. Dose is based on prior asthma therapy. See package insert for specific dosing instructions.

4. Only approved for use in children 1-8 years old.
**Inhaled Beta-2 Agonists, Long-Acting**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Some Available Formulations</th>
<th>Adult Dosage</th>
<th>Pediatric Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salmeterol – Serevent Diskus (GSK)</td>
<td>DPI (60 inh/unit) 50 mcg bid</td>
<td>4 yrs: 50 mcg bid</td>
<td></td>
</tr>
<tr>
<td>Formoterol – Foradil Aerolizer (Merck)</td>
<td>DPI (60 inh/unit) 12 mcg bid</td>
<td>5 yrs: 12 mcg bid</td>
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</tr>
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**Inhaled Corticosteroid/Long-Acting Beta-2 Agonist Combinations**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Some Available Formulations</th>
<th>Adult Dosage</th>
<th>Pediatric Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluticasone/salmeterol – Advair Diskus (GSK)</td>
<td>DPI (60 inh/unit) 100, 250, 500 mcg/50 mcg per blister</td>
<td>1 inhalation bid</td>
<td>4-11 yrs: 1 inhalation (100/50 mcg) bid</td>
</tr>
<tr>
<td>Advair HFA (GSK)</td>
<td>HFA MDI (60, 120 inh/unit) 45, 115, 230 mcg/21 mcg per inhalation</td>
<td>2 inhalations bid</td>
<td>≥12 yrs: 1 inhalation bid</td>
</tr>
<tr>
<td>Budesonide/formoterol – Symbicort HFA (AstraZeneca)</td>
<td>HFA MDI (60, 120 inh/unit) 80, 160 mcg/4.5 mcg per inhalation</td>
<td>2 inhalations bid</td>
<td>≥12 yrs: 2 inhalations bid</td>
</tr>
<tr>
<td>Mometasone/formoterol – Dulera (Merck)</td>
<td>HFA MDI (120 inh/unit) 100, 200 mcg/5 mcg per inhalation</td>
<td>2 inhalations bid</td>
<td>≥12 yrs: 2 inhalations bid</td>
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**Leukotriene Modifiers**

<table>
<thead>
<tr>
<th>Drug</th>
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<th>Pediatric Dosage</th>
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</thead>
<tbody>
<tr>
<td>Montelukast – Singulair (Merck)</td>
<td>10 mg tabs, 4, 5 mg chew tabs, 4 mg oral granules</td>
<td>10 mg PO once/d</td>
<td>≥1 yr: 4 or 5 mg PO once/day</td>
</tr>
<tr>
<td>Zafirlukast – generic Accolate (AstraZeneca)</td>
<td>10, 20 mg tabs</td>
<td>20 mg PO bid</td>
<td>5-11 yrs: 10 mg PO bid</td>
</tr>
<tr>
<td>Zileuton – Zyflo (Cornerstone) extended-release Zyflo CR</td>
<td>600 mg tabs</td>
<td>600 mg PO qid</td>
<td>≥12 yrs: 600 mg PO qid</td>
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**Anticholinergics**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Some Available Formulations</th>
<th>Adult Dosage</th>
<th>Pediatric Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipatropium – generic</td>
<td>Solution for nebulization</td>
<td>500 mcg qid PRN</td>
<td>———</td>
</tr>
<tr>
<td>Atrovent HFA (Boehringer Ingelheim)</td>
<td>HFA MDI (200 inh/unit) 17 mcg/inhalation</td>
<td>2 inhalations qid PRN</td>
<td>———</td>
</tr>
<tr>
<td>Tiotropium – Spiriva HandiHaler (Boehringer Ingelheim)</td>
<td>DPI (5, 30, 90 inh/unit) 18 mcg/capsule</td>
<td>18 mcg once/d</td>
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**Anti-IgE Antibody**

<table>
<thead>
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<th>Pediatric Dosage</th>
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</thead>
<tbody>
<tr>
<td>Omalizumab – Xolair (Genentech) Powder for injection 150 mg/5 mL vial</td>
<td>150-300 mg SC q4wks or 225-375 mg SC q2wks</td>
<td>≥12 yrs: 150-300 mg q4wks or 225-375 mg q2wks</td>
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</table>

