ASTHMA IN CHILDREN

Method of
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CURRENT DIAGNOSIS

- Recurrent wheeze, cough, and shortness of breath are typical asthma symptoms.
- A personal or family history of atopy is associated with an increased risk of developing asthma.
- Atopy, allergic rhinitis, eczema, or nasal polyps are common comorbidities in patients with asthma.
- Specifically elicit symptom triggers such as allergens, irritants, exercise, stress, cold, or infection.
- At initial diagnosis, outline symptom frequency, intensity, and timing to classify severity.
- Physical examination of asthmatic children is often normal, but mucosal edema of nasal turbinates, eczematous skin rashes, tachypnea, tachycardia, expiratory wheezes, and lung hyperexpansion may be observed.
- In children older than 5 years spirometry revealing an obstructive pattern at least partially reversible with bronchodilators confirms the diagnosis. In children younger than 5 years, diagnosis is based on history, physical examination, and a trial of antiasthma medications.
- Chest x-ray, complete blood count (CBC), and IgE levels are not routinely recommended but may be useful in certain situations.

CURRENT THERAPY

- The goal of asthma management is to reduce impairment of activities and decrease risk of exacerbations.
- Initial assessment of asthmatics should focus on symptom frequency, timing, and effect on activities to classify the degree of severity as intermittent, mild persistent, moderate persistent, or severe persistent.
- The four central components of management are continual assessment and monitoring, patient education, controlling environmental triggers, and appropriate use of medication.
- Short-acting inhaled β2-adrenergic receptor agonists such as albuterol (Proventil HFA) are the mainstay of acute therapy in an episode of bronchoconstriction. Anticholinergics such as ipratropium bromide (Atrovent HFA)1 and systemic steroids are important components of managing an acute exacerbation. Magnesium sulfate,1 epinephrine (Adrenalin), and terbutaline (Brethine)1 are reserved for refractory cases, and terbutaline is only approved for children 12 years and older.
- Inhaled corticosteroids are the most effective daily controller medications for children. Long-acting β2-agonists, leukotriene-receptor antagonists, and mast cell stabilizers are commonly used adjunctive therapies.
- Visits should be scheduled frequently in the outpatient setting to reassess symptom severity, adjust medications accordingly, and emphasize patient education.
- Consider increasing medication therapy only after assessing the patient’s adherence and technique with medications. Consider a step down in therapy only after 3 months of adequate control of symptoms.
- Involve both children and their caregivers in designing a written asthma action plan to empower patients in recognizing and managing escalating symptoms.
- Refer to a pulmonologist or allergist if there is any question regarding diagnosis or if symptoms are not adequately controlled with standard treatment.

Epidemiology

Asthma prevalence in the United States has been on the rise since the 1990s. It is currently estimated that 9.6% of children younger than 18 years (7.1 million children) carry the diagnosis of asthma. Male sex, African American or Puerto Rican ethnicity, and lower socioeconomic status are associated with an increased risk of developing asthma. Prevalence estimates for these groups are as high as 11% to 16%.

Asthma has a significant impact on both school attendance and health care expenditures. According to the National Health Statistic Report in 2007, children made 640,000 emergency department visits and were hospitalized 157,000 times as a result of asthma. In 2008 it was estimated that there were 10.5 million missed school days, and about 5% of children reported long-term limitations on their usual activities due to asthma symptoms.

Although no significant difference in asthma prevalence between urban areas and suburban or rural areas has been found, there do seem to be broader geographic trends with higher prevalence in the Northeast and Midwest. Mortality rates remain low, but preventable deaths attributable to asthma exacerbations persist.

Risk Factors

No clear precipitating factors have been associated with the onset of asthma in children, but multiple risk factors for the development of this disease have been identified. Perhaps the strongest link is that between a family history of atopy, atopic dermatitis in infancy, or elevated serum immunoglobulin (IgE) levels and subsequent sensitization to aeroallergens at 5 years of age. Other associations including sensitization to dust mites, preterm birth, exposure to tobacco smoke, and certain respiratory infections such as respiratory syncytial virus (RSV) have been identified.
Pathophysiology
Asthma is a chronic disease with recurrent episodes of reversible airway obstruction. It is thought to consist of three major pathophysiologic components: bronchoconstriction, airway inflammation, and bronchial hyperresponsiveness. Bronchoconstriction results from bronchial smooth muscle contraction in response to exposure to allergens, irritants, stress, infection, exercise, or certain medications such as aspirin and nonsteroidal antiinflammatory drugs (NSAIDs). Inflammation occurs via the T helper 2- (Th2) and IgE-mediated pathways. Examination of the airways of asthmatics reveals inflammatory infiltrates consisting of neutrophils, eosinophils, lymphocytes, and activated mast cells. These mast cells release histamine along with other inflammatory mediators, causing airway edema, mucous hypersecretion, and airway hyperresponsiveness to environmental stimuli. Over time remodeling can occur, with airway thickening and smooth muscle hyperplasia, with a resulting decline in lung function and reduced response to therapeutic interventions.

Long-term observational studies have suggested that declining lung function is most commonly seen in children with symptom onset before 3 years of age. It still remains unclear whether older children or adults experience the same reductions in lung function.

Prevention
Primary prevention of asthma is a well-studied topic, yet few studies have successfully identified effective strategies for preventing asthma. The effect of breast-feeding on asthma prevalence has been a focus of extensive research. Much of the literature regarding breast-feeding as primary prevention for asthma suggests a protective effect of breast-feeding, but this has not been borne out consistently. One study of 952 patients showed no evidence that avoidance of antigens (milk, eggs, nuts) by breast-feeding mothers during pregnancy or lactation decreased asthma or eczema in children.

Although reducing exposure to inhalant allergens such as mites and pet dander can improve symptoms in patients with diagnosed asthma, there is conflicting evidence regarding allergen avoidance to prevent the onset of asthma. In the randomized, controlled Childhood Asthma Prevention Study, dust mite avoidance and dietary fatty acid modifications from 0 to 5 years of age did not decrease the prevalence of asthma or atopy at 8 years.

Other studies combining a reduction in exposure to multiple allergens have been more hopeful. One study demonstrated that in infants with at least one first-degree relative with atopy, decreasing dust mite exposure and following a diet that includes hydrolyzed milk formula (not cow’s milk), and avoiding cow’s milk (both mother and child) for 4 months decreased the risk of wheezing in the first 12 months of life. A systematic review of multifaceted interventions to reduce or avoid allergen exposure in high-risk children found a decreased rate of asthma diagnosis later in childhood; however, the reliability of the data was limited by subjective reporting of symptoms and by potentially confounding variables. The topic of primary prevention of asthma warrants further study to clearly establish feasible preventive measures.

Clinical Manifestations
Asthma is characterized by recurrent episodes of wheezing, chest tightness, and shortness of breath. Asthma can also manifest as a chronic dry cough, especially if occurring at night. Young children commonly present with chronic cough alone, a form of asthma called cough-variant asthma. Wheezing that recurs in the setting of specific, predictable triggers is also a manifestation of asthma.

Diagnosis
A focused history revealing recurrent episodes of wheezing, shortness of breath, or cough suggests asthma and merits further investigation. In infants, the symptoms of asthma can involve difficulty feeding. Parents might also report intermittent grunting or loud breathing.

When taking the history it is important to ask about symptom triggers, time course, and frequency of symptoms to assess severity. It is also important to discuss any family history of atopy, asthma, eczema, or nasal polyps. Triggers such as exposure to inhaled allergens (mold, dust, pollen, pet dander), irritants (chemicals, cigarette smoke), weather changes, intense emotion, physical activity, and viral illnesses should be elicited specifically (Box 1).

Begin the physical examination with measurements of height and weight and inspection of the growth chart. Most children do not have a significant growth or height reduction as a result of asthma. If a child’s growth chart demonstrates a marked decrease in growth velocity it is prudent to seriously consider alternative diagnoses.

Owing to the intermittent nature of asthma symptoms, children with asthma often have an entirely normal examination. Upper airway findings can include nasal polyps or mucosal edema of nasal turbinites. The skin examination might reveal signs of atopic dermatoses such as eczema or urticaria. Lung examination may be remarkable for wheezing, hyperexpanded barrel chest, increased respiratory rate, or tachycardia, depending on severity of symptoms.

In children older than 5 years, spirometry is a useful means of obtaining objective data on lung function and presence of obstructive disease. Assessment with spirometry before and after short-acting β-agonist inhalation should show reversibility of obstruction. A rise in forced expiratory volume in 1 second (FEV1) of 200 mL and 12% above baseline after bronchodilator is consistent with reversible obstruction. In children younger than 5 years such studies might not be feasible. In these cases diagnosis is based on history and physical. A trial of bronchodilator is helpful in establishing the diagnosis as well as ruling out other possible etiologies of symptoms.

A common presenting symptom of asthma in children is chronic cough. In cough-variant asthma, spirometry may be entirely normal. A trial of antiasthma medication that results in resolution of cough confirms the diagnosis. Peak flow meters are useful in monitoring symptom severity but should not be used to make a diagnosis owing to wide variations in individual results and normal values.

Chest x-ray should be considered when ruling out alternative diagnoses but is not recommended in routine diagnostic testing for asthma. Allergy skin testing can identify potentially avoidable...
inhalant indoor allergens and, when appropriate, guide immunotherapy. Finally, checking a complete blood count with differential and serum IgE levels is not clearly indicated in making a diagnosis but may be useful in guiding treatment. Eosinophilia (greater than 4%) can indicate the need for controller medications, and patients with high levels of IgE have been shown to have a particularly good response to inhaled corticosteroids.

**Differential Diagnosis**
The differential diagnosis of recurrent respiratory symptoms is broad and must be considered when initiating diagnostic work-up. When creating a list of other diagnoses it can be useful to consider the airway from the top down, as is shown in Box 2. Also keep in mind that the age of the patient and the chronicity of symptoms can point to certain diagnoses in your differential.

**Treatment**
To treat asthma in children appropriately, the severity of symptoms must first be assessed. This initial evaluation should be followed by an ongoing assessment that monitors response to therapy. The general tenets of asthma treatment are to reduce the functional limitations caused by asthma symptoms and decrease the risk of exacerbations, decline in lung function, and side effects of medications. The Expert Panel Report 3 on the National Asthma Education and Prevention Program released in 2007 describes a patient-oriented and clinically relevant approach to asthma management. Emphasis is placed on organized primary care visits and patient education. It is important to plan routine visits with a child’s pediatrician or family doctor until symptoms are adequately controlled.

Once the diagnosis of asthma is made in a child, symptom severity should be assessed. Symptoms are classified as intermittent, mild persistent, moderate persistent, or severe persistent. To determine severity, the frequency of daytime symptoms, nighttime symptoms, frequency of using short acting β2-agonists, impairment of activities, frequency of exacerbations requiring oral steroids, and lung function must be considered (Table 1). Once severity has been classified, treatment can be started based on the stepwise approach outlined in Table 2. This stepwise approach is intended to be a guideline only. Clinical judgment is necessary when applying these guidelines to the individual patient. Children 12 years and older may be assessed and treated according to the guidelines described for adults.

Assessing adequacy of symptom control is essential to the management of asthma. At each follow-up visit, discussion should focus on how often the patient is having asthma symptoms and how much those symptoms are interfering with normal activities. Tools such as the Asthma Control Test (ACT) or the Childhood Asthma Control Test are helpful in measuring symptom control in a standardized fashion. Symptom assessment determines adequacy of control and guides changes in treatment, as shown in Table 2 and 3. Frequency of primary care visits depends on severity of symptoms and can initially occur every 2 to 6 weeks. As control improves, visits may be decreased to every 1 to 6 months. At each visit, medications can be reviewed, doses adjusted, and education reiterated on recognizing symptoms and using medication and spacers.

Only after at least 3 months of adequate control should a decrease in therapy be considered. When stepping down, do so gradually, with frequent reassessment for reemerging symptoms. In the same way, therapy should be increased only after ensuring that the patient has been adherent with medications and is using the inhaler properly and that comorbid conditions have been addressed.

Referral to a pulmonologist or allergist is recommended if there is any question about the accuracy of diagnosis or if symptoms are difficult to control. The National Hearth, Lung, and Blood Institute (NHLBI) recommends consultation if a child older than 5 years requires step 4 or higher level of therapy (step 3 or higher therapy in children younger than 5 years).

Allergen avoidance is currently recommended in the management of all asthmatics, but there is limited evidence that these interventions are effective. Various studies have analyzed the effects of controlling dust mite exposure with specially designed mattress and pillow covers and the use of air filtration units to reduce the burden of airborne pet dander. None of these studies have demonstrated clear benefits in decreasing symptoms.

Influenza vaccination is of questionable benefit. Although it is clear that giving the vaccine does not increase the risk of an exacerbation immediately after vaccination (except in infants receiving live intranasal vaccine [FluMist]), it is uncertain whether the vaccine reduces exacerbations triggered by influenza infection. Despite this, the Centers for Disease Control and Prevention (CDC) recommends influenza vaccination in asthmatics owing to the potential for increased asthma complications from influenza infection.

Finally, management of comorbid conditions has been implicated in improving asthma control. Sinusitis, allergic rhinitis, gastroesophageal reflux disease (GERD), and obesity are thought to contribute to asthma symptoms. Research has shown, however, that treatment of GERD with lansoprazole (Prevacid) in children with poorly controlled asthma not only had no effect on asthma symptoms but also led to a significant increase in respiratory infections.

**Medications**
Asthma management requires both fast-acting rescue medications and long-term controller medications. The goal of therapy is to find a daily controller medicine that reduces symptoms to such a degree that rescue medications are needed only rarely. Patients and their caretakers must be educated regarding the different roles of these two classes of medication to ensure the best possible outcome and the patient’s safety.

**Rescue Medications**
Fast-acting bronchodilators are important in both the mildest and the most-severe forms of asthma. Short-acting β2-adrenergic receptor agonists lead to smooth muscle relaxation and airway dilation. Racemic albuterol (Proventil) is a commonly used member of this group, but levalbuterol (Xopenex) is an alternative. Initially levalbuterol was thought to have fewer side effects, but studies have shown similar tolerability between racemic albuterol and levalbuterol. There is no significant difference in efficacy between

**Box 2**
Differential Diagnosis

<table>
<thead>
<tr>
<th>Upper Airway</th>
<th>Sinusitis</th>
</tr>
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<tbody>
<tr>
<td>Allergic rhinitis</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Large Airway Obstruction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vocal cord dysfunction</td>
</tr>
<tr>
<td>Laryngotracheomalacia (infants)</td>
</tr>
<tr>
<td>Tracheal stenosis (infants)</td>
</tr>
<tr>
<td>Vascular rings</td>
</tr>
<tr>
<td>Tracheal webs</td>
</tr>
<tr>
<td>Inhaled foreign body</td>
</tr>
<tr>
<td>Tumor or enlarged lymph nodes compressing airway</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Small Airway Obstruction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral bronchiolitis</td>
</tr>
<tr>
<td>Pneumonia</td>
</tr>
<tr>
<td>Obliterative bronchiolitis</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
</tr>
<tr>
<td>Bronchopulmonary dysplasia</td>
</tr>
<tr>
<td>Heart failure</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastroesophageal reflux disease</td>
</tr>
<tr>
<td>Swallowing mechanism dysfunction leading to aspiration</td>
</tr>
</tbody>
</table>

Inhaled corticosteroids are the most effective long-term controller medications. Some commonly used inhaled corticosteroids are fluticasone (Flovent), budesonide (Pulmicort), beclomethasone (Qvar), mometasone (Asmanex), and funisolide (Aerobid).\(^2\) No single formulation of inhaled corticosteroid is superior to another. These medications reduce frequency of exacerbations and hospitalizations and are superior to leukotriene receptor antagonists and mast cell stabilizers. They are available as both metered-dose inhalers and dry-powder inhalers. A significant concern related to their use is that inhaled corticosteroids have been linked to reduced growth velocity, but several studies have shown that at low to medium doses they do not consistently or significantly affect growth.\(^2\) To minimize potential side effects, continuous monitoring, reevaluation, and consideration of step-down treatment is imperative.

Long-acting \(\beta\)-agonists include salmeterol (Serevent) and formoterol (Foradil). They are an adjunctive therapy to inhaled corticosteroids and should be considered in step 3 of management of symptoms in children aged 5 to 11 years and in step 4 in children 0 to 4 years old. Long-acting \(\beta\)-agonists carry a risk of increased asthma-related deaths, intubations, and hospitalizations when used alone. This risk was most prominent in children 4 to 11 years of age. Long-acting \(\beta\)-agonists should never be used as monotherapy and are not recommended for use during exacerbations. In combination with inhaled corticosteroids, however, long-acting \(\beta\)-agonists reduce exacerbations, increase asthma control days, and improve lung function. For children younger than 5 years, data are lacking.

**Controller Medications**

**Long-acting \(\beta\)-agonists**

<table>
<thead>
<tr>
<th>COMPONENTS OF SEVERITY</th>
<th>AGE (Y)</th>
<th>INTERMITTENT</th>
<th>MILD</th>
<th>MODERATE</th>
<th>SEVERE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td>All</td>
<td>≤ 2 d/wk</td>
<td>&gt; 2 d/wk but not daily</td>
<td>Daily</td>
<td>Throughout the day</td>
</tr>
<tr>
<td>Nighttime awakenings</td>
<td>0–4</td>
<td>0</td>
<td>1–2 ×/mo</td>
<td>3–4 ×/mo</td>
<td>&gt; 1 ×/wk</td>
</tr>
<tr>
<td></td>
<td>≥ 5</td>
<td>≤ 2 ×/mo</td>
<td>≥ 2 ×/mo</td>
<td>≥ 1 ×/wk but not nightly</td>
<td>Often 7 ×/wk</td>
</tr>
<tr>
<td>SABA for symptom control</td>
<td>All</td>
<td>≤ 2 d/wk</td>
<td>&gt; 2 d/wk but not daily</td>
<td>Daily</td>
<td>Several ×/day</td>
</tr>
</tbody>
</table>

Interference with normal activity

Lung Function

<table>
<thead>
<tr>
<th>FEV(_1) (predicted) or PEF (personal best)</th>
<th>0–4</th>
<th>&gt; 80%</th>
<th>&gt; 80%</th>
<th>60%–80%</th>
<th>&lt; 60%</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV(_1)/FVC</td>
<td>5–11</td>
<td>&lt; 85%</td>
<td>&lt; 80%</td>
<td>Reduced 5%</td>
<td>Reduced &gt; 5%</td>
</tr>
</tbody>
</table>

Risk

| Exacerbations requiring oral corticosteroids | 0–4 | < 1/y | > 2 × in 6 mo or > 4 wheezing episodes/y lasting > 1 d and risk factors for persistent asthma |
|---------------------------------------------|-----|-------|-------|------------------|
|                                             | 5–11| < 1/y | < 1/y | > 2 ×/y* |
|                                             | ≥ 12| < 1/y |       |           |

Starting Treatment

<table>
<thead>
<tr>
<th>Recommended step</th>
<th>0–4</th>
<th>5–11</th>
<th>≥ 12</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starting Treatment</td>
<td>Step 1</td>
<td>Step 1</td>
<td>Step 1</td>
<td>Step 1</td>
</tr>
<tr>
<td></td>
<td>Step 2</td>
<td>Step 2</td>
<td>Step 2</td>
<td>Step 2</td>
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<tr>
<td></td>
<td>Step 3</td>
<td>Step 3</td>
<td>Step 3</td>
<td>Step 3</td>
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<tr>
<td></td>
<td>Step 3</td>
<td>Step 3</td>
<td>Step 3</td>
<td>Step 3</td>
</tr>
<tr>
<td></td>
<td>Step 4 or 5</td>
<td>Step 4 or 5</td>
<td>Step 4 or 5</td>
<td>Step 4 or 5</td>
</tr>
<tr>
<td></td>
<td>Consider short course of oral corticosteroids</td>
<td>Consider short course of oral corticosteroids</td>
<td>Consider short course of oral corticosteroids</td>
<td>Consider short course of oral corticosteroids</td>
</tr>
</tbody>
</table>


Abbreviations: FEV\(_1\) = forced expiratory volume in 1 second; FVC = forced vital capacity; PEF = peak expiratory flow; SABA = short-acting \(\beta\)-adrenergic receptor agonist.