**Theophylline**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Some Available Formulations</th>
<th>Adult Dosage</th>
<th>Pediatric Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>generic</td>
<td>100, 125, 200, 300 mg ER caps; 400 mg ER tabs; 80 mg/15mL oral elixir</td>
<td>300-600 mg/once day or divided bid</td>
<td>10 mg/kg/d</td>
</tr>
<tr>
<td>Theo-24 (UCB Pharma)</td>
<td>400 mg ER tabs</td>
<td>300-600 mg once/day</td>
<td>———</td>
</tr>
<tr>
<td>Uniphyl (Purdue)</td>
<td>400 mg ER tabs</td>
<td>400-600 mg once/day</td>
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5. Use of a long-acting beta-2 agonist (LABA) alone without concomitant use of a long-term asthma controller medication is contraindicated in the treatment of asthma.
6. Only the 100 mcg/50 mcg formulation is approved for use in children.
7. Montelukast is taken once daily in the evening, with or without food. Montelukast granules must be taken within 15 minutes of opening the packet.
8. Zafirlukast is taken 1 hour before or 2 hours after a meal. Zileuton is taken within one hour after morning and evening meals.
9. Montelukast is approved for prevention of exercise-induced bronchoconstriction only in patients ≥15 years. Dosage for 12-23 months: one packet of 4-mg oral granules; for 2-5 yrs: 4-mg chewable tab once/d or one packet of 4 mg oral granules; for 6-14 yrs: 5-mg chewable tab once/d.
10. Extended-release formulations may not be interchangeable. If Theo-24 is taken <1 hr before a high fat meal, the entire 24-hour dose can be released in a 4-hour period.
11. Starting dose. Usual maximum is 16 mg/kg/day in children >1 year old; in infants 0.2 x (age in weeks) + 5 = dose in mg/kg/day.
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recognize anaphylaxis and told to self-inject epinephrine promptly if it occurs.19

IMMUNOTHERAPY

In selected patients with allergic asthma, specific immunotherapy ("allergy shots") may provide long-lasting benefits in reducing asthma symptoms and the need for medications.20

BRONCHIAL THERMOPLASTY

Approved by the FDA in 2010 for use in adults with severe persistent asthma not well controlled on an ICS and a LABA, bronchial thermoplasty has been shown to modestly improve lung function and asthma symptoms.21 Patients undergo fiberoptic bronchoscopy on 3 separate occasions 3 weeks apart. During the procedure, the walls of the central airways are treated with radiofrequency energy that is converted to heat (target tissue temperature 65°C), resulting in ablation of airway smooth muscle. Adverse effects, mainly worsening of asthma, are common in the weeks immediately following bronchial thermoplasty. A long-term study found that lung function appears to remain stable for at least 5 years following the procedure.22

TREATMENT FAILURE

Failure of pharmacologic treatment can usually be attributed to lack of adherence to prescribed medications, uncontrolled co-morbid conditions or continued exposure to tobacco smoke and other airborne pollutants, allergens or irritants. Smoking and exposure to second-hand smoke can cause airway hyperresponsiveness and decrease the effectiveness of ICSs. Some patients with asthma may concurrently be taking aspirin or other NSAIDs that can cause asthma symptoms. Oral or topical nonselective beta-adrenergic blockers, such as propranolol (Inderal, and others) or timolol, can precipitate bronchospasm in patients with asthma and decrease the bronchodilating effect of beta-2 agonists.

Patients with moderate or severe asthma may benefit from meeting with trained asthma educators to have their inhaler technique checked and develop a personalized asthma management plan.23

MANAGING EXACERBATIONS

Intensifying treatment at home when symptoms begin can prevent exacerbations from becoming severe. Self-management of asthma exacerbations, guided by a written asthma action plan, generally calls for increased doses of a SABA and, sometimes, initiation of a short course of an oral glucocorticoid. Doubling the dose of an ICS is not effective and quadrupling the dose is only marginally effective.24

Treatment of acute asthma in the urgent care setting or emergency department generally involves supplemental oxygen to relieve hypoxemia and a SABA (sometimes in combination with ipratropium), usually administered by face mask and nebulizer. In moderate or severe exacerbations, an oral or intravenous glucocorticoid is added to reduce airway inflammation. Severe asthma exacerbations unresponsive to these measures may respond to intravenous magnesium sulphate, especially in children, or to inhalation of heliox (typically a mixture of helium 79% and oxygen 21%) to decrease airflow resistance and improve delivery of aerosolized medications.25

EXERCISE-INDUCED BRONCHOCONSTRICTION

Exercise-induced bronchoconstriction (EIB) may be the only manifestation of asthma in patients with mild disease. EIB may also be a transient phenomenon in non-asthmatic athletes.26 SABAs used just before exercise will prevent EIB for 2-3 hours after inhalation in most patients. LABAs prevent EIB for up to 12 hours, but if they are taken regularly, the protection may wane and not last throughout the day. Montelukast decreases EIB in up to 50% of patients within 2 hours after administration; the protection may last for up to 24 hours and does not wane with repeated use. In some patients, EIB occurs because of poorly-controlled persistent asthma; in these patients, daily anti-inflammatory medications should be started or increased in dosage.3

ASTHMA IN PREGNANCY

Maternal asthma increases the risk of pregnancy-related complications including pre-eclampsia, perinatal mortality, preterm birth and low birth weight.27 Albuterol is the preferred SABA for use in pregnancy. ICSs (budesonide is the best studied) are the preferred long-term controller medications in pregnancy; they do not appear to cross the placenta or have any effects on fetal adrenal function and are therefore unlikely to have adverse effects on fetal growth and development.27,28 The safety of low-to-moderate doses of ICSs has been confirmed in a cohort study of 13,280 pregnancies; the incidence of major congenital malformations was increased with use of higher ICS doses (>1000 mcg/day beclomethasone equivalent) during the first trimester.29 LABAs and montelukast appear to be safe in pregnancy.30 Teratogenicity in animals has been reported with zileuton.
ASTHMA IN CHILDREN

For children with mild intermittent asthma, a SABA should be used as needed. For mild, moderate or severe persistent asthma, ICSs are the preferred long-term treatment for control of symptoms; ICSs do not, however, alter the underlying severity or progression of the disease. In young children, a SABA or an ICS may best be delivered through a metered-dose inhaler with a valved holding chamber and face mask or mouthpiece, or through a nebulizer. Dry powder inhalers are not suitable for use in young children, who cannot reliably inhale rapidly or deeply enough to use them effectively. Nebulized budesonide is FDA-approved for use in children as young as one year of age. ICSs given in low doses for years are generally safe for use in children, but linear growth should be monitored. Low- or medium-dose ICSs administered regularly may reduce growth velocity slightly during the first year of treatment, but final adult height does not appear to be affected.31-33

Montelukast can be used as the controller in children whose parents prefer not to use an ICS. It may also be used instead of a LABA as an add-on to an ICS, but it is generally less effective.

ASTHMA IN THE ELDERLY

Asthma in the elderly is often associated with co-morbidities, such as cardiovascular disease, diabetes, dementia, depression and frailty, and with polypharmacy. Elderly asthmatic patients are more likely to have fixed airway obstruction with features that overlap COPD. The elderly have more adverse effects from ICSs, including skin bruising, cataracts, increased intraocular pressure, hyperglycemia and accelerated loss of bone mass. They may have both a reduced response to beta-adrenergic bronchodilators, especially if concomitantly taking a beta blocker, and an increased incidence of tachycardia, arrhythmias and tremors. In these patients, tiotropium can be a useful bronchodilator. Some older patients have difficulty inhaling any medication from a metered-dose or dry-powder inhaler and may require a nebulizer.31-33

ASTHMA AND CO-MORBID DISEASES

Asthma is often associated with other co-morbid conditions including allergic rhinitis, gastroesophageal reflux disease (GERD), obesity, sinusitis, depression and anxiety. Such co-morbidities can make asthma more difficult to treat.34