These medications. Short-acting \(\beta\)-adrenergic receptor agonists should be reserved for relief of acute symptoms. Frequent use is discouraged and can indicate inadequate control of symptoms. See Table 4 for usual dosing of rescue medications.

**Abbreviations:** ACQ = Asthma Control Questionnaire; ACT = Asthma Control Test; ATAQ = Asthma Therapy Assessment Questionnaire; FEV1 = forced expiratory volume in 1 second; FVC = forced vital capacity; ICS = inhaled corticosteroid; PEF = peak expiratory flow; SABA = short-acting β2-adrenergic receptor agonist.

### Immunomodulators

Immunomodulators are reserved for the most refractory cases of asthma. Omalizumab (Xolair), an anti-IgE agent, functions by blocking the binding of IgE to mast cells and basophils. It is effective in children with allergic triggers for their asthma but carries a risk of anaphylaxis with administration. When used in conjunction with guideline-based treatment it improves asthma control and reduces seasonal peaks of exacerbations.

Theophylline (Theochron) was previously a mainstay of asthma management but is no longer a first-line medication. With the development of alternative treatments and because of theophylline’s risk for toxicity, theophylline now has a smaller role in asthma management. Currently it is used as an alternative treatment in the chronic management of patients with symptoms refractory to or intolerant of standard therapies. Use of this medication requires frequent monitoring of drug serum levels. It can cause nausea, vomiting, or tachyarrhythmias if dosing is too high. See Table 5 for usual dosing of controller medications.

### Acute Asthma Exacerbations

Exacerbations consist of worsening wheezing, cough, or shortness of breath. They can vary in severity from mild to life threatening. When deciding how to treat a patient in an exacerbation, use the history and physical examination to determine severity. As in all emergency situations first assess airway, breathing, and circulation. In a life-threatening exacerbation the patient can appear confused or obtunded, may be bradycardic, and can have minimal respiratory effort, indicating imminent respiratory arrest. A child in a severe exacerbation can appear short of breath even at rest, may be agitated, and might only be speaking one word at a time. The child is likely tachycardic and tachypneic, with obvious use of accessory muscles. In certain cases, lung examination might not reveal wheezing owing to severe impairment of aeration; only after treatment does the wheezing become audible as air movement improves. In mild to moderate exacerbations the patient might only be short of breath with walking, might speak in short phrases or

<table>
<thead>
<tr>
<th>COMPONENTS OF CONTROL</th>
<th>AGE (Y)</th>
<th>WELL CONTROLLED</th>
<th>NOT WELL CONTROLLED</th>
<th>VERY POORLY CONTROLLED</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Impairment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptoms</td>
<td>0–4</td>
<td>≤ 2 d/wk but ≤ 1 x/day</td>
<td>&gt; 2 d/wk or multiple times on ≤ 2 d/wk</td>
<td>Throughout the day</td>
</tr>
<tr>
<td></td>
<td>5–11</td>
<td>≤ 2 d/wk</td>
<td>&gt; 2 d/wk</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥ 12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nighttime awakenings</td>
<td>0–4</td>
<td>≤ 1 x/mo</td>
<td>&gt; 1 x/mo</td>
<td>≥ 1 x/wk</td>
</tr>
<tr>
<td></td>
<td>5–11</td>
<td>≤ 1 x/mo</td>
<td>&gt; 2 x/mo</td>
<td>≥ 2 x/wk</td>
</tr>
<tr>
<td></td>
<td>≥ 12</td>
<td>≤ 2 x/mo</td>
<td>1–3 x/wk</td>
<td>≥ 4 x/wk</td>
</tr>
<tr>
<td>Interference with normal activity</td>
<td>All</td>
<td>≤ 2 d/wk</td>
<td>&gt; 2 d/wk</td>
<td>Several x/day</td>
</tr>
<tr>
<td>SABA for symptoms</td>
<td>All</td>
<td>None</td>
<td>&gt; 2 d/wk</td>
<td>Several x/day</td>
</tr>
<tr>
<td><strong>Lung Function</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV1 (predicted) or PEF (personal best)</td>
<td>≥ 5</td>
<td>&gt; 80%</td>
<td>60%–80%</td>
<td>&lt; 60%</td>
</tr>
<tr>
<td></td>
<td>5–11</td>
<td>&lt; 80%</td>
<td>75%–80%</td>
<td>&lt; 75%</td>
</tr>
<tr>
<td><strong>Validated Questionnaires</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATAQ</td>
<td>≥ 12</td>
<td>≥ 0.75</td>
<td>≥ 1.5</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>≥ 12</td>
<td>≥ 20</td>
<td>16–19</td>
<td></td>
</tr>
<tr>
<td><strong>Risk</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exacerbations requiring oral corticosteroids</td>
<td>0–4</td>
<td>≤ 1 x/year</td>
<td>2–3 x/yr</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5–11</td>
<td>≤ 1 x/year</td>
<td>≤ 2 x/yr</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥ 12</td>
<td>≥ 1 x/year</td>
<td>&gt; 3 x/yr</td>
<td></td>
</tr>
<tr>
<td>Reduction in lung growth</td>
<td>5–11</td>
<td>Evaluation requires long-term follow-up care</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loss of lung function</td>
<td>≥ 12</td>
<td>Evaluation requires long-term follow-up care</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment-related adverse effects</td>
<td>All</td>
<td>Medication side effects can vary in intensity from none to very troublesome and worrisome</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Recommended Treatment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recommended treatment actions</td>
<td>All</td>
<td>Maintain current step Regular follow-up q1–6 mo Consider stepping down if well controlled for ≥ 3 mo</td>
<td>Step up 1 step</td>
<td>Step up 1–2 steps and consider short course of oral corticosteroids</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Before stepping up, review adherence to medication, inhaler technique, environmental control, comorbid conditions If an alternative treatment option was used in a step, discontinue and use the preferred treatment for that step Reevaluate the level of asthma control in 2–6 wk and adjust therapy accordingly For side effects, consider alternative treatment options</td>
<td></td>
<td></td>
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</tbody>
</table>

Throughout the day
TABLE 3  Stepwise Treatment of Asthma in Children Younger than 12 Years

<table>
<thead>
<tr>
<th>STEP</th>
<th>0–4 YEARS OLD</th>
<th>5–11 YEARS OLD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 1: Intermittent</td>
<td>SABA as needed</td>
<td>SABA as needed</td>
</tr>
<tr>
<td>Step 2: Mild persistent</td>
<td>Add low-dose daily ICS or cromolyn or montelukast (Singular)</td>
<td>Add low-dose daily ICS or cromolyn, LTRA, nedocromil (Tilade) or theophylline</td>
</tr>
<tr>
<td>Step 3: Moderate persistent</td>
<td>Increase ICS to medium dose</td>
<td>Increase ICS to medium dose or continue low dose ICS plus either LTRA, LABA or theophylline</td>
</tr>
<tr>
<td>Step 4: Severe persistent</td>
<td>Medium-dose ICS plus either LABA or montelukast</td>
<td>Medium-dose ICS plus LABA, or medium-dose ICS plus either LTRA or theophylline</td>
</tr>
<tr>
<td>Step 5: Severe persistent</td>
<td>High dose ICS plus either LABA or montelukast</td>
<td>High-dose ICS plus LABA, or high-dose ICS plus LTRA or theophylline</td>
</tr>
<tr>
<td>Step 6: Severe persistent</td>
<td>Step 5 plus oral glucocorticoids</td>
<td>Step 5 plus oral glucocorticoids</td>
</tr>
</tbody>
</table>

**Step-Down Therapy**
- If control is adequate for 3 mo, may consider gradual decrease in treatment.
- Reassess every 1–3 mo.

**Children ≥12 years:** May be treated according to adult guidelines.

**Children 5–11 years:** Consider subcutaneous allergen immunotherapy if the child has allergic asthma in steps 2 to 6.

**All children:** Treat comorbid conditions to improve asthma control.

**For exacerbations that occur at all levels:**
- SABA 2–4 puffs every 4–6 h for 24 h with physician consultation.
- Consider 3- to 10-day course of oral glucocorticoids for moderate to severe exacerbation.


**Abbreviations:** ICS = inhaled corticosteroid; LABA = long-acting β-agonist; LTRA = leukotriene receptor antagonist; SABA = short-acting β₂-adrenergic receptor agonist.

---

**TABLE 4** Usual Dosing of Rescue Medications

<table>
<thead>
<tr>
<th>DRUG</th>
<th>BRONCHOSPASM*</th>
<th>ACUTE EXACERBATION†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albuterol (Proventil HFA, AccuNeb)</td>
<td>&gt; 4 yr old: 2 inhalations q4–6 h prn</td>
<td>4–8 inhalations q20 min × 3 doses, then q1–4 h prn; add mask in children &lt; 4 yr</td>
</tr>
<tr>
<td>     </td>
<td>&gt; 2 yr old (min 15 kg): 0.083% nebulized soln (AccuNeb) inhaled over 5–15 min 3–4 × daily prn</td>
<td>0.15–0.3 mg/kg up to 10 mg q1–4 h prn</td>
</tr>
<tr>
<td>Levalbuterol (Xopenex)</td>
<td>Age 0–4 yr: 0.31–1.25 mg nebulized soln q4–6 h prn</td>
<td>0.075 mg/kg (min 1.25 mg) q20 min × 3 doses, then 0.075–0.15 mg/kg up to 5 mg q1–4 h prn</td>
</tr>
<tr>
<td>     </td>
<td>Age 5–11 yr: 0.31–0.63 mg q8h prn</td>
<td>     </td>
</tr>
</tbody>
</table>

*Symptoms of obstruction, cough, wheeze, breathlessness.
†Symptoms of obstruction not responsive to initial SABA use.

**Abbreviations:** SABA = short-acting β₂-adrenergic receptor agonist; soln = solution.


full sentences, and can appear anxious but not necessarily agitated. Lung examination can reveal wheezing.

The cornerstone of treatment of asthma exacerbations is rapid recognition of symptoms, correction of hypoxemia, and early initiation of short-acting β₂-adrenergic receptor agonists and corticosteroids. Oxygen administration should be employed to maintain oxygen saturation at greater than 94%. Short-acting β-agonists are essential to relieve bronchoconstriction and may be combined with ipratropium (Atrovent), especially if the patient is not responsive to initial therapy with a short-acting β₂-adrenergic receptor agonist alone. In 2006 a systematic review showed that metered-dose inhalers with a spacer are as effective in administering β-agonists as nebulizers are in children older than 2 years. It was noted in the same study that length of stay in the emergency department was reduced in those using the spacers.

Corticosteroids given systemically are also considered rescue medications, although onset of action is 1 to 2 hours and duration of action is 18 to 36 hours. They work primarily as antiinflammatory and are an important treatment in exacerbations. Early use of systemic steroids, either oral or intravenous, reduced rates of relapse and decreased admissions to the hospital. The greatest benefit of systemic steroids was seen in patients having a severe attack and those who were not already on a course of steroids. Studies have shown that oral steroids are as effective as intravenous or intramuscular preparations. Even a short course of oral steroids can reduce relapse and decreases the need for rescue inhalers. Systemic corticosteroids should be continued for 3 to 10 days after an exacerbation. A taper is not necessary if the course is less than 1 week or less than 10 days in a patient who is also using an inhaled corticosteroid. Prolonged use of systemic corticosteroids carries significant risk for side effects such as adrenal suppression, osteoporosis, reduced growth, and cataracts, and thus their use should be minimized. Despite some evidence that use of inhaled corticosteroids in acute exacerbations can reduce admission rates, it is unclear how much benefit they have when used in conjunction with systemic steroids.

Use of intravenous magnesium sulfate (a smooth muscle relaxer) should be reserved for severe exacerbations only. Its use has not been shown to reduce admission rates in milder exacerbations but can improve lung function in those with only a partial response to short-acting β-agonists. Similarly, subcutaneous epinephrine, and subcutaneous terbutaline should be reserved for emergency situations.
department settings when patients are not responding to short-acting $\beta_2$-adrenergic receptor agonists, anticholinergics, or corticosteroids or when air entry is so diminished that inhaled medications are not effective.

Finally, not enough evidence exists to make a recommendation regarding routine use of antibiotics during an acute asthma exacerbation. In some circumstances when there are findings consistent with bacterial infections (such as consolidation on chest x-ray) their use may be warranted. See Table 6 for usual dosing of medications used in acute exacerbations.

**Monitoring**

Asthma is a dynamic disease whose symptoms fluctuate based on a number of variables. Routine scheduled appointments with a pediatrician or family physician are essential to monitor symptoms and adjust therapy. Initial management can require visits every 2 to 6 weeks; as control of symptoms improves the interval may be increased to every 3 to 6 months.

Patient education is essential to successfully controlling this disease. Education should be focused on the theory behind controller and rescue medications as well as how to administer these medications properly. The National Asthma Education and Prevention Program Expert Panel 3 emphasizes the importance of asthma action plans to empower patients in recognizing and treating escalating symptoms of asthma. Action plans also provide recommendations on reducing exposure to irritants, allergens, and triggers. Some plans are based on peak flow levels, but studies show that symptom-based written action plans are better at decreasing acute care visits. Examples of asthma actions plans can be found on the National Heart Lung and Blood Institute website.

### Usual Dosing of Controller Medications

<table>
<thead>
<tr>
<th>DRUG</th>
<th>FORMAT</th>
<th>DOSSING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Budesonide (Pulmicort)</td>
<td>200 µg/puff</td>
<td>Low: 100–200 µg Medium: 200–400 µg High: &gt; 400 µg</td>
</tr>
<tr>
<td>Beclomethasone (Qvar)</td>
<td>40 or 80 µg/puff</td>
<td>Low: 80–160 µg Medium: 160–320 µg High: &gt; 320 µg</td>
</tr>
<tr>
<td>Mometasone fumarate (Asmanex)</td>
<td>110, 220 µg/puff</td>
<td>110 µg daily is max per guidelines for 4–11 y</td>
</tr>
<tr>
<td>Flunisolide (Aerobid)²</td>
<td>250 µg/puff</td>
<td>Low: 500–750 µg Medium: 1000–1250 µg High: 1250 µg</td>
</tr>
<tr>
<td>Triamcinolone acetonide (Azmacort)²</td>
<td>100 µg/puff</td>
<td>Low: 400–800 µg Medium: 800–1200 µg High: &gt; 1200 µg</td>
</tr>
<tr>
<td>Salmeterol (Serevent)</td>
<td>Dry powder inhaler 50 µg/blister</td>
<td>&gt; 5 y: 1 blister q12</td>
</tr>
<tr>
<td>Formoterol (Foradil)</td>
<td>Dry powder inhaler 12 µg/cap</td>
<td>&gt; 5 y: 1 cap q12h</td>
</tr>
<tr>
<td>Montelukast (Singularair)</td>
<td>&lt; 5 y: 4 mg hs 6–14 y: 5 mg hs</td>
<td></td>
</tr>
<tr>
<td>Zafirlukast (Accolate)</td>
<td>Ages 5–11 y: 10 mg bid</td>
<td></td>
</tr>
<tr>
<td>Cromolyn sodium (Intal)</td>
<td>nebulized soln (20 mg/2 mL), MDI 800 µg</td>
<td>&gt; 2 y: nebulized soln: inhale 20 mg qid Age &gt; 2: MDI: 2 puffs qid</td>
</tr>
<tr>
<td>Theophylline</td>
<td>Starting dose: 10 mg/kg/d &lt;1 y: max dose 0.2 × (age in weeks) + 5 = mg/kg/d ≥ 1 y: max dose 16 mg/kg/day</td>
<td></td>
</tr>
</tbody>
</table>

²Not available in the United States.
Abbreviations: cap = capsule; MDI = metered-dose inhaler; soln = solution.

### Usual Dosing of Medications Used in Exacerbations

<table>
<thead>
<tr>
<th>DRUG</th>
<th>DOSING</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chronic Management</strong></td>
<td></td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>0.25–2 mg/kg daily or every other day</td>
</tr>
<tr>
<td>(methylprednisolone, prednisolone, prednisone)</td>
<td></td>
</tr>
<tr>
<td><strong>Acute Exacerbation</strong></td>
<td></td>
</tr>
<tr>
<td>Ipratropium bromide</td>
<td>Age 0–5 y: 250 µg nebulized × 2, then q4h prn Age 5–11: 500 µg nebulized × 2, then q4h prn</td>
</tr>
<tr>
<td>(Duoneb)¹</td>
<td></td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>1–2 mg/kg/day (max 60 mg/day) in 2 divided doses × 3–10 d</td>
</tr>
<tr>
<td>(methylprednisolone, prednisolone, prednisone)</td>
<td></td>
</tr>
<tr>
<td><strong>Severe Acute Exacerbation</strong></td>
<td></td>
</tr>
<tr>
<td>Magnesium sulfate¹</td>
<td>25–50 mg/kg IV up to 2 g over 10–20 min</td>
</tr>
<tr>
<td>Terbutaline¹</td>
<td>0.01 mg/kg SC q20min for 3 doses, then every 2–6 hr prn</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>0.01 mg/kg up to 0.3–0.5 mg SC q20min for 3 doses</td>
</tr>
<tr>
<td><strong>Related to Allergic Reaction</strong></td>
<td></td>
</tr>
<tr>
<td>Epinephrine</td>
<td>1:1000: 0.01 mL/kg SC (max 0.3 mL)</td>
</tr>
</tbody>
</table>

¹Not FDA approved for this indication.
Abbreviation: SABA = short-acting $\beta_2$-adrenergic receptor agonist.
Complications

The most worrisome complications of asthma include reduced lung function, pneumonia, pneumothorax, and death. More common complications include chronic cough, fatigue due to poor sleep, missed school days and worse academic performance, and limited ability to participate in sports.

References


Kramer MS, Kakuma R. Maternal dietary antigen avoidance during pregnancy or lactation, or both, for preventing or treating atopic disease in the child. Cochrane Database Syst Rev 2006;(3):CD001333.


ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

Method of

Harris Stroffoff, MD, and Craig L. Donnelly, MD

CURRENT DIAGNOSIS

- Patients with ADHD have several impairing inattentive symptoms or hyperactive/impulsive symptoms, or both.
- The DSM-IV inattentive core symptoms of ADHD include difficulty sustaining attention, making careless mistakes, increased distractibility, forgetfulness, not seeming to listen when spoken to, not following through on instructions, difficulties with organization, reluctance to engage in schoolwork, and a tendency to lose things.
- The DSM-IV hyperactive/impulsive core symptoms of ADHD include being fidgety; running or climbing excessively; having difficulty awaiting a turn, staying seated, or being quiet; acting as if “driven by a motor”; talking excessively, blurtting out answers, and interrupting others.
- Stimulant medications (e.g., methylphenidate [Ritalin, Methylin, Concerta] and amphetamine preparations) and atomoxetine (Strattera) are the primary treatments for ADHD in children and adults.
- Medication should be implemented collaboratively, with the child’s parents and teachers providing feedback about treatment efficacy and tolerability.
- Psychosocial therapies can add benefit to pharmacotherapy and may be necessary for patients who cannot use pharmacotherapy due to intolerability or preference.

Attention-deficit/hyperactivity disorder (ADHD) is among the most commonly diagnosed illnesses in pediatric medicine. Approximately 4% to 8% of children are diagnosed with ADHD. ADHD is most commonly diagnosed in children between the ages of 6 and 12 years, although it is also diagnosed and treated in children as young as age 3. Although previously thought to largely abate in adolescence and adulthood, ADHD is now considered to be a chronic condition. More than 60% of children with ADHD have impairing symptoms well into adolescence and adulthood. ADHD can cause social problems, academic and learning problems, emotional problems, delinquency, and increased risk-taking behavior, including substance abuse.

ADHD is highly heritable. Approximately 10% to 35% of immediate family members of children with ADHD have ADHD themselves, and approximately 30% of siblings of children with ADHD also have the disorder. Parents of children with ADHD are at high risk for ADHD themselves, and appropriate assessment and potential treatment of ADHD in the parents can improve the child’s environment. ADHD is thought to reflect decreased dopamine and norepinephrine transmission in the brain. Maternal smoking and alcohol use, low birth weight, and lead exposure are associated with increased rates of ADHD. Social factors are not thought to play a major role in the development of ADHD.