Allergic Rhinitis – Up to 95% of patients with asthma also suffer from persistent rhinitis. Concurrent pharmacologic treatment of both asthma and rhinitis improves asthma outcomes.35 Patients with concomitant allergic rhinitis and allergic asthma may benefit from specific immunotherapy with standardized allergens.20

GERD – Patients with poorly controlled asthma have a higher prevalence of GERD, but no cause-and-effect relationship has been demonstrated. In asthma patients who have concomitant GERD symptoms, treatment with a proton pump inhibitor may slightly improve pulmonary function and asthma-related quality of life.36 In asthma patients with asymptomatic GERD, treatment with a proton pump inhibitor does not improve asthma control.37

Obesity – Obesity has been associated with asthma persistence and severity.4 Overweight and obese asthmatic patients may have a diminished response to ICSs.38 Weight loss may improve lung function and responsiveness to treatment. Bariatric surgery has been reported to improve asthma control and airway hyper-responsiveness in overweight adults.39

17. NA Hanania et al. Omalizumab in severe allergic asthma inadequately
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36. TO Kiljander et al. Effect of esomeprazole 40 mg once or twice daily on asthma: a randomized, placebo-controlled study. Am J Respir Crit Care Med 2010; 181:1042.

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Questions start on next page
1. Inhaled corticosteroids have been shown to be more effective than which of the following in clinical trials?
   a. long-acting beta-2 agonists
   b. leukotriene modifiers
   c. theophylline
   d. all of the above

2. Montelukast is less likely than zafirlukast or zileuton to:
   a. be effective
   b. be safe in pregnancy
   c. cause hepatotoxicity
   d. prevent exercise-induced asthma

3. A 25-year-old woman with asthma has been taking a low dose of an inhaled corticosteroid for 3 months. She has had some improvement in her asthma symptoms but still requires use of an inhaled short-acting beta-2 agonist about 4 days per week. You decide to add an inhaled long-acting beta-2 agonist to her regimen. Addition of salmeterol or formoterol in patients with persistent asthma not well controlled on low-dose inhaled corticosteroids:
   a. improves lung function
   b. decreases symptoms
   c. reduces rescue use of short-acting beta-2 agonists
   d. all of the above

4. Omalizumab:
   a. is indicated only for allergic asthma
   b. is given subcutaneously
   c. has caused anaphylaxis
   d. all of the above

5. Which of the following may be sufficient for asthma that is mild and intermittent?
   a. an oral corticosteroid
   b. omalizumab
   c. an inhaled short-acting beta-2 agonist
   d. an inhaled long-acting beta-2 agonist

6. Inhaled short-acting beta-2 agonists:
   a. reduce airway inflammation
   b. can prevent exercise-induced bronchoconstriction
   c. should be taken twice a day
   d. have a 12-hour duration of action

7. Failure of pharmacologic asthma treatment can usually be attributed to:
   a. lack of adherence
   b. uncontrolled co-morbid conditions
   c. exposure to smoke
   d. all of the above

8. Inhaled corticosteroids:
   a. can cause dysphonia
   b. are only effective in high doses
   c. are effective even after they are discontinued
   d. significantly affect adult height when used chronically in children

9. Inhaled long-acting beta-2 agonists:
   a. should not be used with an inhaled corticosteroid
   b. are contraindicated in patients with allergic asthma
   c. have been associated with an increased risk of asthma-related death
   d. are the first-line treatment for patients with mild asthma

10. Which of the following statements about inhaled anticholinergics is true?
    a. Both ipratropium and tiotropium are FDA-approved for use in patients with COPD.
    b. Ipratropium is used off-label as an alternate reliever medication in asthma patients intolerant to short-acting beta-2 agonist therapy.
    c. Tiotropium was as effective as a long-acting beta-2 agonist in patients with asthma not controlled on an inhaled corticosteroid in one study.
    d. all of the above

11. Which of the following is the least safe for use during pregnancy?
    a. albuterol
    b. zileuton
    c. salmeterol
    d. montelukast

12. Peak theophylline concentrations should be:
    a. 5-10 mcg/mL
    b. 10-15 mcg/mL
    c. 15-20 mcg/mL
    d. above 20 mcg/mL