Diagnosis

Children with ADHD tend to have profound difficulties in maintaining or sustaining attention, and/or they are hyperactive or impulsive. The core inattentive and hyperactive/impulsive symptoms of ADHD are defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV). ADHD is classified according to three subtypes: predominantly inattentive type, predominantly hyperactive/impulsive type, and combined type, which is the most common subtype.

The predominantly inattentive type of ADHD is characterized by at least six of the inattention core symptoms but fewer than six of the hyperactive/impulsive symptoms (see Current Diagnosis box). The predominantly hyperactive/impulsive type of ADHD involves six of nine hyperactive/impulsive symptoms but fewer than six of the inattention symptoms. If a patient has at least six of the inattention and six of the hyperactive/impulsive symptoms, the diagnosis is combined-type ADHD. These symptoms must also cause significant impairment in the child’s life in more than one domain (e.g., in school and home settings) to meet the criteria for ADHD. Symptoms of ADHD must have been present before the age of 7 years to meet the full criteria, although lack of this specifier alone should not preclude treatment.

ADHD is diagnosed by clinical interviews of the child and parents and from information from outside sources, especially from the child’s school or daycare. Standardized assessment tools and rating scales, such as the Medium SNAP IV (developed by...
Attention-Deficit/Hyperactivity Disorder

Stimulants

For approximately 75% of children with ADHD, treatment with stimulants decreases their symptoms. As a class, stimulants are fast acting (i.e., improvements are usually evident in the first few days of treatment) and usually well tolerated. Several types of stimulant medications are available. No stimulant has consistently proved to be more effective than another. Choice of a first stimulant medication for the treatment of ADHD is typically based on the desired duration of effect, frequency of dosing, percentage of short-acting medication versus long-acting medication, and the desired delivery system.

The two major classes of stimulant medications are methylphenidate (e.g., Ritalin, Methylin, Concerta) and amphetamine-type preparations. Figure 1 summarizes the medications FDA approved for the treatment of ADHD. Because the data equally support short-acting (immediate-release) and longer-acting stimulant preparations, most clinicians begin with longer-acting preparations, which are thought to offer a smoother level of medication effect and need to be dosed only once daily, which tends to improve compliance. Reasons to consider a shorter-acting medication include wanting to change to a different stimulant preparation. Melatonin1,7 is commonly used as an adjunct therapy for the treatment of stimulant-induced insomnia.

Stimulants can cause or exacerbate vocal and motor tics. Stimulants may also cause insomnia. 1-Blocking agents such as clonidine (Catapres)1 or guanfacine (Tenex)1 are sometimes used in addition to stimulant medication to treat the side effects of insomnia or tics. Insomnia can sometimes be managed by decreasing the dose of the stimulant, changing the timing of the dose, or changing to a different stimulant preparation. Melatonin1,7 is commonly available as a dietary supplement.

Nonstimulants

Atomoxetine is an FDA-approved medication used to treat children, adolescents, and adults with ADHD. Although the degree of effect tends to be somewhat lower than those found with stimulant treatments of ADHD, it is typically effective and well tolerated. Atomoxetine works less quickly than stimulants (peak effectiveness usually apparent around weeks 4 to 6), but it may provide longer duration (i.e., 24-hour) coverage. Atomoxetine is less likely to exacerbate anxiety or cause tics compared with...
<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosing</th>
<th>Typical starting dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Methylphenidate preparations</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methylphenidate (generic name)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Brand name formulations)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ritalin</td>
<td>bid to tid</td>
<td>5 mg bid</td>
<td>available in both liquid and chewable tablet forms</td>
</tr>
<tr>
<td>Methylin</td>
<td>bid to tid</td>
<td>5 mg bid</td>
<td>capsule can be opened and contents can be sprinkled into food, longer-acting formulation</td>
</tr>
<tr>
<td>Methylin ER</td>
<td>once daily</td>
<td>10 mg qam</td>
<td>capsule can be opened and contents can be sprinkled into food, longer-acting formulation</td>
</tr>
<tr>
<td>Metadate ER</td>
<td>once daily</td>
<td>10 mg qam</td>
<td>capsule can be opened and contents can be sprinkled into food, longer-acting formulation</td>
</tr>
<tr>
<td>Metadate CD</td>
<td>once daily</td>
<td>20 mg qam</td>
<td>capsule can be opened and contents can be sprinkled into food, longer-acting formulation</td>
</tr>
<tr>
<td>Ritalin SR</td>
<td>once daily</td>
<td>10 mg qam</td>
<td>uses osmotic pump mechanism, longer-acting formulation</td>
</tr>
<tr>
<td>Ritalin LA</td>
<td>once daily</td>
<td>20 mg qam</td>
<td></td>
</tr>
<tr>
<td>Concerta</td>
<td>once daily</td>
<td>18 mg qam</td>
<td></td>
</tr>
<tr>
<td>Daytrana patch</td>
<td>apply once daily, then remove at end of the day</td>
<td>10 mg patch</td>
<td></td>
</tr>
<tr>
<td>D-Methylphenidate (generic name)</td>
<td></td>
<td></td>
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<td>(Brand name formulations)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Focalin</td>
<td>bid to tid</td>
<td>2.5 mg bid</td>
<td>capsule can be opened and contents can be sprinkled into food, longer-acting formulation</td>
</tr>
<tr>
<td>Focalin XR</td>
<td>once daily</td>
<td>5 mg qam</td>
<td></td>
</tr>
<tr>
<td><strong>Dextroamphetamine (generic name)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Brand name formulations)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adderall</td>
<td>qd to bid</td>
<td>3–5 y: 2.5 mg qam; ≥6 y: 5 mg qd to bid</td>
<td>capsule can be opened and contents can be sprinkled into food, longer-acting formulation</td>
</tr>
<tr>
<td>Adderall XR</td>
<td>once daily</td>
<td>≥6 y: 10 mg qam</td>
<td></td>
</tr>
<tr>
<td><strong>Lisdexamphetamine (generic name)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Brand name formulations)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vyvanse</td>
<td>once daily</td>
<td>30 mg qam</td>
<td>is a pro-drug, thus must be enzymatically cleaved in the gastrointestinal tract in order to yield active d-amphetamine. Not thought to be abusable intranasally</td>
</tr>
<tr>
<td><strong>Non-stimulant medication</strong></td>
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</tr>
<tr>
<td>Atomoxetine (generic name)</td>
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</tr>
<tr>
<td>(Brand name formulations)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strattera</td>
<td>once daily (also can be given divided bid)</td>
<td>patients &lt;70 kg: 0.5 mg/kg/day for 4 days; then 1 mg/kg/day for 4 days; then 1.2 mg/kg/day</td>
<td>less likely to exacerbate anxiety in some children, not thought to be abusable</td>
</tr>
<tr>
<td>Guanfacine (generic name)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Brand name formulations)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intuniv</td>
<td>once daily</td>
<td>1 mg/day increasing by 1 mg each week to a max of 4 mg/day</td>
<td>little abuse potential, may cause somnolence</td>
</tr>
<tr>
<td>Clonidine (generic name)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Brand name formulations)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kapvay</td>
<td>once daily</td>
<td>1 mg/day</td>
<td>little abuse potential, may cause somnolence</td>
</tr>
</tbody>
</table>

**Figure 1.** Medications commonly used to treat ADHD. Abbreviations: bid = twice daily; ER = extended release; LA = long acting; qam = every morning; qd = once daily; SR = sustained release; tid = three times daily; XR = extended release.
stimulant medications. Atomoxetine has no abuse liability and is not a controlled substance.

Side effects include increased heart rate and blood pressure, and it should be used with caution in children with structural or conductive cardiac abnormalities. Atomoxetine carries an FDA black box warning recommending monitoring for the potential emergence of suicidality in patients taking this medication. Atomoxetine can markedly elevate hepatic enzymes and bilirubin, although hepatic failure is thought to be a rare event. Patients who exhibit symptoms such as jaundice or other indices of liver disease should stop taking this medication and receive medical work-up. Other potential side effects of atomoxetine include agitation, gastrointestinal upset, and headaches, although overall, this medication is thought to be well tolerated.

α-Adrenergic agonists such as clonidine and guanfacine are antihypertensive medications that have been used off-label for many years for the treatment of ADHD, lacking FDA approval for this purpose. Although these medications can improve functioning in patients with ADHD, clinical response is usually less robust than with stimulants. Clonidine and guanfacine are potentially useful in the treatment of hyperactive/impulsive symptoms and are most commonly used adjunctively with stimulants in children with ADHD to treat stimulant-induced tics and insomnia. Clonidine requires three to four doses throughout the day, and guanfacine is typically dosed twice daily. These medications should be used with caution because they carry risks of sedation, orthostasis, potential cardiac side effects, and rare reports of sudden cardiac death with overdose. They should be started at low doses and then titrated slowly. These medications should not be discontinued without a gradual taper over the course of 1 to 2 weeks because of the potential of rebound hypertension and irritability. The FDA has recently approved two long-acting versions of the α-adrenergic agents guanfacine (Intuniv) and clonidine (Kapvay).

Certain antidepressant medications are used to treat children and adults with ADHD, although they do not carry FDA approval for this purpose. Some studies have shown that the antidepressant bupropion (Wellbutrin) improves symptoms of ADHD in children and adults, and it is efficacious in treating depression and ADHD in children and adults who suffer from these comorbid conditions. Potential side effects of bupropion include increases in pulse and blood pressure and potential lowering of a person’s seizure threshold. Bupropion, like all antidepressants, carries an FDA black box warning about the potential of these medications to increase suicidality in youths and young adults.

Although rarely used for this purpose and not FDA approved, the tricyclic antidepressants desipramine (Norpramin), imipramine (Tofranil), and nortriptyline (Pamelor) are thought to have some efficacy in the treatment of ADHD. These medications are used less commonly because of significant side effects such as ECG changes (prolonged QTc), sedation, and risk of sudden cardiac death with overdose.

Modafinil (Provigil) is FDA approved for the treatment of narcolepsy, shift-work sleep disorder, and obstructive sleep apnea/hypopnea syndrome, and it is thought to improve vigilance and decrease distractibility. It is sometimes used to treat ADHD. Modafinil is not thought to be as easily abused as the stimulant medications.

Stimulant pharmacotherapy should be the initial treatment for most cases of ADHD. Formal dosing guidelines of stimulants should be followed. Titration of the dose until sufficient improvement is gained or limiting side effects emerge is the best way to optimize stimulant treatment outcome. There is sufficient evidence to suggest switching to another stimulant if treatment with the initial agent is suboptimal (e.g., switching from an amphetamine preparation to a methylphenidate preparation), and if the second stimulant trial fails, consideration should be given to a third stimulant trial. If there is a partial response to a stimulant trial, consider augmentation with atomoxetine or the addition of an α-blocking agent if insomnia or tics are mitigating side effects.

Although ADHD tends to be a chronic condition, not all children with ADHD progress to become adults with ADHD. Children who are being treated for ADHD should be reassessed yearly to determine if treatment for ADHD is still indicated. In the treatment of adults with ADHD, the same treatment strategies apply, although adults may require higher doses of medication. Stimulants and atomoxetine are the primary treatments for adults with ADHD. Because of higher rates of substance abuse comorbidity in adults, the risks of potential stimulant abuse and diversion may be higher in this population.

Psychosocial Treatments

Psychosocial therapies can be a useful and sometimes necessary adjunct to pharmacotherapy for the treatment of ADHD. Behavior therapy can be effective in helping to manage symptoms of ADHD, and parents and teachers are essential for implementing behavioral strategies and for continually assessing ADHD symptoms and treatment side effects. Parent training groups are effective at maximizing children’s compliant behaviors, and several books (e.g., Barkley’s *Your Defiant Child*, Forehand and Long’s *Parenting the Strong-Willed Child*) are available for training parents and clinicians to teach and reinforce behavioral therapy.

Classroom management techniques are an important part of any psychosocial approach to the treatment of ADHD in children and adolescents. Teachers of students with ADHD have found it helpful to increase the structure in classrooms, use consistent rewards and punishments, and use daily report cards to communicate school performance to parents at home.

Psychosocial interventions alone are not highly effective for the treatment of children with ADHD. For children with uncomplicated ADHD, psychosocial interventions may not significantly add benefit to pharmacotherapy alone. Because of the high rates of comorbidity in children and adolescents with ADHD, additional psychopharmacies (and sometimes pharmacotherapies) may be necessary to treat these more complex presentations.

References

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Not FDA approved for this indication.
The maturation of the fetus and transition to neonatal life requires the precise coordination of an immensely complex cascade of biochemical and physiologic events. As a result, the late fetal and early neonatal period is also the time of life exhibiting the highest mortality rate of any pediatric age interval. The infant mortality rate includes both the neonatal (days 1–28) and the post-neonatal (days 28–365) periods and is expressed as the number of deaths per 1000 live births. Despite considerable advances in neonatal and obstetrics care over the past few decades, the infant mortality rate in the United States in 2008 was 6.6 per 1000 live births, with congenital malformations and prematurity or low birth weight as the top two causes of infant death. Early identification and initiation of appropriate care of these high-risk neonates is essential to improving their outcome.

Care of the high-risk neonate begins with appropriate delivery, management, and resuscitation of the infant. The goals of resuscitation are to maintain or establish effective ventilation and oxygenation, maintain or restore adequate cardiac output and tissue perfusion, and maintain or restore normal body temperature. The steps needed to achieve these goals are based on the common ABC (airway, breathing, circulation) principles that are relevant to all infants. However, after adequate resuscitation, the care of the high-risk neonate is dictated by the diagnosis of the infant’s problem. Most of these diagnoses and the treatment approach for each can be categorized into prematurity, abnormal transition, infection, intestinal malformations, or pulmonary hypoplasia.

**Prematurity**

**Epidemiology**

The mean duration of a spontaneous singleton pregnancy is 40 postmenstrual weeks. An infant delivered before the completion of the 37th week is considered preterm. Preterm infants can be further classified according to birth weight: low birth weight (LBW) if less than 2500 g, very low birth weight (VLBW) if less than 1500 g, and extremely low birth weight (ELBW) if less than 1000 g. The rate of preterm births increased to 12.3 in 2008, up 20% since 1990. This is a result mostly of increases in late preterm births, which, in turn, can be attributed to a significant rise in both indicated preterm births and multifetal gestations associated with assisted reproductive technology.

**Clinical Manifestations and Treatment**

Besides the risk for death, prematurity is also associated with an increased risk of morbidity in nearly every organ system, and this risk increases dramatically as both the gestational age and birth weight decrease. The approach to the common problems associated with the premature neonate is presented in Box 1.

**Complications**

One of the most difficult decisions faced by families and health care professionals regards the treatment of infants at the threshold of viability. Although this threshold has decreased since the 1970s, most neonatologists recognize 22 to 24 weeks’ gestation as the limit of viability. Survival rates for infants born at 23 weeks’ gestation (23 0/7 to 23 6/7 days) range from 15% to 30%, whereas survival increases to between 30% and 55% for infants born at 24 weeks’ gestation. Within this group of survivors, 30% to 50% will have moderate to severe disability, including blindness, deafness, developmental delays, and cerebral palsy. Up-to-date preterm birth outcome estimates are available at the National Institute of Child Health and Human Development (www.nichd.nih.gov/about/org/cdbpm/pp/prog_epbo/index.cfm). The American Academy of Pediatrics recommends that decisions regarding lifesustaining treatment of these infants should be based on the best interests of the newborn, and the Academy also recognizes that parents should have the primary role in choosing aggressive versus palliative care of their infant. Making decisions within this gestational range requires accurate information regarding the mortality and morbidity risks for this population and thorough communication with the family.

**Abnormal Transition**

The transition from fetal to neonatal life involves a dramatic process of pulmonary adaptation that includes evacuation of fluid from the lungs, expansion of the lungs with air, decreasing pulmonary vascular resistance, and initiating respiratory effort. Often, this transition is delayed or disrupted and the respiratory status of the newborn is compromised. A few conditions associated with an abnormal transition are reviewed.

**Transient Tachypnea of the Newborn**

**Epidemiology**

Transient tachypnea of the newborn (TTN) is a mild condition affecting term and late preterm infants and is the most common respiratory cause of admission to the special care nursery. By definition, TTN is self-limiting, rarely causes hypoxic respiratory failure (hypoxia requiring ventilator support), and has no increased risk of pulmonary dysfunction later in life.

**Risk Factors**

TTN is classically seen in term or late preterm infants, especially after cesarean birth before the onset of spontaneous labor.

**Pathophysiology**

Traditional explanations for the pathophysiology of TTN involve impaired fluid clearance from the lungs because of decreased Starling forces and pulmonary squeeze normally encountered during movement through the birth canal. However, the bulk of pulmonary fluid clearance during labor is mediated by activation of sodium channels in the respiratory epithelial cells. In addition, some studies suggest TTN might also involve a mild surfactant deficiency.

**Clinical Manifestation**

TTN usually manifests with significant grunting along with tachypnea, nasal flaring, mild retractions, and mild hypoxia.
Common Problems and Treatment in Premature Infants

**Delivery Room**
Anticipation and preparation are key. The delivery team should include a neonatologist, neonatal nurse, and respiratory therapists. Dry and warm the infant immediately. Ventilate with a bag mask if the heart rate is low or there is no respiratory effort. Use mask continuous positive airway pressure (CPAP) if the heart rate is good and the infant has good respiratory effort. Intubate if there is no response from bag mask ventilation. Avoid high pressures.

**Pulmonary**
Respiratory distress syndrome owing to surfactant deficiency is common in preterm infants. Care is supportive with supplemental oxygen, CPAP, or gentle ventilation as needed. To reduce risk of chronic lung disease, use the lowest support needed to achieve oxygen saturations of 91% to 95% and Paco2 of 50 to 65 mm Hg. Use exogenous surfactant when indicated. Apnea is common and is treated with caffeine citrate (Cafcit) 20 mg/kg bolus, 5 mg/kg every 24 hours maintenance.

**Cardiovascular**
Hypotension can require inotropic (epinephrine or dopamine) support. Avoid large fluid boluses in extremely-low-birth-weight (ELBW) infants. Some hypotensive preterm infants are adrenal deficient and might respond to hydrocortisone (Solu-Cortef). Patent ductus arteriosus (PDA) occurs in 50% of ELBW infants. Medical treatment consists of fluid restriction and indomethacin (Indocin IV, 0.2 mg/kg/dose for four doses3). Surgical ligation of the PDA may be needed.

**Nutrition**
Parenteral nutrition is required in most infants younger than 32 weeks' gestation while enteral feedings are increased and will require placement of a percutaneous central venous catheter. Premature infants require higher-calorie (24 to 30 calories/ounce) preterm formula or human milk supplemented with preterm fortifiers.

**Fluids and Electrolytes**
Total fluid requirements for premature infants start at 80 mL/kg/day on day 1 of life and increase by 20 mL/kg/day each day to a maximum of 140 to 160 mL/kg/day. Fluid intake needs can vary depending on the clinical status of the infant. Sodium and potassium supplements are added on day 2. Hypernatremia is caused by increased free water loss.

**Gastrointestinal**
Necrotizing enterocolitis is a devastating complication of prematurity and is characterized by abdominal distention, feeding intolerance, bloody stools, and evidence of pneumatosis intestinalis, portal venous gas, and/or free air on abdominal radiographs. Early medical management includes decompressing the bowel, stopping enteral feedings, and giving intravenous antibiotics. Surgery is indicated in patients with intestinal perforation or failed medical treatment.

**Anemia**
Because of frequent blood draws and delayed activation of erythropoiesis, most ELBW infants require a transfusion of packed red blood cells (10 to 20 mL/kg) during their hospital stay.

**Hyperbilirubinemia**
Bilirubin central nervous system toxicity occurs at a lower level in preterm infants, and as a result phototherapy needs to be initiated sooner in this population.

**Central Nervous System**
Intraventricular hemorrhage remains a significant problem in premature infants. The risk increases with decreasing gestational age, stress, sepsis, birth asphyxia, rapid shifts in volume status, and hypotension. A head ultrasound should be obtained at 7 to 10 days of age to evaluate for intraventricular hemorrhage and afterward as needed depending on the severity of the findings.

Diagnosis
TTN is primarily a clinical diagnosis. Chest x-rays often demonstrate mild pulmonary congestion, with small accumulations of extrapleural fluid, especially in the minor fissure on the right side. Symptoms usually improve rapidly and resolve within the first 24 to 36 hours.

Differential Diagnosis
TTN is a diagnosis of exclusion and it is important that other potential causes of respiratory distress in the newborn such as infection, pneumothorax, meconium aspiration, polycythemia, and congenital heart disease are excluded.

Treatment
Management is mainly supportive. Supplemental oxygen is provided to keep the O2 saturations greater than 91%. Continuous positive airway pressure is rarely needed and may increase the risk of pneumothorax in this population. If symptoms last longer than 2 to 3 hours, infants are usually given intravenous fluids and not fed orally until their tachypnea resolves.

Meconium Aspiration

**Epidemiology**
Meconium stained amniotic fluid occurs in 12% to 15% of all deliveries, and this rate increases in postterm gestation and in African American infants. In contrast to meconium-stained amniotic fluid, meconium aspiration syndrome is rare, occurring in 2% of deliveries with meconium-stained amniotic fluid, although the reported incidence varies and trends suggest this incidence is decreasing.

**Risk Factors**
Risk factors for meconium aspiration include meconium stained fluid, in utero stress, and postterm gestation.

**Pathophysiology**
Traditional explanations for the pathophysiology of meconium aspiration syndrome suggest that fetal stress leads to passage of meconium in utero. Once this meconium is aspirated, it can cause airway obstruction, pneumothorax, chemical pneumonitis, and pulmonary hypertension. However, recent reports that describe infants born through clear amniotic fluid with respiratory distress and other clinical findings similar to meconium aspiration syndrome suggest this traditional explanation may be incorrect.
Clinical Manifestation
Meconium aspiration syndrome manifests as severe respiratory failure and pulmonary hypertension.

Diagnosis
By definition, the diagnosis of meconium aspiration syndrome includes delivery through meconium-stained amniotic fluid along with respiratory distress and a characteristic chest x-ray appearance of patchy infiltrates with areas of hyperlucency throughout the lung fields.

Differential Diagnosis
Other potential causes of respiratory distress in the newborn such as infection, surfactant deficiency, pneumothorax, and congenital heart disease must be considered.

Treatment
Until recently, aggressive suctioning of the airway in infants delivered through meconium stained fluid was considered the key to preventing meconium aspiration syndrome. Now the Neonatal Resuscitation Program protocol for delivery room management no longer recommends tracheal suctioning for vigorous infants (depressed infants should have their airways cleared as needed), implying that establishment of ventilation should take precedence over attempting to suction an unobstructed airway.

The treatment of meconium aspiration syndrome has dramatically improved in recent years, leading to decreases in morbidity, mortality, and the use of extracorporeal membrane oxygenation (ECMO). Most of these advances have come from treatment of pulmonary hypoplasia with selective pulmonary vasodilators such as inhaled nitric oxide (iNO). These agents improve oxygenation, which in turn decreases the need for ventilator support and the risk of air leak and chronic lung disease. Administration of exogenous surfactant (Survanta) may be another useful treatment modality.

Persistent Pulmonary Hypertension of the Newborn

Epidemiology
Persistent pulmonary hypertension of the newborn (PPHN) occurs when the normal cardiopulmonary transition of the delivered infant fails. Estimates indicate that severe PPHN occurs in 2 per 1000 liveborn term infants, but PPHN complicates the clinical course of up to 10% of all neonates with respiratory failure.

Risk Factors
Risk factors for developing PPHN include sepsis, pneumonia, congenital malformations, and all conditions associated with pulmonary hypoplasia.

Pathophysiology
At delivery, the normal decrease in pulmonary vascular resistance requires relaxation of pulmonary arteriolar smooth muscle, distention of alveoli, and a change in endothelial cell shape. When pulmonary development is hypoplastic or the fetus experiences significant intratruculent stress or hypoxemia, there is an increase in both pulmonary arteriolar reactivity and proliferation of medial smooth muscle of the pulmonary vessels. When these vessels are subjected to hypoxemia or acidosis, they are more prone to constriction, which subsequently induces right-to-left shunting of deoxygenated blood.

Clinical Manifestation
PPHN typically manifests with severe hypoxemia in the setting of respiratory failure with a more than 5% differential in preductal and postductal oxygen saturations. Often, hypotension secondary to right heart failure and decreased left ventricular filling is also present. PPHN symptoms may be isolated or occur in combination with the primary cause of stress or respiratory failure.

Diagnosis
PPHN is diagnosed with an echocardiogram, which reveals elevated right ventricular pressures and right-to-left shunting across the foramen ovale and ductus arteriosus. In severe PPHN, right ventricular pressures are equal to or greater than systemic pressures.

Differential Diagnosis
The primary cause of stress or respiratory failure in PPHN such as sepsis, pneumonia, and pulmonary hypoplasia must always be considered. In addition, congenital heart disease must be excluded.

Treatment
The first goal of PPHN therapy is optimal oxygenation and ventilation. However, care must be taken not to induce significant over-distention of alveoli and pulmonary injury. Often the short-term benefit of improving carbon dioxide levels or oxygen saturations by a few points is not worth the risk of lung injury and bronchopulmonary dysplasia. As a result, targeting an oxygen saturation of 91% to 95%, arterial pH levels of 7.25 to 7.35, and carbon dioxide levels of 50 to 65 mm Hg usually achieves a good balance between short-term and long-term goals.

The treatment of PPHN has significantly improved since the turn of the 21st century owing to pharmacologic interventions that specifically reduce pulmonary vascular resistance. Of these, iNO (dose 5-20 ppm) is the best studied and has demonstrated a clear benefit in the setting of PPHN caused by meconium aspiration syndrome or sepsis. Other pulmonary vasodilators, including sildenafil (Revatio),1 bosentan (Tracleer),1 and prostacyclin (epoprostenol, Flolan)1 are increasing in use. When adequate ventilation and pulmonary vasodilators fail in patients with PPHN, ECMO may be considered.

Hypoxic-Ischemic Encephalopathy

Epidemiology
Despite significant advances in obstetric and neonatal care, the incidence of hypoxic-ischemic encephalopathy (HIE) remains at 1 to 2 infants per 1000 term births. Although HIE was once thought to result from brain injury sustained only during the perinatal period, recent data show that most brain injury occurs well before labor and only 10% of neonatal brain injury is related to perinatal or intrapartum events.

Risk Factors
Several clinical measures such as fetal heart rate abnormalities, meconium-stained amniotic fluid, low Apgar scores, large size for gestational age, and the need for resuscitation in the delivery room suggest an increased risk for developing HIE. However, all of these indicators have a very high false-positive rate and therefore do not reliably identify infants who will develop HIE.

Pathophysiology
The brain injury referred to as HIE occurs when oxygen delivery to the brain is insufficient to meet the metabolic demands, resulting in hypoxia, hypercarbia, and metabolic acidosis. This asphyxia is due most often to an interruption of placental blood flow or gas exchange. Although HIE is initiated by a hypoxic event, a growing body of evidence now suggests that there is also a reperfusion phase of brain injury, and several emerging neuroprotective therapies are targeting this phase of injury.

Clinical Manifestation
HIE is clinically characterized by a depressed level of consciousness, seizures and abnormalities in muscle tone (hypotonia initially followed by hypertonia), reflexes (usually decreased initially), and respiratory effort. If other organ systems are involved, infants can also present with signs of heart, kidney, and liver failure.

1Not FDA approved for this indication.
Diagnosis
HIE is a clinical diagnosis. The Sarnat staging system is often used to classify the severity of the brain injury. Sarnat stage 1 infants have a good prognosis. Sarnat stage 2 infants have long-term neurologic impairment in 20% to 25% of cases, and more than 80% of Sarnat stage 3 infants develop long-term neurologic sequelae. Although brain imaging studies such as magnetic resonance imaging (MRI) are often used to assess the location and severity of brain injury, correlating MRI findings with long-term neurologic outcome is difficult.

Differential Diagnosis
The findings of HIE usually result from hypoxic injury, but they can also result from exposure to toxins or from metabolic, neuromuscular, and chromosomal abnormalities.

Treatment
First-line therapy in infants with HIE is supportive. Adequate ventilation and systemic perfusion should be established using ventilator and inotropic support as needed. If seizures occur, phenobarbital is a good first-line antiepileptic agent in these infants.

Cooling therapy is recommended in infants with HIE. In infants with moderate to severe HIE, whole-body cooling decreased the risk of death or moderate to severe disability by 18%. Current recommendations suggest the following clinical parameters in order to qualify for cooling: gestational age 36 weeks or older, umbilical artery pH less than 7.00 or a base deficit at least 16 mEq/L, and evidence of an abnormal neurologic examination, seizures, or abnormal electroencephalogram (EEG).

Infection
Epidemiology
Neonatal sepsis is a significant cause of morbidity and mortality in term and preterm infants, and the risk of infection increases as the gestational age decreases. Neonatal sepsis is generally divided into two categories: early and late onset. Early-onset sepsis occurs in the first 3 days of life at a rate of approximately 1.9% of VLBW infants. Early-onset sepsis is caused by bacteria residing in the mother’s genital tract such as Escherichia coli, group B Streptococcus (GBS), and Listeria monocytogenes. The incidence of GBS disease has significantly decreased since the institution of screening and treatment for GBS colonization in mothers during the third trimester. Late-onset sepsis occurs between days 3 and 28 and is more common, with an incidence of 21% of VLBW infants. Late-onset sepsis is caused by a variety of bacteria including Staphylococcus epidermidis, Staphylococcus aureus, Escherichia coli, Klebsiella, Enterococcus, Pseudomonas, and Streptococcus pneumoniae. Ultimately 18% to 36% of infected VLBW infants die; those who survive have a significantly prolonged hospital stay and increased morbidity when compared to uninfected infants.

Risk Factors
The risk for neonatal infection is inversely proportional to gestational age. African American race and male sex are additional risk factors for neonatal infection. Specific risk factors for early-onset sepsis include prolonged rupture of membranes (>24 hours), chorioamnionitis, maternal infection, and prematurity. The risk for late-onset sepsis is increased by the presence of central venous catheters, peripheral intravenous catheters, endotracheal tubes, umbilical vessels, and electronic monitoring devices.

Pathophysiology
Although infants are protected by maternal antibodies transferred across the placenta during the third trimester, compared with older children or adults, the neonatal immune system is still deficient. Innate immunity is defective at several levels. Skin and mucosal barriers are poorly developed, and bacterial translocation across these barriers is common. Antibacterial proteins such as lysozyme, lactoferrin, and lectins are decreased. Neutrophil chemotaxis, phagocytosis, and intracellular killing are limited. In addition to these defects in innate immunity, humoral and cell-mediated immune functions are also poorly developed.

Clinical Manifestation
Neonatal sepsis can manifest with a variety of nonspecific signs including lethargy, poor feeding, temperature instability, decreased tone, increased work of breathing, apnea, cyanosis, bradycardia, abdominal distention, and altered perfusion. Petechiae and purpura may be present during disseminated intravascular coagulation. Although fever and localizing symptoms are common in older children and adults with infection, neonatal sepsis rarely manifests with these symptoms.

Diagnosis
The gold standard for diagnosing sepsis is a positive blood culture. However, the sensitivity of a blood culture in an infected neonate is between 30% and 60% depending on the volume of blood used for the culture. Therefore, the diagnosis of sepsis in the neonate is more often based on clinical suspicion than laboratory evaluation.

All infants in whom sepsis is suspected should have a thorough clinical examination to evaluate the infant for signs of infection and assess his or her clinical stability. A complete blood count (CBC), cerebrospinal fluid (CSF) culture, and urine culture can also be sent as part of the work-up for neonatal infection, but the value of each of these tests is uncertain. A white blood cell count less than 5000 or greater than 40,000, a total neutrophil count less than 1000, and a band-neutrophil-to-total-neutrophil ratio of greater than 0.2 all correlate with an increased risk of infection, but these tests have a sensitivity for detecting infection that is less than 50%. In addition, because CBC values are often abnormal in healthy neonates, the positive predictive value of an abnormal CBC is less than 18%. Therefore, a normal CBC only weakly supports that the infant is uninfected, and likewise an abnormal CBC only weakly supports the diagnosis of infection.

Many institutions send a CSF for culture, Gram stain, cell count, and protein and glucose levels as part of the evaluation of every infant with suspected sepsis. In contrast, some institutions only send CSF for analysis if the blood culture is positive. The latter method is based on the assumption that because of the inability to isolate infections and the poorly developed blood–brain barrier in the neonate, all neonates with meningitis also have positive blood cultures. This approach is refuted by studies that demonstrate negative blood cultures in up to 50% of infants with meningitis. However, there is still uncertainty regarding the benefit to subjecting every neonate with suspected sepsis to a lumbar puncture.

Differential Diagnosis
The differential diagnosis of neonatal sepsis includes respiratory distress syndrome, TTN, PPHN, metabolic disorders, and congenital heart disease.

Treatment
Ampicillin and gentamicin for 10 to 14 days remains the most effective first-line therapy against most organisms responsible for early-onset sepsis. The antibiotic choice can be tailored once the identity of the organism and antibiotic sensitivities are determined. If meningitis is present, improved penetration of the blood–brain barrier with a third-generation cephalosporin is recommended. Late-onset sepsis is treated with a similar approach but the antibiotic choice may be modified depending on the exposure history of the infant, all neonates with meningitis also have positive blood cultures. This approach is recommended in infants with hypoxic injury and neurologic impairment in 20% to 25% of cases, and more than 80% of Sarnat stage 3 infants develop long-term neurologic sequelae. Although brain imaging studies such as magnetic resonance imaging (MRI) are often used to assess the location and severity of brain injury, correlating MRI findings with long-term neurologic outcome is difficult.
After initiating appropriate antibiotic coverage, the remaining therapy for neonatal sepsis is supportive. Adequate oxygenation and ventilation can require ventilator support. Blood pressure and urine output are monitored to determine the need to treat septic shock with fluids or inotropic agents. Pulmonary vasodilators may be needed to treat exacerbations of pulmonary hypertension associated with sepsis.

**Intestinal Malformations**

**Intestinal Obstruction**

**Epidemiology**

Obstruction of the gastrointestinal tract can be complete (atresia) or partial (stenosis) and occur at any point from the esophagus to the anus. Obstruction of the intestinal tract occurs in 1 out of 1500 live births.

Esophageal atresia occurs in 1 out of 4000 live births. Of infants with esophageal atresia, 85% have a tracheoesophageal fistula and approximately 40% of infants with tracheoesophageal fistula have other associated anomalies as part of the VACTERL syndrome, which includes vertebral, anal, cardiac, tracheal, esophageal, renal, and limb anomalies.

Duodenal atresia occurs in 1 out of 5000 live births and is often associated with trisomy 21. Seventy percent of duodenal atresia cases are associated with other malformations such as cardiac anomalies, intestinal malrotation, annular pancreas and imperforate anus. In the jejunum and ileum, atresia is more common than stenosis, and ileal lesions are more common than jejunal lesions. Malrotation is associated with other gastrointestinal lesions including duodenal atresia, gastrochisis, omphalocele, and congenital diaphragmatic hernia.

Hirschsprung’s disease occurs in 1 out of 5000 live births and is the most common cause of large bowel obstruction in neonates. It is more common in boys, siblings of infants with Hirschsprung’s disease, and infants with trisomy 21.

Imperforate anus occurs in 1 out of 5000 live births.

**Pathophysiology**

All intestinal atresia or stenosis occurs as a result of either an incomplete formation during development or a vascular accident in utero. Regardless of the location or cause, the obstruction will lead to dilatation of the bowel proximal to the narrowing and atrophy of the bowel distally. If the proximal bowel is not decompressed, distention can lead to injury and necrosis.

Malrotation is caused by the incomplete rotation and fixation of the bowel as it returns to the abdominal cavity during development, with abnormally fixed bands crossing the duodenum. Malrotated intestine is at increased risk for volvulus, which causes strangulation of the superior mesenteric artery and occlusion of blood flow to the intestine.

Hirschsprung’s disease is caused by defective migration of neural crest cells to the distal colon, resulting in a distal segment of colon that is aganglionic and dysfunctional.

**Clinical Manifestation**

Infants with atresia or stenosis of the intestinal tract present with signs of obstruction. Infants with esophageal atresia present with excessive oral secretions, inability to feed, gagging, and respiratory distress when feeding is attempted. Infants with duodenal atresia present with abdominal distention and vomiting shortly after the first feeding. Patients with jejunal and ileal atresia also present with abdominal distention and vomiting, but the emesis may be delayed until the second or third feeding.

Malrotation and volvulus manifest as abdominal distention and bilious emesis. As this condition rapidly progresses, hematochezia, hypotension, and disseminated intravascular coagulation can develop.

Hirschsprung’s disease can manifest with failure to pass meconium in the first 24 hours of life, constipation, abdominal distention, explosive stool output with rectal examination, vomiting, and poor feeding.

Imperforate anus manifests with abdominal distention, lack of stool output, and the finding of imperforate anus on clinical examination.

**Diagnosis**

The diagnosis of esophageal fistula is often suggested by clinical symptoms and the inability to pass a feeding catheter into an infant with poor feeding skills. The diagnosis is then confirmed by chest radiographs with a feeding catheter looped in the obstructed proximal esophagus.

Duodenal atresia is diagnosed by the characteristic duodenal gaseous distention on radiograph (the double bubble sign) and contrast radiographic study of the upper gastrointestinal tract. Malrotation, jejunal atresia, and ileal atresia are all suggested by plain radiographs showing distention of the proximal small bowel and confirmed by contrast radiographic study of the upper gastrointestinal tract. If true bilious emesis occurs and malrotation is suspected, these patients are considered a medical emergency because the integrity of the bowel will be quickly compromised by vascular occlusion and these patients will rapidly progress to a fulminant and even fatal condition without surgical intervention.

Hirschsprung’s disease is suggested by clinical history and examination, plain radiograph revealing intestinal distention, and contrast radiograph of the distal bowel revealing proximal dilation and distal narrowing of the aganglionic segment. The diagnosis is confirmed by rectal biopsy revealing the absence of ganglia.

Imperforate anus is diagnosed by clinical examination.

**Treatment**

The first stage of therapy in all intestinal obstructions is to decompress the tract proximal to the obstruction with a repogle and stabilize the infant with intravenous fluids. The infant should be evaluated for associated anomalies, when indicated, by echocardiogram and renal ultrasound. Once the infant is stable, the obstruction is repaired by surgical removal of the lesion or dysfunctional bowel and reanastomosis. Often the defect can be repaired primarily, but in certain severe cases a diverting ostomy is required until the final repair can be completed.

**Complications**

In severe cases, intestinal obstruction is complicated by compromise of significant segments of bowel, requiring removal of large portions of the intestinal tract. When large sections are removed, absorption of nutrients is deficient and long-term parental nutrition may be needed.

**Gastrochisis and Omphalocele**

**Epidemiology**

The combined incidence of omphalocele and gastrochisis is 1 in 4000 live births. Of these two defects, gastrochisis is more common. In infants with omphalocele, 35% have other gastrointestinal defects and 20% have congenital heart defects. Other anomalies including trisomies 13 and 18, urinary tract anomalies, and Beckwith-Wiedemann syndrome are associated with omphalocele. In contrast, associated congenital or chromosomal anomalies are rare in gastrochisis patients, but these patients do have higher rates of malrotation, intestinal atresia, and necrotizing enterocolitis.

**Risk Factors**

Pregnancies complicated by infection, young maternal age, smoking, or drug abuse can increase the rate of gastrochisis. Interestingly, owing to unknown causes, the incidence of gastrochisis has increased in recent years.

**Pathophysiology**

Gastrochisis is caused by a cleft in the abdominal wall to the right of the umbilical cord that allows abdominal contents to herniate into the amniotic fluid. By definition, gastrochisis is not covered...
by a sac. In addition to being at risk for torsion and necrosis during this herniated state, the prolonged exposure of the bowel to the amniotic fluid causes a severe inflammatory response that results in intestinal injury and ileus.

Omphalocele results when the abdominal contents herniate through the base of the umbilical cord into a sac covered by peritoneum and amniotic membrane. The sac covering the defect is thin and can rupture in utero or during delivery. The size of the defect can range from small (containing only a small amount of intestine), to large (containing most of the abdominal organs), to giant (containing the majority of the liver). Giant omphaloceles are rare (1 in 10,000 births) and are often associated with pulmonary hypoplasia.

Clinical Manifestation and Diagnosis
Polyhydramnios is noted in utero in both conditions. Ten percent of infants with omphalocele and 60% of those with gastroschisis are born prematurely. Diagnosis of gastrochisis and omphalocele is initially made by prenatal ultrasound and confirmed by physical examination after delivery. Early prenatal diagnosis allows proper counseling of the family and referral to a tertiary care center for further management. Infants with omphalocele are also at risk for congenital heart defects and should be evaluated by echocardiogram. Infants with gastrochisis should be evaluated for areas of intestinal torsion, necrosis, or atresia at the time of their initial physical examination.

Treatment
Cesarean section is recommended in giant omphalocele to decrease the risk of rupture of the omphalocele sac, but cesarean section does not improve the outcome in smaller omphaloceles or gastrochisis. If the infant is stable, small omphalocele defects can be closed primarily, but larger defects require a staged repair and can be postponed as long as the sac is intact. Treatment of the intact omphalocele before closure includes intestinal decompression with a repogle to minimize gastrointestinal distention. Although protocols for topical care of the omphalocele sac vary, many cover the sac with petroleum-impregnated gauze and then wrap the sac with gauze to support the viscera on the abdominal wall. Prognosis worsens if the sac is ruptured; therefore there should be no attempt to reduce the omphalocele.

Initial treatment of gastrochisis involves placement of a nasogastric tube to suction, covering the exposed intestine with saline-soaked gauze, and wrapping the exposed intestine and lower half of the infant with a sterile bag to minimize fluid loss and injury to the bowel. Aggressive fluid management is required to compensate for extra fluid loss from the exposed bowel. Many institutions place the infant on antibiotics to cover for infection caused by bowel flora.

In 10% of infants with gastrochisis, single-stage primary closure is possible. In most infants with gastrochisis, a silicone elastic silo is placed over the exposed bowel, allowing gradual reduction of the intestine into the abdomen over a period of several days. Once the bowel is completely reduced, the defect is surgically closed. Postoperative care of infants with gastrochisis involves a prolonged recovery phase of the bowel during which the infants will require parenteral nutrition and a gradual advancing of enteral feeds.

Pulmonary Hypoplasia
Epidemiology
Lung development begins during the first trimester, progresses through several rounds of branching morphogenesis during the remaining months of gestation, and is not completed until the second or third year of life. Perturbation of lung development during any phase of gestation can result in pulmonary hypoplasia. Because of the variety of conditions associated with pulmonary hypoplasia, the true incidence is unknown.

Risk Factors
The most common risk factors for pulmonary hypoplasia include prolonged rupture of membranes, fetal renal dysplasias and obstructive uropathies, congenital diaphragmatic hernia, and congenital cystic lung lesions.

Pathophysiology
For lung development to proceed normally, the volume of the thorax must be adequate for lung expansion, and amniotic fluid must enter the lung through fetal breathing. Conditions that externally compress the lung (congenital diaphragmatic hernia, cystic lung lesions, pleural effusions with fetal hydrops, malformations of the thorax, abdominal mass lesions) or conditions that decrease amniotic fluid levels (prolonged rupture of membranes, renal agenesis, cystic kidney disease, and urinary tract obstruction) inhibit the branching morphogenesis of the lung and development of the gas exchange interface. As a result, hypoplastic lungs have reduced lung weight and alveolar number, fewer branching of airways, fewer pulmonary arteries, and an increase in both pulmonary arteriole reactivity and proliferation of medial smooth muscle in pulmonary vessels.

Clinical Manifestation
In addition to the manifestations associated with the primary disease, infants with pulmonary hypoplasia also present with significant respiratory and cardiac signs. The presentation is highly dependent on the severity of the pulmonary hypoplasia. Most infants with pulmonary hypoplasia present with increased work of breathing and significant hypoxia and acidosis. Shunting across the ductus arteriosus is evident on pre- and postductal oxygen saturations. Hypotension secondary to right heart failure and decreased left ventricular filling is often present.

Diagnosis
The diagnosis is based on a clinical history of an anomaly associated with pulmonary hypoplasia. Chest radiographs reveal small bell-shaped lungs or space-occupying chest mass depending on the cause of the hypoplasia. Pulmonary hypertension is often evident on echocardiogram.

Differential Diagnosis
The differential diagnosis of pulmonary hypoplasia includes pneumonia, cyanotic congenital heart disease, primary PPHN, and sepsis.

Treatment
In the fetus with pulmonary hypoplasia, a few interventions can improve prognosis. These include amniofusions in the setting of prolonged rupture of membranes and nephrostomy tubes in obstructive uropathy.

A portion of these infants have relatively mild disease and require only minimal support; however, many have profound hypoxia as a result of severe pulmonary hypertension. In these infants, the first goal is to establish adequate oxygenation and ventilation. However, care must be taken not to induce significant overdistention of alveoli and pulmonary injury. Targeting an oxygen saturation of 91% to 95%, arterial pH levels of 7.25 to 7.35, and carbon dioxide levels of 50 to 65 mm Hg usually achieves a good balance between short-term benefit and long-term pulmonary injury. Pulmonary vasodilators have significantly improved the care of infants with pulmonary hypertension associated with pulmonary hypoplasia. Of these, inhaled nitric oxide, 5 to 20 ppm, is the best studied. Other pulmonary vasodilators, including sildenafil,1 bosentan,1 and prostacyclin,1 are increasing in use. Often long-term pulmonary vasodilators are needed to promote lung remodeling and growth.

1Not FDA approved for this indication.
CHILDHOOD INCONTINENCE

Method of Walid A. Farhat, MD, and Kristin Kozakowski, MD

Urinary incontinence is defined by the International Continence Society as “involuntary loss of urine, objectively demonstrable, and constituting a social or hygienic problem.” In contrast to adults, in whom incontinence is always considered pathologic, pediatric urinary incontinence must be evaluated in the context of the child’s developmental age. An infant voids approximately 20 times a day via a vesicovesical reflex mechanism mediated by the spinal cord. As the child develops, the neural pathways in the spinal cord mature. In the first 18 to 24 months of life, this primitive voiding reflex is gradually inhibited, bladder capacity increases, and voiding becomes less frequent. Eventually, the more complex voiding reflex develops, and the coordination of voiding control becomes mediated by the pons and midbrain, the pontine micturition center. By the age of 2 years, children become consciously aware of bladder fullness, which leads to the ability to postpone voiding.

Although most children are toilet trained by 3 years of age, there can be a wide variation. Bloom and associates found that the mean age ranged from 0.75 to 5.25 years, with girls being trained earlier (2.25 years) than boys (2.56 years). In two other studies, Wnydaele and colleagues found that 12% of Belgian schoolchildren aged 10 to 14 years had incontinence episodes, and Dahm and colleagues found that 29% of 7- to 8-year-old Danish children had symptoms of underdeveloped bladder control. However, by the age of 5 years and entry into school, children can be expected to have developed volitional urinary control. Therefore, urinary incontinence after age 5, specifically daytime urinary incontinence, is a matter of both social and clinical concern.

Classification of Pediatric Urinary Incontinence

Clinical management of pediatric urinary incontinence is often complicated by a lack of standardized definitions as to what exactly constitutes different types of incontinence in children. This stems from the fact that a large percentage of wetting in children is sporadic and can be considered a variation of normal behavior. Parents and children are often embarrassed or desensitized to the incontinence and fail to bring it to their doctor’s attention. It is also important to recognize that urinary incontinence is frequently related to an underlying disease process (organic urinary incontinence). This is distinct from functional urinary incontinence, in which no anatomic or neurologic abnormality is present. Organic incontinence is subdivided into structural and neurologic causes. Structural incontinence includes all congenital, traumatic, and iatrogenic factors that interfere with the bladder’s ability to store and empty urine. Neurologic causes include congenital or acquired conditions that interfere with the innervation of the bladder and urinary sphincter (Figure 1).

To address this problem, the International Children’s Continence Society (ICCS) published a report in 1997 that attempted to standardize and define lower urinary tract dysfunction in children; this was updated in 2006. They defined incontinence as the uncontrollable leakage of urine, which can be broadly classified as continuous or intermittent (Figure 2). Continuous urinary incontinence is constant urine leakage with no dry periods. This is almost exclusively associated with organic urinary incontinence. Intermittent incontinence is urine leakage in discrete amounts, which can occur day or night and is applicable to children older than 5 years of age. Bedwetting, also termed “enuresis,” is intermittent incontinence that occurs at night. Accidents that occur during the day are classified as daytime incontinence. Patients with both daytime incontinence and bedwetting have two separate diagnoses; the term “diurnal incontinence” is now obsolete.

Enuresis

Enuresis, often termed “nocturnal enuresis,” is a normal void that occurs while the child is sleeping, usually without the child’s being aroused by the wetting. Bedwetting is usually not considered pathologic before the age of 7 years, and it is an extremely common occurrence. In a recent large-scale, longitudinal study, at least 20% of children in the first grade occasionally wet the bed, and 4% wet the bed two or more times per week. Bedwetting is more common in boys and can often show a familial tendency. The ICCS subdivides enuresis into two types: monosymptomatic enuresis (no other lower urinary tract symptoms) and non-monosymptomatic enuresis (other lower urinary tract symptoms are present). Primary enuresis means that the child never had any dry periods at night; children who had at least 6 months of nighttime dryness are said to have secondary enuresis.

Most cases of enuresis resolve with time and when the child becomes more focused on changing the behavior. The treatment of

<table>
<thead>
<tr>
<th>COMMON CAUSES OF ORGANIC INCONTINENCE</th>
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<tbody>
<tr>
<td><strong>Structural</strong></td>
</tr>
<tr>
<td>Ectopic ureter</td>
</tr>
<tr>
<td>Exstrophy/epispadias complex</td>
</tr>
<tr>
<td>Posterior urethral valves</td>
</tr>
<tr>
<td><strong>Neurologic</strong></td>
</tr>
<tr>
<td>Spina bifida</td>
</tr>
<tr>
<td>Tethered cord</td>
</tr>
<tr>
<td>Sacral agenesis</td>
</tr>
<tr>
<td>Cerebral palsy</td>
</tr>
<tr>
<td>Spinal cord injury</td>
</tr>
</tbody>
</table>

**Figure 1.** Common causes of organic incontinence.

enuresis begins with behavioral modification, including reducing evening fluid intake, increasing daytime voiding frequency, and the use of alarm therapy to condition the child to awaken with wetting. Pharmacologic therapy with desmopressin (DDAVP), which reduces overnight production of urine, is usually reserved for situations such as overnight visits and summer camp; this is no longer considered acceptable as a first-line agent or for regular usage. Tricyclic antidepressants are no longer used because of their adverse side-effect profiles.

Daytime Wetting Conditions
The classification of daytime wetting conditions is difficult, because children often have overlapping symptoms that can change as they age. The ICCS recommends that clinicians focus on four symptom parameters when assessing children with wetting accidents: incontinence (presence, absence, and frequency), normal voiding frequency, voided volumes, and fluid intake. There are several recognized syndromes that affect the pediatric population, and incontinence may occur in any of them.

Overactive Bladder and Urge Incontinence
The hallmark symptom of overactive bladder is urgency. The imperative urge to void is usually accompanied by holding maneuvers such as squatting and often results in the socially inappropriate loss of urine. Urgency is caused by overactive detrusor contractions early in the bladder filling phase; these are then countered by voluntary pelvic floor contractions or maneuvers to compress the urethra. In these children with overactive bladder, normal voiding frequency may be high, and bladder capacity is often small for age. This type of incontinence occurs more commonly in girls and can progress to a very severe form of dysfunctional voiding.

Urgo incontinence is treated with a combination of behavioral therapy, specifically timed voiding programs, and anticholinergic agents such as oxybutynin (Ditropan), which can help to reduce bladder overactivity. Oxybutynin can have side effects such as constipation, dry mouth, drowsiness, and flushing, which lead to discontinuation of its use in approximately 10% of children.

Voiding Postponement
Children who continuously postpone the urge to urinate at normal voiding intervals experience wetting accidents because they do not void unless their bladder is full and contracts involuntarily due to overcapacity. These children infrequently void and are often observed performing holding maneuvers. Children who routinely postpone the need to void often do so because of aversion to public bathrooms or because of not being allowed to use the bathroom during class. These children also may have comorbid psychological or behavioral disturbances.

Management consists of behavioral modification and, specifically, of strictly timed voiding bladder retraining programs. In extreme cases in which the child refuses to void, clean intermittent catheterization becomes necessary to empty the bladder.

Dysfunctional Voiding
Dysfunctional voiding patterns, specifically staccato and fractionated voiding, involve some form of overactivity of pelvic floor musculature during voiding, with an uncoordination between the detrusor and the musculature of the external sphincter or pelvic floor or both. These children habitually contract the urethral sphincter during voiding, but the condition is not related to any dysfunction of bladder storage.

Staccato voiding is a pattern characterized by periodic contractions of the pelvic floor musculature during voiding and interruptions in the flow of urine, leading to prolonged voiding time and residual urine. Fractionated voiding is characterized by small voided volumes with incomplete bladder emptying and an underactive detrusor muscle. Some children augment this voiding pattern with Valsalva maneuvers. These patients usually have large-capacity bladders and detrusor hypoactivity. Dysfunctional voiding can have serious long-term consequences, including high-pressure voiding, chronic urinary tract infections, vesicoureteral reflux, and decompensation of the detrusor muscle.

These dysfunctional voiding patterns are often very difficult to treat. Behavioral modification and biofeedback therapy are the most useful tools.

Underactive Bladder
Children with underactive bladder typically void only once or twice per day. They have increased bladder capacity and diminished bladder sensation to void and carry a high postvoid residual. They also typically need to strain to urinate and show decreased detrusor activity. The leakage that occurs is due to overflow incontinence.

The first line of therapy for these patients is timed-voiding and double-voiding bladder retraining programs. If this treatment fails, clean intermittent catheterization must be used to empty the bladder.

Non-Neurogenic Neurogenic Bladder Syndrome
Non-neurogenic neurogenic bladder, also called Himmann-Allen syndrome, is the most severe form of dysfunctional voiding. This occurs when there is chronic voluntary tightening of the external sphincter during an overactive detrusor contraction, resulting in learned failure to relax the external sphincter during voluntary voiding. This pattern results in bladder-sphincter dyssynergy and eventually leads to detrusor decompensation. These children present with symptoms of daytime and nighttime wetting, overflow and urge incontinence, and recurrent urinary tract infections, and their bladders show severe trabeculations and high postvoid residuals. Often, they have acquired vesicoureteral reflux and hydrourephrosis from the decreased bladder compliance. Despite the abnormal findings, they are neurologically normal.

The treatment for these children is a combination of behavioral modification, biofeedback therapy, and possibly prophylactic antibiotics and anticholinergic medications. These patients need aggressive treatment.

Giggle Incontinence
Giggle incontinence, which occurs most commonly in girls, is a large-volume loss of urine that happens exclusively with laughter. Patients have no other voiding symptoms, and their bladder is otherwise completely normal.

Treatment is a combination of timed-voiding programs and use of anticholinergic medications to suppress the bladder contraction. For patients in whom excessive muscle relaxation is thought to be the cause, α-sympathomimetic agents or methylphenidate (Ritalin) has been used.

Vaginal Voiding
Patients with vaginal reflux present with urine leakage that occurs within 10 minutes after voiding, usually after standing up; foul-smelling urine; and frequent nonfebrile urinary tract infections. It occurs because of urine backflow into the vagina caused by labial fusion or failure to adequately separate the legs while voiding due to obesity or improper voiding posture.

Vaginal voiding is treated by mechanical or pharmacologic (hormonal cream) separation of labial fusion or by adjusting the voiding position.

Constipation
Treatment of underlying constipation is vital in the management of pediatric urinary incontinence. The combination of a high-fiber diet and agents such as polyethylene glycol (MiraLax) has been shown to maintain a regular bowel routine and help in addressing urinary incontinence.

1Not FDA approved for this indication.
Diabetes mellitus is a group of metabolic disorders that have hyperglycemia as a common feature caused by inadequate insulin secretion, insulin action, or both. Chronic hyperglycemia and its numerous downstream effects lead to micro- and macrovascular complications involving the eyes, kidneys, nerves, and blood vessels. Childhood and adolescent years are periods of rapid physical growth and psychosocial change, and these two factors make the care of children and adolescents with diabetes both challenging and rewarding. The health care professional must balance the important goals of optimal glycemic control and normal growth and development along with the risks of hypoglycemia and the
challenges of expected glycemic excursions during childhood. Multidisciplinary care is the hallmark of successful diabetes management for the child and adolescent with diabetes and for family members.

The American Diabetes Association (ADA) classifies diabetes mellitus into four main types: type 1 diabetes (T1D), type 2 diabetes (T2D), other specific types, and gestational diabetes mellitus (Table 1). T1D is caused by insulin deficiency, which results from the autoimmune destruction of the pancreatic β cells. There are multiple genetic loci in the major histocompatibility region of chromosome 6 that predispose (DR 3/4, DQ 0201/0302, DR 4/4, and DQ 0300/0302) or protect against (DQB1*0602, DQA1*0102) the development of T1D. T2D is caused by the combination of insulin resistance and relative insulin deficiency. Type 1 diabetes is most common in pediatrics.

Genetic forms of diabetes include maturity-onset diabetes in the young (MODY), neonatal diabetes, mitochondrial diabetes, and certain syndromes of insulin resistance. MODY is characterized by young age of onset, autosomal dominant inheritance, the lack of association with obesity, and a variable phenotype. The most common disease of the exocrine pancreas that causes diabetes in children and adolescents is cystic fibrosis. Glucocorticoids used in the treatment of systemic illnesses are also commonly associated with hyperglycemia and diabetes. Certain genetic syndromes, such as Down syndrome, Klinefelter’s syndrome, and Turner’s syndrome, increase the risk for diabetes.

Diagnosis
The diagnosis of T1D in children and adolescents is typically straightforward. The classic symptoms of polyuria, polydipsia, polyphagia, and weight loss over a several-week period are common. A thorough history and physical exam may reveal perineal candidiasis or thrush. Such symptoms may be followed by nausea, abdominal pain, vomiting, lethargy, and Kussmaul respirations if diabetic ketoacidosis (DKA) and lactic acidosis develop. The presentation of T2D in children and adolescents can be more subtle and sometimes even clinically silent. However, approximately a third of adolescents with T2D have ketosis and a quarter have ketoacidosis at presentation.

The Current Diagnosis box outlines the diagnosis of diabetes mellitus.

Table 1: Classification of Diabetes Mellitus*

<table>
<thead>
<tr>
<th>Type 1 diabetes</th>
<th>Type 2 diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic defects of β-cell function</td>
<td>Genetic defects of β-cell function</td>
</tr>
<tr>
<td>MODY 1: chromosome 20, HNF-α</td>
<td>MODY 2: chromosome 7, glucokinase</td>
</tr>
<tr>
<td>MODY 3: chromosome 12, HNF-1β</td>
<td>MODY 4: chromosome 13, IPF-1</td>
</tr>
<tr>
<td>MODY 5: chromosome 17, HNF-1β</td>
<td>MODY 6: chromosome 2, NeuroD1</td>
</tr>
<tr>
<td>Mitochondrial diabetes</td>
<td>Neonatal diabetes</td>
</tr>
<tr>
<td>Genetic defects in insulin action</td>
<td>Genetic defects in insulin action</td>
</tr>
<tr>
<td>Leprachainism</td>
<td>Leprechauism</td>
</tr>
<tr>
<td>Rubson-Mendenhall syndrome</td>
<td>Diseases of the exocrine pancreas</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>Acromegaly</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>Cushing’s syndrome</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>Glucagonoma</td>
</tr>
<tr>
<td>Endocrinopathies</td>
<td>Pheochromocytoma</td>
</tr>
<tr>
<td>Acromegaly</td>
<td>Drug or chemical induced</td>
</tr>
<tr>
<td>Cushing’s syndrome</td>
<td>Glucocorticoids</td>
</tr>
<tr>
<td>Glucagonoma</td>
<td>Infecions</td>
</tr>
<tr>
<td>Pheochromocytoma</td>
<td>Congenital rubella</td>
</tr>
<tr>
<td>Drug or chemical induced</td>
<td>Cytomegalovirus</td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td>Other genetic syndromes associated with diabetes</td>
</tr>
<tr>
<td>Infecions</td>
<td>Down’s syndrome</td>
</tr>
<tr>
<td>Congenital rubella</td>
<td>Klinefelter’s syndrome</td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td>Turner’s syndrome</td>
</tr>
<tr>
<td>Other genetic syndromes associated with diabetes</td>
<td>Gestational diabetes mellitus (GDM)</td>
</tr>
</tbody>
</table>

*Table is not all-inclusive and gives examples of each subtype of diabetes mellitus. For complete list, see American Diabetes Association: Diagnosis and classification of diabetes mellitus. Diabetes Care 2010;33:S62–69.

Abbreviation: MODY = maturity-onset diabetes in the young.

Diabetic Ketoacidosis
Approximately 25%–30% of children with newly diagnosed T1D present with diabetic ketoacidosis (DKA). Children who are younger (less than 4 years), without a first-degree relative with T1D, and from a family of lower socioeconomic status are at higher risk of DKA at onset of T1D. The majority of DKA episodes occur in patients with established diabetes, not in those newly diagnosed. Children or adolescents with established T1D are at higher risk for DKA if they are in poor metabolic control, have had a previous episode of DKA, are peripubertal/adolescent girls, have a psychiatric disorder, or are from a disadvantaged background.

Management of DKA in children and adolescents is based on the same principles used in adults and therefore is covered in a separate chapter in this book. The development of cerebral edema, however, warrants discussion because this complication is seen primarily in children and is associated with both high morbidity and mortality. Risk factors for the development of cerebral edema include lower initial partial pressure of carbon dioxide, higher initial serum urea nitrogen concentrations, treatment with bicarbonate, and an attenuated rise in measured serum sodium concentrations during therapy. Current recommendations endorse fluid rehydration (generally 10 mL/kg NS bolus) followed by initiation of an insulin drip (0.05–0.1 U/kg/h) without an insulin bolus and continued cautious rehydration. In addition, children who are younger (less than 5 years), have new-onset T1D, and longer duration of symptoms may also be at an increased risk. A high index of suspicion is needed with mannitol (Osmitrol) or 3% NS nearby to allow for timely intervention.

Initiation of Insulin Replacement Therapy
Subcutaneous insulin is initiated in the patient who does not present in DKA or following intravenous insulin therapy in the child with resolved DKA who is tolerating oral intake (pH >7.3, tCO₂ >18, anion gap 12 ± 2 mEq/L). The starting dose of insulin replacement therapy depends on the age, weight, and pubertal status of the patient, as well as the presence or absence of DKA.
For the prepubertal child without DKA, the starting dose is usually 0.25 to 0.5 U/kg/day. For the prepubertal child with resolved DKA, the usual starting dose is 0.5 to 0.75 U/kg/day. For the pubertal child without DKA, the starting dose is 0.5 to 0.75 U/kg/day and for the pubertal child with resolved DKA, 0.75 to 1 U/kg/day. This total daily dose (TDD) of insulin is typically divided into a multiple daily injection program with basal bolus insulin therapy or occasionally two injections per day, with the former the preference for implementation of intensive therapy (Figure 1). The twice-daily regimen may be selected if the psychosocial assessment determines that fewer injections per day would be beneficial. The use of an insulin pump at diagnosis remains within the research realm currently.

When the patient is metabolically stable, the focus turns to the psychosocial assessment of the child or adolescent and caregiver(s) and the initiation of diabetes education. A licensed social worker or other mental health professional evaluates each family and screens for circumstances that might complicate diabetes management: family composition, alternative caregiver(s), financial concerns, lack of health insurance, psychiatric or medical illness in a family member, or severe emotional distress of caregiver secondary to the diabetes diagnosis.

Diabetes education can be provided in the inpatient or outpatient setting by a certified diabetes nurse educator (CDE) and focuses on the set of essential skills needed to keep a child or adolescent with diabetes safe at home and school. These survival skills include techniques of blood glucose monitoring, urine or blood ketone measurement, drawing up and administration of subcutaneous insulin and glucagon, recognition and treatment of hypoglycemia and hyperglycemia, basics of sick day management, and indications for and methods of contacting the child’s diabetes team. In addition to the survival skills, the child or adolescent and family should meet with a registered dietitian who will assist them in developing an individualized meal plan and introduce the family to the concept of carbohydrate counting or exchanges. Once the child or adolescent (if developmentally appropriate) and caregiver(s) demonstrate the knowledge and skills needed, they are discharged with the expectation of daily phone contact with a member of their diabetes team to further titrate insulin doses and answer questions. When available and clinically indicated, a visiting nurse may assist with ongoing home-based education and support in the short term.

### Outpatient Diabetes Care

The management of children and adolescents with diabetes requires a multidisciplinary team approach. Members of this team include either a pediatric endocrinologist or pediatrician with training in diabetes, a pediatric CDE, a dietician, and a mental health professional (social worker and psychologist). Members of this team need to be easily accessible to the family in times of illness or metabolic crisis. Another member of the child/adolescent’s team is a pediatrician or family doctor who will continue to provide routine well child care including anticipatory guidance, immunizations, and general medical care.

In the first few months of outpatient diabetes care, patients are seen frequently by members of the diabetes team to assess the family’s adaptation to the new diagnosis, reinforce skills and knowledge learned during the first few days, and expand on the skills and knowledge needed for intensive diabetes management. Patients are subsequently seen at a minimum frequency of every 3 months, alternating between their CDE and their pediatric endocrinologist. Visits with the dietician are recommended yearly or more frequently if circumstances warrant (e.g., young child or toddler, desired weight loss, initiating pump therapy, etc.).

### Diabetes Education

Diabetes education is an ongoing process with continuous need for review of previously learned material and introduction of new concepts as the family develops a more sophisticated understanding of intensive diabetes management. The educator should evaluate the patient and his or her caregiver’s knowledge and skills regularly. In addition, age-appropriate issues need to be discussed as the patient matures (e.g., driving guidelines, issues related to alcohol and smoking, etc.). Diabetes education needs to be tailored to each family taking into account their educational level and cultural practices. The educator must be sensitive to the age and developmental stage of the child or adolescent, and shift his or her educational efforts from the caregiver(s) to the adolescent when it is developmentally appropriate. Continued parental involvement and supervision of the adolescent with diabetes is crucial to good metabolic control.

The health care provider should complete a focused interval history at each visit that includes recent illnesses, visits to the emergency department, hospitalizations, medications prescribed other than insulin, types of insulin and current doses, daily routine including meal plan, dietary pattern, and activity level, self-care behaviors and identifying who performs them, episodes of hypoglycemia and their precipitants, school performance, emotional health, and a review of systems focusing on symptoms of hyperglycemia (polyuria, polydipsia, polyphagia, weight loss, candidal infections) and the possible development of other autoimmune disorders. If appropriate, a history of tobacco, alcohol, recreational drugs, and sexual activity should be elicited. A focused physical examination that includes measurement of blood pressure and heart rate, weight, height, body mass index (BMI), and examination of the thyroid gland, sites of blood glucose monitoring, and insulin injections

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**Figure 1.** Initiation of Insulin Replacement Therapy. Half of the daily dose (TDD) is given as basal insulin (usually long-acting insulin analogue) and half is given as bolus insulin (usually rapid-acting analogue) before meals and snacks. Two thirds of the total daily dose (TDD) is given at breakfast and further divided into NPH (two thirds) and short/rapid-acting insulin (one third). The remaining one third is either given in one injection at dinner (in a twice-daily regimen) or divided between dinner and bedtime (in a thrice-daily regimen), and should also be divided into NPH or long-acting analogue (two thirds) and short/rapid-acting insulin (one third). Short/rapid-acting insulin can be regular (Humulin R), lispro (Humalog), aspart (NovoLog), or glulisine (Apidra).
goals of therapy

the incidence of microvascular complications was reduced with improved blood glucose control (hemoglobin A1C approximately 7%). The reduction in complications, however, was accompanied by an increased risk of severe hypoglycemia. Because young children are more vulnerable to hypoglycemia (reduced catecholamine response to hypoglycemia, decreased ability to communicate symptoms of hypoglycemia, and risk for neuro-psychologic impairment from hypoglycemia), the ADA has developed age-specific glycemic targets (Table 2).

insulin therapy

the ideal insulin replacement therapy would be one that mirrors the basal and prandial insulin secretion in individuals without diabetes. Numerous insulin preparations are available that vary in time to onset, peak, and duration of action (Table 3). No single regimen is superior to another; thus individualization of the insulin regimen to the child or adolescent and family remains a major determinant. Important factors for consideration include blood glucose monitoring frequency, number of daily injections the family can perform, the need for flexibility in meal planning, and the unique family schedule. Regimens range in intensity from twice-a-day injections with a set dose of premixed insulin to intensive diabetes management with multiple injections per day of two or more types of insulin or use of an insulin pump (continuous subcutaneous insulin infusion [CSII]).

Typical regimens that children or adolescents begin at diagnosis were described previously (Figure 1). Some centers initiate a basal-bolus regimen in which insulin is replaced in a manner that attempts to mimic physiologic insulin release. Basal-bolus regimens include the insulin pump and glargine (Lantus) given once a day with rapid-acting insulin (lispro [Humalog] or aspart [NovoLog], or glulisine [Apidra]) is used in the insulin pump, discontinuation of insulin delivery can result in ketone production within hours. Increased vigilance, therefore, is necessary to ensure proper functioning of the insulin pump with frequent blood glucose monitoring and checking for ketones if hyperglycemia develops.

self-monitoring

one of the main goals of diabetes education is to teach and empower the patient and family in the self-management of diabetes. Self-management of diabetes includes measuring blood glucose and blood/urine ketone levels, recording the results along with amount of carbohydrate intake and amount of insulin administered, and the ability to make insulin dosing decisions based on the interpretation of these records. Monitoring blood glucose four or more times daily is recommended in children with T1D. Additional monitoring may be necessary postprandially, overnight, or during periods of increased physical activity to help optimize control and prevent severe hypoglycemia. Preschool or early school-age children may require more frequent monitoring because of their inability to recognize symptoms or to communicate during episodes of hypoglycemia. In addition, children and adolescents using the insulin pump typically check their blood sugar six or more times per day. Ketone measurements should be done whenever the blood glucose is greater than 250 to 300 mg/dL and/or if the patient is ill, especially with nausea, vomiting, or abdominal pain. Ketones can be measured either in the urine (acetocetate and acetone) or blood (β-hydroxybutyric acid). Measurement of blood ketones is now available on a home meter and is the preferred method in the current era stressing blood glucose monitoring. The key to successful intensive diabetes management is frequent blood glucose monitoring, good record keeping, and communication of these results with the diabetes team at frequent intervals so that timely modifications can be made to the insulin regimen and/or meal plan. Continuous glucose monitoring technologies may help achieve target glycemic control with less hypoglycemia.
### TABLE 3 Insulin Analogues

<table>
<thead>
<tr>
<th>INSULIN PREPARATION</th>
<th>ONSET OF ACTION</th>
<th>PEAK ACTION</th>
<th>EFFECTIVE DURATION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rapid Acting</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin lispro</td>
<td>5–15 min</td>
<td>30–90 min</td>
<td>2–4 h</td>
</tr>
<tr>
<td>Insulin aspart</td>
<td>5–10 min</td>
<td>60–180 min</td>
<td>3–5 h</td>
</tr>
<tr>
<td>Insulin glulisine</td>
<td>5–15 min</td>
<td>30–90 min</td>
<td>3–5 h</td>
</tr>
<tr>
<td><strong>Short Acting</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regular</td>
<td>30–60 min</td>
<td>2–3 h</td>
<td>3–6 h</td>
</tr>
<tr>
<td><strong>Intermediate Acting</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPH (isophane insulin)</td>
<td>2–4 h</td>
<td>4–10 h</td>
<td>10–16 h</td>
</tr>
<tr>
<td><strong>Long Acting</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin detemir</td>
<td>1.1 h</td>
<td>None</td>
<td>24 h</td>
</tr>
<tr>
<td>Intermediate acting</td>
<td>2–3 h</td>
<td>6–14 h</td>
<td>16–24 h</td>
</tr>
<tr>
<td>Insulin Mixtures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>70/30 human mix* (70% NPH, 30% regular)</td>
<td>30–60 min</td>
<td>Dual</td>
<td>10–16 h</td>
</tr>
<tr>
<td>70/30 aspart analog mix (70% intermediate, 30% aspart)*</td>
<td>5–15 min</td>
<td>Dual</td>
<td>10–16 h</td>
</tr>
<tr>
<td>75/25 lispro analogue mix* (75% intermediate, 25% lispro)</td>
<td>5–15 min</td>
<td>Dual</td>
<td>10–16 h</td>
</tr>
<tr>
<td>70/30 lispro analogue mix (50% intermediate, 50% lispro)</td>
<td>5–15 min</td>
<td>Dual</td>
<td>10–16 h</td>
</tr>
<tr>
<td>50/50 lispro analogue mix (50% intermediate, 50% lispro)</td>
<td>5–15 min</td>
<td>Dual</td>
<td>10–16 h</td>
</tr>
</tbody>
</table>

In many countries, including the United States, insulin preparations contain 100 U/mL and are referred to as U-100 insulin. Highly concentrated U-500 short-acting insulin is available and used primarily in adults with severe insulin resistance.

Profiles for each insulin preparation are reasonable estimates only, based on data from adult study participants. There is variation between individuals, and time of onset, peak, and duration are also affected by size of dose, site and depth of injection, dilution, exercise, and temperature. Some studies include children.

*Typically used in fixed doses in twice-a-day insulin regimens.

### Medical Nutrition Therapy

The meal plan remains an important component of management aimed at good glycemic control, although it is often the most difficult aspect of intensive diabetes management for families. A dietician trained in pediatric nutrition and diabetes should meet with the family at the time of T1D diagnosis and periodically thereafter. The dietician should help develop a meal plan that is individualized to the patient’s daily schedule, food preferences, cultural influences, and physical activity. The meal plan is more likely to be successful if it is designed to fit into the family’s already established schedule and preferences. The patient and family should also be instructed on carbohydrate counting so that either carbohydrate exchanges or insulin-to-carbohydrate ratios can be used. Like the child without diabetes, the total number of recommended calories follows the child’s growth requirements along with consideration of the need for weight gain or loss. Growth velocity, weight gain, and BMI should be monitored at every visit to ensure that the meal plan is sufficient to meet the energy requirements of the patient. Unexpected weight loss or poor weight gain should prompt consideration of suboptimal metabolic control, as well as eating disorders, thyroid dysfunction, or gastrointestinal disease.

The ADA does not have pediatric specific guidelines for medical nutrition therapy, but the recommendations for adults can be extrapolated to children. The ADA recommends that carbohydrates provide 45% to 65% of total calories, with protein and fat contributing 15% and 30%, respectively. The patient and family should be educated to avoid foods high in cholesterol, saturated fat, and concentrated sweets and select foods high in complex carbohydrate and dietary fiber.

All children and adolescents are recommended to have three meals per day. If they receive intermediate–acting insulin preparations, they should also receive three snacks per day (morning, afternoon, and bedtime) to match anticipated peaks of insulin action. If the child or adolescent is on a basal-bolus regimen, snacks are optional and require insulin coverage based on insulin-to-carbohydrate ratios.

### Exercise

Exercise, or periods of sustained physical activity, can be beneficial to the patient by contributing to a sense of well-being, helping achieve the recommended BMI, improving glycemic control (exercise enhances insulin sensitivity), improving the lipid panel (increasing HDL), and lowering blood pressure and improving cardiovascular fitness. All children and adolescents, especially those with diabetes, should be encouraged to participate in routine physical activity.

The child or adolescent with diabetes needs to take precautions to avoid hypoglycemia during periods of increased physical activity. The patient and family need to check blood glucose before the initiation of activity, every hour during sustained activity, and at the completion of physical activity. For the first several days of increased activity, the child should also check his or her blood glucose frequently during the 12-hour postexercise period because there is often a delayed drop in the blood glucose following exercise (i.e., the lag effect). Some children require additional carbohydrate before, during, and after activity; lower insulin doses on the days of increased physical activity; or both. It is suggested that the child take 5 to 15 g of carbohydrates, depending on age and exercise intensity, before exercise if the blood sugar is below target, and repeat the 5 to 15 g of carbohydrate for every 30 minutes of sustained activity. Rapid-acting carbohydrate should be readily available, and coaches and trainers should be aware of the diagnosis of diabetes and trained in the treatment of hypoglycemia.

### Psychosocial Support

The mental health professional is an important member of the diabetes team. A thorough family assessment generally accompanies the diabetes diagnosis with appropriate referrals for additional services as needed. Thereafter, children or adolescents should be referred back to a mental health professional if social, emotional, or economic barriers to the achievement of good glycemic control are identified. Family conflict, especially conflict over diabetes care, can be associated with deterioration in glycemic control. Encouragement of ongoing family teamwork in the management of...
Sick Day Management
The goals for the management of children and adolescents during sick days are never omit insulin, prevent dehydration and hypoglycemia, monitor blood glucose frequently (every 2 to 4 hours), monitor for ketosis, provide supplemental rapid- or short-acting insulin doses (5% to 20% of TDD) depending on degree of hyperglycemia and ketosis, treat underlying illness, and have frequent contact with the diabetes team. The majority of DKA among children or adolescents with established diabetes is caused by insulin omission or errors in administration of insulin. Inadequate insulin therapy in the context of an intercurrent illness accounts for the remaining small percentage. Although it is more common for children to require more insulin during illnesses, some children require a reduction of the basal and/or rapid-acting insulin dose if he or she is unable to eat and the blood glucose is less than 150 to 180 mg/dL.

Families need to be educated about symptoms that warrant immediate medical attention, including signs of dehydration (dry mouth, sunken eyes, cracked lips, weight loss, dry skin), persistent vomiting for more than 2 to 4 hours, persistence of blood glucose levels greater than 300 mg/dL or ketones for more than 12 hours, or symptoms of DKA (nausea, abdominal pain, chest pain, vomiting, ketotic breath, hyperventilation, or altered consciousness). It is helpful for the diabetes team to review sick day management annually with the family (can accompany flu immunization) to avoid metabolic decompensation during intercurrent illness.

Hypoglycemia
Fear of hypoglycemia can be a common occurrence in the management of childhood diabetes, especially among caregivers, and can be a barrier to optimal glycemic control. Recognition and treatment of hypoglycemia are important topics for diabetes education. Families are trained to treat hypoglycemia with 10 to 15 g of rapid-acting carbohydrate, recheck blood glucose in 15 minutes, repeat treatment with 10 to 15 g if blood glucose remains below target, and follow with a protein-containing snack if a meal will not follow within 1 to 2 hours. This technique avoids the natural tendency to overtreat low blood glucose levels. Caregivers should also receive glucagon training (20 to 30 μg/kg; maximum 1 mg) for severe hypoglycemia and low-dose glucagon (1 U on an insulin syringe for every year of life up to 15 years) for impending hypoglycemia, for example, in the context of a gastrointestinal illness or inadvertent insulin administration (lispro given instead of NPH). A member of the diabetes team should assess frequency, treatment, awareness, and circumstances of hypoglycemia at each visit.

Screening for Diabetes-Related Complications
Patients, families, and caregivers worry about the risk of diabetes-related complications, and therefore the diabetes team must educate families and screen for complications with sensitivity and optimism, emphasizing prevention of complications and the maintenance of health. Screening for nephropathy, hypertension, dyslipidemia, and retinopathy are indicated.

Microalbuminuria (MA) is the first sign of diabetic nephropathy, and patients who develop persistent MA are at increased risk of progression to macroalbuminuria. Poor glycemic control, smoking, and a family history of essential hypertension are risk factors for the development of MA and nephropathy. Identification of persistent MA provides an opportunity for intervention and prevention of progressive renal disease through improvements in glycemic control and/or therapy with angiotensin-converting enzyme (ACE) inhibitors. There are currently no pediatric data on the use of angiotensin receptor blockers (ARBs). Table 4 outlines definitions, screening recommendations, and treatment.

Hypertension is an important predictor of the progression of diabetic nephropathy to end-stage renal disease. Hypertension in children and adolescents may go unrecognized because providers are not familiar with the gender-, age-, and height-specific definitions. Blood pressure should be measured every 3 months with standardized technique, using the proper size cuff. If elevated blood pressures are detected and confirmed, the first step is to exclude causes not related to diabetes. Table 4 outlines the definitions, screening recommendations, and treatment.

Dyslipidemia and diabetes are established risk factors for cardiovascular disease, and recent research suggests that a significant proportion of adolescents with diabetes already have evidence of atherosclerosis. Low-density lipoprotein (LDL) cholesterol is most closely associated with cardiovascular disease, and therefore, the ADA has developed guidelines for LDL cholesterol. Screening may be delayed until puberty if family history is negative for cardiovascular disease. A lipid profile should be performed on prepubertal children with diabetes who are older than 2 years if there is a positive family history of atherosclerotic cardiovascular disease. Table 4 outlines definitions, screening recommendations, and treatment for children with diabetes who are older than 2 years or at risk of developing atherosclerosis.

TABLE 4
Screening for Diabetes-Related Complications

<table>
<thead>
<tr>
<th>COMPLICATION</th>
<th>HOW TO SCREEN</th>
<th>DEFINITION</th>
<th>WHEN TO SCREEN</th>
<th>THERAPY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microalbuminuria</td>
<td>Spot urine sample, timed overnight, or 24-h collection</td>
<td>Spot urine albumin/creatinine ratio 30–299 μg/g or AER 20–199 μg/min from timed collection</td>
<td>Annual screening begins at 10 y or after &gt;5 y duration of diabetes</td>
<td>Optimize glucose control, smoking cessation, normalize BP</td>
</tr>
<tr>
<td>Persistent microalbuminuria</td>
<td>2/3 of urine samples meet above criteria</td>
<td></td>
<td></td>
<td>Above, plus addition of ACE inhibitor</td>
</tr>
<tr>
<td>High-normal BP</td>
<td>Manual BP measurement with standard technique</td>
<td>Systolic or diastolic BP within the 90th–95th percentile for age, gender, and height</td>
<td>At every clinic visit</td>
<td>Dietary intervention, weight control, and exercise; if target BP not reached within 3–6 mo, then initiate pharmacologic therapy</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Systolic or diastolic BP above the 95th percentile for age, gender, and height, or &gt;130/80 on &gt;3 occasions (whichever is lower)</td>
<td></td>
<td></td>
<td>Above, plus pharmacologic therapy titrated to achieve target BP</td>
</tr>
</tbody>
</table>

Note: Urine collection should not be performed following vigorous exercise, during an acute infection, during a female patient’s menstrual cycle, or following an episode of severe hypoglycemia. Once angiotensin-converting enzyme (ACE) inhibitor is started, microalbumin excretion should be monitored q3–6 mo.

Target BP is <110/80 or <90th percentile for age, gender, and height. Initial drug treatment is ACE inhibition. Angiotensin II receptor blockers (ARBs) are FDA approved to treat hypertension in pediatric patients >6 years old.

Abbreviations: AER = albumin excretion rate; BP = blood pressure.
history of cardiovascular disease hyperlipidemia, or if the family history is unknown. If the LDL cholesterol is less than 100 mg/dL, screening can be repeated every 5 years. The mainstay of therapy for dyslipidemia is dietary management (saturated fat less than 7% of calories and less than 200 mg/day of cholesterol). Children with levels between 130 and 159 mg/dL should be started on medication if diet and lifestyle modification are unsuccessful after 6 months or if the child has additional risk factors for cardiovascular disease, such as obesity or hypertension. Pharmacotherapy is recommended if the LDL cholesterol is more than 160 mg/dL. The LDL goal for children with diabetes is less than 100 mg/dL.

Diabetic retinopathy is a feared complication because it is the leading cause of vision loss. According to the ADA, the first ophthalmologic exam should be performed when the child is 10 years or older within 5 years after the onset of diabetes. Examinations with an eye care professional with expertise in diabetic retinopathy should occur early.

**Screening for Other Autoimmune Diseases**

Children and adolescents with T1D are at an increased risk for other autoimmune diseases and should be screened accordingly. Approximately 15% of patients with T1D also have autoimmune thyroid disease. All children and adolescents should be screened for autoimmune thyroid disease at the time of diabetes diagnosis and once metabolic control is established. TSH measurement is a useful initial screen, along with measuring the presence of thyroid autoantibodies. Screening should be repeated yearly or if there is any clinical suspicion of thyroid disease (abnormal growth rate, symptoms of hypo- or hyperthyroidism, goiter on examination, erratic blood glucose control).

Another commonly associated disorder is celiac disease. Nearly 6% of patients with T1D have elevated levels of circulating autoantibodies to tissue transglutaminase. Celiac disease can cause diarrhea, weight loss or failure to gain weight, abdominal pain, fatigue, and unexplained hypoglycemia or erratic blood glucose secondary to malabsorption. Patients with T1D should be screened with circulating IgA autoantibody to tissue transglutaminase. A quantitative serum IgA level should be drawn at the same time to rule out IgA deficiency as a cause for falsely low IgA tissue transglutaminase levels. Positive antibodies should be confirmed with a second measurement, and if positive, a referral should be made to a gastroenterologist for small bowel biopsy. If the diagnosis is confirmed, celiac disease is treated with a gluten-free diet with recommendations and support from a registered dietician with pediatric expertise in diabetes and celiac management.

**Type 2 Diabetes Mellitus in Youth**

With the increasing prevalence of childhood obesity during the last two decades, there is an increased occurrence of T2D in youth. Based on National Health and Nutrition Examination survey data, the prevalence of obese children (defined as a body mass index greater than the 95th percentile for children and youth) increased from 5% in the 1970s to more than 15% by 1999. The epidemic of obesity follows the increased consumption of fast foods, increased consumption of soft drinks, increased sedentary behavior with more television watching, video games, and decreased physical activity. Mirroring this epidemic of childhood obesity is the occurrence of T2D in children and adolescents. Before 1990, T2D in youth was a rare occurrence. By 2000, between 8% and 45% of all newly diagnosed cases of childhood diabetes were caused by T2D. T2D occurs most commonly in those with a family history of T2D; individuals from certain racial and ethnic minority groups including Native Americans, Hispanics, African Americans, and Asian and Pacific Islanders; those with overweight/obesity falling above the 85th percentile for BMI based on age and gender; and in association with markers of insulin resistance (Table 5). Markers of insulin resistance include the occurrence of acanthosis nigricans and polycystic ovarian syndrome (PCOS). In addition, other well-known risk factors include hypertension and hyperlipidemia.

As noted earlier, the diagnosis of T2D is based on elevated fasting plasma glucose (FPG), 2-hour glucose value during an OGTT, and a casual glucose level or A1C determined in a laboratory on two occasions. Because T2D often goes without symptoms, individuals who are overweight, have a positive family history of T2D, come from one of the high-risk racial and ethnic minority groups, and/or have markers of insulin resistance warrant screening for T2D. Screening can be performed with a FPG or OGTT when clinical concerns are high and the FPG is normal.

Currently one oral medication is approved for the treatment of T2D in youth. This medication is metformin (Glucophage), which is also available in a liquid formulation. The maximum recommended daily dose of metformin (Glucophage) in youth is 2000 mg/day divided as 1000 mg twice daily. Often patients with T2D present in ketoacidosis and require initial insulin therapy. The goal of management of the child with T2D is initial stabilization often with insulin therapy, metformin (Glucophage) directed at managing the insulin resistance, and education. Once glucose levels are stabilized, insulin dosage may be lowered along with continued treatment with metformin (Glucophage) and approaches to lifestyle management. Lifestyle management involves a healthy diet, increasing exercise, and decreasing sedentary behaviors.

### Table 5: Risk Factors and Screening for Type 2 Diabetes in Children

<table>
<thead>
<tr>
<th>CRITERIA</th>
<th>AGE OF INITIATION</th>
<th>FREQUENCY</th>
<th>METHOD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overweight (BMI ≥ 85th percentile for age and gender), weight for height ≥ 85th percentile, or weight ≥ 120% of ideal for height</td>
<td>10 y or at pubertal onset if puberty occurs at a younger age</td>
<td>q2y</td>
<td>Fasting plasma glucose and/or A1C</td>
</tr>
<tr>
<td>Plus 2 of the following risk factors:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family history of T2D in 1st- or 2nd-degree relative</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Race/ethnicity (American Indian, African American, Hispanic, Asian/Pacific Islander)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Signs of or conditions associated with insulin resistance (acanthosis nigricans, PCOS, HTN, dyslipidemia)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


**Note:** Clinical judgment should be used to test for diabetes in high-risk patients who do not meet these criteria.

**Abbreviations:** BMI = body mass index; T2D = type 2 diabetes; HTN = hypertension; PCOS = polycystic ovarian syndrome.
Other medications used to treat T2D include second-generation sulfonylureas, meglitinides, thiazolidinediones, α-glucosidase inhibitors, GLP-analogues, and DPP-4 inhibitors, none of which is currently approved for use in pediatric patients. There are ongoing studies to assess the efficacy and safety of these medications (Table 6).

### TABLE 6  Medications to Treat Type 2 Diabetes

<table>
<thead>
<tr>
<th>CLASS</th>
<th>MECHANISM OF ACTION</th>
<th>ADVERSE EFFECTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biguanides (metformin)*</td>
<td>Decrease hepatic glucose production</td>
<td>Gastrointestinal upset</td>
</tr>
<tr>
<td></td>
<td>Increase peripheral glucose disposal</td>
<td>Lactic acidosis</td>
</tr>
<tr>
<td>Sulfonylureas (glimepiride, glyburide, glipizide)</td>
<td>Insulin secretagogues</td>
<td>Hypoglycemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Weight gain</td>
</tr>
<tr>
<td>Meglitinides (repaglinide, nateglinide)</td>
<td>Insulin secretagogues</td>
<td>Hypoglycemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Weight gain</td>
</tr>
<tr>
<td>α-Glucosidase inhibitors (acarbose)</td>
<td>Decrease gut carbohydrate absorption</td>
<td>Gastrointestinal upset</td>
</tr>
<tr>
<td>Thiazolidinediones (rosiglitazone and pioglitazone)</td>
<td>Decrease hepatic glucose production</td>
<td>Weight gain Edema</td>
</tr>
<tr>
<td></td>
<td>Increase peripheral glucose disposal</td>
<td>Increased liver enzymes Anemia</td>
</tr>
<tr>
<td>GLP-1 analogues</td>
<td>Increase insulin response</td>
<td>Gastrointestinal upset</td>
</tr>
<tr>
<td></td>
<td>Decrease glucagon response to eating</td>
<td>Acute pancreatitis Possible increased thyroid cancer risk</td>
</tr>
<tr>
<td></td>
<td>Slow down gastric emptying</td>
<td></td>
</tr>
<tr>
<td>DPP-4 inhibitors</td>
<td>Increase insulin response</td>
<td>Possible interference with immune function</td>
</tr>
<tr>
<td></td>
<td>Decrease glucagon response to eating</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Slow down gastric emptying</td>
<td></td>
</tr>
</tbody>
</table>

*Metformin (Glucophage) is the only medication with FDA approval for use in children.
*Thiazolidinediones have restricted use and/or safety concerns; thus their use in pediatric patients should be avoided at this time, pending additional studies or FDA recommendations.


Epilepsy can be associated with comorbidities such as depression and anxiety. Successful management includes referrals for specialty care.

**CURRENT THERAPY**

- Selection of an anticonvulsant should be made based on the type of seizure.
- General principles include the use of a single agent at the lowest effective dosage with the goal of no side effects.
- Epilepsy can be associated with comorbidities such as depression and anxiety. Successful management includes referrals and/or management of these and associated psychosocial issues.
A seizure can be defined as clinical signs or symptoms resulting from abnormal neuronal activity (typically abnormally hypersynchronous firing). Epilepsy is defined as recurrent, unprovoked seizures and associated psychological, social, and cognitive consequences. Approximately 3% to 5% of the U.S. population has had a seizure (mostly febrile seizures). Nearly 1% of the U.S. population is being treated actively for seizures at any given time. Infants and children represent one of the two major peaks in seizure incidence, making this a very common diagnosis in pediatric practice.

Risk Factors
The primary risk factors for epilepsy in any age group include a history of meningitis, encephalitis, brain trauma, complicated perinatal course, and febrile seizures. Other risk factors for seizures include cortical or developmental malformations, certain inborn errors of metabolism, congenital infections, stroke, intracranial hemorrhage, acute metabolic abnormalities, and drug withdrawal.

Pathophysiology
Because the primary abnormality is abnormal neuron firing, many different types of pathology can lead to seizures. Abnormalities in neuronal networks (e.g., cortical malformations), structure (e.g., abnormal dendrite structure in trisomy 21), or ion channels (e.g., KCNQ2) can lead to seizures. In many cases, an underlying cause of seizures cannot be identified. Some forms of epilepsy have been linked to various genetic mutations, although the exact relationship between specific genotypes and phenotypes is unclear for most.

Clinical Manifestations
Broadly speaking, the clinical manifestations of seizures vary depending on which brain structures are involved. Although most people think of seizures only as generalized tonic-clonic seizures (GTCS), a wide variety of signs and symptoms can be caused by seizures. Furthermore, a GTCS may be the initial manifestation of a seizure (i.e., as seen in primary generalized epilepsy) or it may be the end result of a seizure that started in one brain location and then spread to the rest of the brain (e.g., a focal-onset seizure with secondary generalization). These two broad categories (generalized versus focal) are approached somewhat differently from a diagnostic and therapeutic perspective. Thus, the approach taken by the International League Against Epilepsy is to classify most seizures as either focal-onset (with or without impaired consciousness or awareness) or generalized.

Signs of a generalized seizure (i.e., those involving simultaneous firing in both sides of the brain) include loss of interaction or staring (absence seizures), myoclonus, tonic posturing, and/or tonic-clonic seizures. Signs of focal-onset seizures can involve specific regions controlling motor, sensory, or autonomic function, a loss of interaction, or automatisms (chewing, lip smacking, repetitive hand motions), to name a few. Patients with focal seizures might have an aura (a warning sign just prior to the seizure). The aura is a altered sensory function that can include salty or metallic taste, tingling sensations, rising sensation in the abdomen, déjà vu, jamais vu, sense of fear, or a nonspecific feeling that something is about to happen. After a seizure, patients also can have a period of postictal lethargy or confusion.

The initial symptoms or signs of a seizure are the most important in determining whether a seizure is generalized or focal in origin because they often localize the anatomic site of pathology. Thus, it is the beginning of a seizure, rather than its end, that is most useful in making a specific diagnosis.

Diagnosis and Management
History and Physical Examination
A detailed history is usually more valuable than any expensive test in diagnosing a seizure or epilepsy. In addition to a description of the actual event, it is useful to inquire about subtle signs that might not be recognized by observers as a seizure, including staring spells, myoclonic jerks, loss of time, and unexplained nocturnal tongue bitting, enuresis, or emesis. The presence of postictal weakness can help localize the region of onset after a focal seizure, even if secondarily generalized. Making the diagnosis of a specific epilepsy syndrome allows the clinician to develop a plan for further diagnosis and treatment and to counsel about prognosis. On physical examination, any signs of focal neurologic deficits can indicate an underlying lesion. A skin examination might identify a neurophakomatosis, such as tuberous sclerosis complex or neurofibromatosis.

Diagnostic Studies
In selected cases, typical clinical findings in the right clinical context strongly support the diagnosis of epilepsy, but an electroencephalogram (EEG) may be required to confirm the diagnosis. Even if the patient does not have a seizure during the EEG recording, interictal findings (when the patient is not having a seizure) can provide enough evidence to make the diagnosis of epilepsy. Under ideal circumstances, a single EEG can detect epileptiform activity in a patient with untreated generalized epilepsy about 95% of the time, making it a very sensitive test. In contrast, an EEG can detect epileptiform activity in a patient with focal-onset seizures only 40% to 50% of the time (although this number increases to about 90% after three EEGs have been done). Conversely, a normal interictal EEG (particularly one that includes sleep and provocative maneuvers such as intermittent photic stimulation and hyperventilation) in an untreated patient suggests, but is not necessarily diagnostic of, a focal rather than generalized onset.

Other ancillary studies can show underlying structural lesions that lead to epilepsy or provide physiologic information. Magnetic resonance imaging (MRI) can be useful in detecting lesions such as tumors, cortical dysgenesis, and strokes (both ischemic and hemorrhagic). Magnetic resonance spectroscopy also can provide information about metabolites in a specific region, which can aid in determining the nature of a lesion before resection (e.g., tumor versus inflammation). Positron-emission tomography (PET) scans may show regions of abnormal metabolism that might not be evident on MRI. Another nuclear medicine study, single photon emission tomography (SPECT), can be used to identify the region of onset of a seizure. Functional MRI (fMRI) studies show regions involved in a specific task.

Magnetoencephalography, when combined with MRI, can be useful in detecting areas of abnormal electrical activity that might not be evident on a scalp EEG recording. Neuropsychology evaluations can aid in localization of regions of dysfunction and also aid in determining risk for loss of function if surgery is performed. The intracarotid amobarbital (Amytal)1 test (Wada test) or intracarotid methohexital (Brevital)1 test is used to lateralize language function and memory; fMRI is being investigated as a replacement for aspects of this invasive test. Some institutions use intracranial electrodes to localize the onset of a seizure prior to a surgical resection and to identify regions of eloquent neurologic function (regions where critical function would be lost if they were resected).

Specific Epilepsy Syndromes
Some of the more common syndromes are described here, listed by typical age at presentation.

Neonatal Seizures
Seizures in neonates can be caused by any type of neurologic pathology, including infections (prenatal or postnatal), strokes, hemorrhages, electrolyte abnormalities, cortical dysgenesis, inborn errors of metabolism (including vitamin B6 dependency), withdrawal, and medications. Some neonatal seizure syndromes (benign idiopathic neonatal seizures and benign familial neonatal seizures) are benign; early infantile epileptic encephalopathy (Ohtahara syndrome) and early myoclonic encephalopathy frequently are refractory to medical treatment and have a poor

1Not FDA approved for this indication.
prognosis for development. Neonatal seizures should be managed in conjunction with specialists.

Febrile Seizures
Febrile seizures are the most common type of seizure, occurring in 3% to 5% of people in the United States. Febrile seizures, even though they can recur, are not diagnostic of epilepsy because they are provoked (i.e., by fever). With an onset between 1 month and 5 years of age (and almost always outgrown by 6 to 7 years of age), these seizures can be generalized or focal in onset. Meningitis and encephalitis also can manifest with seizures and fever and thus are exclusion criteria for febrile seizures because the prognosis and treatment are completely different. Febrile seizures that last longer than 15 minutes, have a focal onset, or occur more than once in a febrile illness are complex febrile seizures; only one of the three criteria are needed to make the diagnosis. Patients with complex febrile seizures are at a higher risk for developing epilepsy, although the overall risk still is low (4%). In patients who lack all three of these factors (i.e., simple febrile seizures), routine imaging, blood work, lumbar puncture, and EEG are not necessary for diagnosing the cause of the seizure. Rather, the work-up should be guided by other concerns, such as dehydration, concern for occult bacteremia, or in the appropriate clinical context, meningitis.

Approximately one third of patients have a recurrence of a febrile seizure. Factors that increase the recurrence risk include very young age at onset, family history of febrile seizures, low-grade fever at onset of the seizure, frequent febrile illnesses, or the occurrence of the seizure in the first hour of the fever. Febrile seizures always are outgrown, so typically, long-term seizure prophylaxis is not used. Oral diazepam (Valium) prophylaxis, started at the onset of fever, prevents febrile seizures but can produce excessive sedation. Patients who have prolonged febrile seizures can benefit from rectal diazepam gel (Dia-stat) or other benzodiazepines given soon after the onset of a febrile seizure to prevent additional prolonged seizures or febrile status epilepticus. A similarly good prognosis is seen in infants and children who have febrile seizures in the setting of acute gastroenteritis (whether febrile or not). The risk of epilepsy is increased after a febrile seizure in the setting of a complex febrile seizure, abnormal development, frequent febrile seizures, or a family history of epilepsy.

Infantile Spasms
With an onset typically around 4 to 8 months of age, infantile spasms consist of a triad of typical seizures (head drops and brief flexor and/or extensor spasms occurring in clusters around sleep transitions), a highly disorganized multifocal EEG pattern called hypsarrhythmia, and developmental delays. Between 70% and 90% of patients have identifiable underlying neurologic pathology associated with this syndrome. This is one of the most medically intractable epilepsy syndromes, and the prognosis for seizure control and development are very poor, except in a small subset of patients with no identifiable underlying pathology. Treatment typically is hormonal with prednisolone (Orapred) or ACTH (Acthar HP), dietary with a ketogenic diet, or medical with vigabatrin (Sabril), which is commonly the first-line treatment in infants with tuberous sclerosis complex (Box 1).

Dravet Syndrome
The typical presentation for Dravet syndrome is a prolonged febrile seizure involving one side of the body (hemiconic) or recurrent GTCS in a previously normal infant. After a relatively quiescent period, seizures (including myoclonic, focal, and absence) appear in the second year of life. Additional features include developmental abnormalities, ataxia, and extrapyramidal signs. Seizures induced by heat (either with fevers or exogenous) may be noted.

Genetic testing for mutations in the SCN1A gene is recommended, because this eliminates the need for other extensive testing for an underlying diagnosis and allows the clinician to prognosticate. The EEG may be normal initially but later shows generalized spike-and-wave complexes. Treatment typically is with anticonvulsant medications; some recommend avoiding...
drugs that block sodium channels, although direct evidence for this is limited. The ketogenic diet may be useful.

**Lennox–Gastaut Syndrome**

Typically occurring between the ages of 1 and 8 years, Lennox–Gastaut syndrome is characterized by mixed seizure types, a markedly abnormal EEG, and abnormal development. Virtually any type of brain pathology can be seen as an antecedent of Lennox–Gastaut syndrome. Patients with Lennox–Gastaut syndrome typically have combinations of tonic, atonic, and absence seizures, although focal-onset seizures and GTCS also occur. The EEG shows slow (less than 2.5 Hz) spike-and-wave complexes and occasionally a paroxysmal fast pattern, although background slowing also is very common. The vast majority of patients have developmental delays. Diagnosis is made in the setting of typical findings. Seizures are very difficult to control but treatment commonly includes medicines and/or nonpharmacologic options (see Box 1). The prognosis for seizure control and development is poor. The differential diagnosis of Lennox–Gastaut syndrome also includes Doose syndrome, characterized by myoclonic and atonic seizures (although other seizure types can occur), which often includes patients with normal development and a good prognosis once seizures are controlled.

**Childhood and Juvenile Absence Epilepsy**

Most clinicians are familiar with childhood and juvenile absence epilepsy. The typical age of onset is 4 to 14 years of age, and there is a slight female predominance. The most common type of seizure is an absence seizure, characterized by staring and loss of interaction lasting 5 to 20 seconds, occurring tens to hundreds of times per day. Patients also can have GTCS (particularly if they present later in childhood) and/or myoclonic seizures. There is no aura and there are no postictal behavior changes. Absence seizures can be induced with 3 to 4 minutes of hyperventilation at the bedside. The interictal EEG shows a 3 Hz generalized spike-and-wave pattern. Treatment includes ethosuximide (Zarontin) if the patient has not had a GTCS (see Box 1). Valproate (Depakene) is the first choice if the patient has had a GTCS. Nearly two thirds of patients grow out of their seizures by young adulthood.

**Benign Epilepsy with Centrtemporal Spikes and Benign Occipital Epilepsy**

One of the more-common epilepsies in childhood, benign epilepsy with centrocortical spikes (benign Rolandic epilepsy) first occurs between the ages of 3 and 13 years. The typical seizure involves the face and/or hand, but GTCS also are common. The most common time for a seizure is within the first few hours of sleep, but a minority of patients have daytime seizures. The diagnosis is based on a typical seizure history and EEG (which shows spikes over bilateral central and temporal regions). Learning disabilities are fairly common in patients with this syndrome, so extra vigilance is warranted.

Benign occipital epilepsy (also known as Panayiotopoulos syndrome) can occur between the ages of 1 and 14 years (with a peak at 4 to 5 years) with autonomic symptoms such as emesis, pallor, flushing, or tachycardia, as well as focal-onset or generalized seizures. Patients also can have visual symptoms. The EEG can show sharp waves in the occipital regions, but abnormal activity has been reported in other brain regions as well.

Because most patients have fewer than six seizures in both syndromes, medicine usually is not prescribed. Seizures typically are outgrown by adolescence. Patients with frequent seizures are treated with medicine. Gastaut occipital epilepsy (not to be confused with Lennox–Gastaut syndrome) occurs in older children and can require anticonvulsant treatment because of seizure recurrence.

**Juvenile Myoclonic Epilepsy**

The most common form of generalized seizures in adolescents, juvenile myoclonic epilepsy first occurs between the ages of 12 and 20 years. Most patients have brief myoclonic seizures that tend to cluster in the early morning hours. Patients often are unaware that these are seizures but on careful questioning report loss of control of a toothbrush or spoon. Many patients also have absence seizures. The interictal EEG typically shows a 4 to 5 Hz generalized spike-and-wave pattern. The prognosis for lifelong remission of seizures is poor, although most patients’ seizures are controlled easily with medicines (see Box 1). There is a subgroup of patients (many of whom had childhood absence epilepsy) whose seizures are very challenging to control.

**Other Epilepsy Syndromes with a Poor Prognosis**

Landau–Kleffner syndrome and epileptic encephalopathy with continuous spike-and-wave during sleep are syndromes characterized by mild seizures, nearly continuous ictal epileptiform activity during sleep, and neuropsychological deterioration. Progressive myoclonus epilepsy represents a family of disorders characterized by medically intractable epilepsy (commonly including myoclonic seizures) and significant neurologic deterioration. Underlying diagnoses include myoclonus epilepsy with ragged red fibers (MERRF), Unverricht–Lundborg disease and Lafora’s disease, among others. Gelastic (laughing) seizures can be caused either by hypothalamic hamartomas or temporal lobe seizures. The prognosis depends on response to medication and/or surgery but is not always bad. Rasmussen syndrome is characterized by medically intractable epilepsy, progressive unilateral neurologic deficits, and cortical atrophy on MRI. Because they are so rare, any suspicion of these diagnoses should prompt referral to a pediatric epilepsy center with expertise in diagnosing and managing these conditions.

**Tumors**

Brain tumors can manifest with seizures and are covered in a separate chapter. Certain developmental tumors are seen with an increased frequency in pediatric epilepsy clinics, including dys-embryoplastic neuroepithelial tumors (DNET) and gangliogliomas. These tumors typically manifest with seizures and can be associated with malformations of cortical development. EEG can show abnormalities over the involved region but can be falsely localizing, as well. MRI shows the location of the tumor but can underestimate the extent of surrounding abnormal tissue. If seizures are not controlled with medicine, or if there is progression in tumor size, resection surgery is recommended.

**Cortical Dysgenesis**

Abnormal brain development can lead to inappropriately wired brain circuitry, which can be the underlying substrate for seizures. Two forms of abnormal cortical development include lissencephaly (abnormally smooth, or simplified, gyral pattern) and polymicrogyria. Another form of cortical dysgenesis, the malformations of cortical development, is graded based on both dyslamination of the normal six-layer cortex and the occurrence of abnormal cell types (including balloon cells). EEG shows epileptiform abnormalities over the involved region. MRI shows the anatomic location of the involved tissue in more-severe cases but may be normal if the abnormality is mild. In patients with focal abnormalities, if seizures are not controlled with medicine, resection surgery is an option. Patients with more-extensive abnormalities can try nonpharmacologic options if medicines do not work.

**Mesial Temporal Lobe Epilepsy with Hippocampal Sclerosis**

The mesial temporal structures (particularly the hippocampus) can become scarred and remaining neurons develop abnormal connections (i.e., mossy fiber sprouting). This can lead to medically intractable seizures. EEG shows interictal epileptiform activity over the temporal regions. Imaging studies show atrophic mesial temporal structures with increased signal on T2-weighted FLAIR (fluid-attenuated inversion recovery) images. A temporal lobectomy should be considered as an option for patients who do not respond to two medications for seizure control.
Comorbidities
The definition of epilepsy includes comorbidities, which in turn can have a significant impact on quality of life. Clinicians must actively probe for these underlying conditions in order to optimize outcomes. People with epilepsy have increased rates of depression and anxiety compared to the general population. Developmental disorders and learning disabilities are more common in children with epilepsy, as are attention-deficit/hyperactivity disorder and migraines. Once identified, these conditions should be managed by clinicians experienced with their treatment.

Differential Diagnosis
The differential diagnosis of seizures depends largely on age. In infants, opisthotonic posturing can be seen in gastroesophageal reflux disease (Sandifer’s syndrome). Some infants have benign myoclonus or shuddering attacks. The EEG in all these disorders is normal, but the diagnosis can be made based on the history. Apparent life-threatening events can appear to be seizures, although apnea rarely is the only manifestation of a seizure. Hyperekplexia is an exaggerated startle response that can be due to abnormal glycine receptor subunits in the spinal cord. Because of potential involvement of the diaphragm, this disorder can be lethal. In children, stereotypies can be paroxysmal and persistent, but the behaviors during these episodes are typical enough that the diagnosis usually is made based on the history.

Breath-holding spells may be associated with an older infant or toddler who is upset, followed by unresponsiveness and either facial pallor or mild cyanosis, lasting less than 1 to 3 minutes. These episodes are typical enough that the history is all that is usually needed to make the diagnosis. Children with pallid breath-holding spells are at higher risk for vasovagal syncope in the adolescent and young adult ages.

Night terrors, one of the parasomnias, occur in toddlers and young children. Persistent screaming (lasting minutes to 1 hour) and lack of memory for the event are seen commonly; the latter raises a question of whether the child had a seizure. Most commonly, these are outgrown by the late preschool years.

Patients with syncope may have a few mild clonic twitches, but this typically does not represent epilepsy. Screening orthostatic blood pressures should be done to rule out one of the orthostatic syndromes. Consideration also should be given to an electrocardiogram or a cardiology consultation in the appropriate clinical context.

Older children and adolescents can have psychogenic nonepileptic events, also known as psychogenic nonepileptic seizures. Considered to be a form of a conversion disorder, the diagnosis is made by noting a normal EEG during a typical clinical episode (and thus should be referred to a neurologist for diagnosis). Cognitive behavioral therapy is helpful in some patients.

In all age groups, focal lesions such as infarctions, hemorrhages, and infections should be considered in the differential diagnosis, although the diagnostic work-up should be guided by the history and physical examination.

Treatment
The goals for treatment are to maximize efficacy and minimize side effects. Medication is the first line of therapy for most patients. Nearly 70% to 80% of patients are treated successfully by one of the first two medications tried. Practically speaking, neurologists try to use a single agent at the lowest tolerated dosage. Suggested medicines for the epilepsy syndromes discussed previously are listed in Box 1. Details about specific medicines are listed in Table 1. If one of the first two medicines tried do not work, there are three major options.

Trials of Additional Medication
Although the first two medicines might not work, new medicines often are introduced into the market. Clinical trials often show that a modest number of patients respond well to newer medicines, although the positive response to newer medicines is no greater overall than response to older medicines, despite lower rates of adverse effects and drug-drug interactions.

Surgery
Any patient who fails to respond to two medications should be assessed for surgery. In patients with a potentially resectable lesion, surgery offers the greatest chance of seizure freedom. Ideal surgical candidates have identifiable lesions on imaging studies and an epileptogenic zone that is distinct from eloquent cortex. Patients without identifiable lesions or those with multifocal or generalized seizures are poor candidates for resection surgery. Options for these patients include the vagus nerve stimulator, which has outstanding compliance and adherence because it is surgically implanted. Although this device significantly decreases seizure frequency in some patients, it rarely leads to seizure freedom. In the future, neurostimulation devices, some of which also include seizure detectors, may become available.

Diet Therapy
The concept of fasting to improve seizure control dates back to Hippocrates, but in modern times, dietary management of epilepsy was implemented using a high-fat, low-carbohydrate (adequate protein) ketogenic diet. More recently, a modified Atkins diet and a low glycemic index treatment have been used successfully, as well. These diets require varying degrees of supervision at a center experienced in their implementation.

Monitoring
Seizure calendars (which can take the form of notebooks or Internet-based tools) are very useful for tracking frequency of events, especially if they are completed on a daily basis. Monitoring for medication-related adverse effects and comorbidities should continue during treatment. In addition, some comorbidities can occur even if seizures have stopped; there is good evidence for this in patients with childhood absence epilepsy, which typically is considered a benign syndrome. Patients taking certain medicines are screened periodically for evidence of renal and/or hepatic abnormalities and abnormal blood cell counts. Scenarios for testing drug levels include the following:

- Assessing adherence to a prescribed drug regimen
- Testing whether symptoms result from drug toxicity
- Determining whether a patient could tolerate higher amounts of medicine when the administered doses are already high

Reminders about seizure-related safety (i.e., what to do in the event of a GTCS) should be reinforced periodically. This counseling typically includes instructions about safety for the patient, including protecting the head and airway (putting the patient on his or her side to prevent aspiration), and not putting anything in the patient’s mouth. Periodic assessments of bone health should be considered for patients taking enzyme-inducing or enzyme-inhibiting medicines. Patients of an appropriate age should seek counseling regarding local driving laws. Adolescent girls should be counseled about the effect of anticonvulsants on hormonal forms of contraception (and vice versa). Consideration should be given to prescribing folate in this group, as well.

Complications
Single GTCS can lead to trauma (e.g., from a fall), tongue biting, pneumothorax, fractures of the vertebrae or limbs, and joint dislocations. A brief physical examination can rule out the more-serious complications of a single GTCS. Adverse effects of medications are listed in Table 1. Surgical resections can lead to a variety of neurologic deficits, depending on which tissue is involved. Vagus nerve stimulator surgery can lead to hoarseness and coughing. Unsupervised diet therapy also can have adverse effects and should be undertaken only by centers with experience. Rarely, patients with epilepsy can die unexpectedly from no apparent cause; this is called sudden unexplained death in epilepsy (SUDEP). The cause is unknown, but most (not all) patients have epilepsy that is resistant to medications. Counseling about this condition should be provided by an epilepsy expert.
**Table 1** Summary of New Commonly Used Antiepileptic Drugs

<table>
<thead>
<tr>
<th>DRUG</th>
<th>MAINTENANCE DOSAGE* (mg/kg/d)</th>
<th>STARTING DOSAGE‡</th>
<th>HALF-LIFE (h)</th>
<th>COMMON SIDE EFFECTS</th>
<th>SERIOUS IDIOSYNCRATIC SIDE EFFECTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clobazam</td>
<td>&gt; 2 y, &lt; 30 kg: 10 mg bid</td>
<td>&gt; 2 y, &lt; 30 kg: 5 mg/d</td>
<td>Parent drug: 36–42 h</td>
<td>Sedation, irritability</td>
<td>Respiratory depression, benzodiazepine withdrawal, Stevens–Johnson syndrome</td>
</tr>
<tr>
<td></td>
<td>&gt; 2 y, &gt; 30 kg: 20 mg bid</td>
<td>&gt; 2 y, &gt; 30 kg: 5 mg bid</td>
<td>Active metabolite: 71–82 h</td>
<td>Needs to be tapered off slowly</td>
<td></td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>5–15</td>
<td>W/valproate: 2–12 y: 0.15 mg/kg/d</td>
<td>14–59 (depending on concomitant seizure medications)</td>
<td>Rash, lethargy, irritability, tremor</td>
<td>Stevens–Johnson syndrome, cytopenias</td>
</tr>
<tr>
<td></td>
<td>Dosage depends on other drugs used w/enzyme inducers:</td>
<td>&gt; 12 y: 25 mg qod</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>10–15</td>
<td>W/enzyme inducer:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>W/valproate: 1–3</td>
<td>2–12 y: 0.6 mg/kg div bid</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Non-valproate noninducer: 4.5–7.5</td>
<td>&gt; 12 y: 50 mg qd</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Non-valproate noninducer: 2–12 y: 0.3 mg/kg div bid</td>
<td>&gt; 12 y: 25 mg qd</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>50–60</td>
<td>10 mg/kg/d, incr in 10-mg/kg increments</td>
<td>6–8</td>
<td>Agitation, behavioral disinhibition, rashes</td>
<td>Suicidal ideation</td>
</tr>
<tr>
<td>(Keppra)</td>
<td>20–60</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>30–60</td>
<td>8–10 mg/kg/d, incr by 10–15 mg/kg</td>
<td>14–59 (depending on concomitant seizure medications)</td>
<td>Rash, lethargy, irritability, tremor</td>
<td>Stevens–Johnson syndrome, cytopenias</td>
</tr>
<tr>
<td>(Trileptal)</td>
<td>2–12 y: 0.15 mg/kg/d</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Topiramate</td>
<td>5–9</td>
<td>1–2 mg/kg/d (not to exceed 25 mg)</td>
<td>21</td>
<td>Irritability, hyperactivity, cognitive slowing, weight loss, kidney stones, metabolic acidosis, oligohydrosis</td>
<td>Rash</td>
</tr>
<tr>
<td>(Topamax)</td>
<td>2–12 y: 0.6 mg/kg div bid</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rufinamide</td>
<td>45 mg/kg/d</td>
<td>10 mg/kg/d</td>
<td>6–10</td>
<td>Nausea, vomiting, somnolence</td>
<td>Seizures, QT shortening</td>
</tr>
<tr>
<td>(Banzel)</td>
<td>20–60</td>
<td>10 mg/kg/d</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vigabatrin</td>
<td>50–150</td>
<td>50</td>
<td>7.5 (5.7 in infants)</td>
<td>Headache, dizziness, fatigue, tremor, swallowing problems, T2-weighted or DWI hyperintensities</td>
<td>Vision loss</td>
</tr>
<tr>
<td>(Sabril)</td>
<td>2–12 y: 0.15 mg/kg/d</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zonisamide</td>
<td>&gt; 16 y: 100–600</td>
<td>&gt; 16 y: 100 mg qd</td>
<td>63</td>
<td>Somnolence, irritability, cognitive slowing, weight loss, renal stones, oligohydrosis</td>
<td>Rash</td>
</tr>
<tr>
<td>(Zonegran)</td>
<td>2–12 y: 0.3 mg/kg div bid</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Dosages should not exceed maximum adult dosages.

Abbreviations: DWI = diffusion-weighted imaging; incr = increase.

References


Method of Michael A. Posencheck, MD, and Phyllis A. Dennery, MD

**Current Diagnosis**

- The direct antiglobulin, or Coombs, test (DAT) on neonatal blood is the cornerstone for differentiating isoimmune from non-immune-mediated hemolysis.
- The presence of a positive antibody screen in maternal blood should raise suspicion for hemolytic disease resulting from minor antibody-antigen reactions.
- In utero monitoring for severe fetal anemia includes maternal antibody screen titers, OD450 measurement, middle cerebral artery peak systolic velocity, and cordocentesis.
14% of pregnancies in the pre-RhIg era to between 1 and 6 per
The incidence of Rh isoimmunization has now fallen from nearly
the major blood group antigens (e.g., A, B) leading to ABO incom-
include Rh factor (D antigen), leading to Rh isoimmunization,
manifests when maternal antibodies cross the placenta and bind
management.

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- Intrauterine transfusion may be indicated in the setting of se-
vere fetal anemia with or without edema or hydrops fetalis.
- Phototherapy, the mainstay of postnatal management of hyper-
bilirubinemia, converts unconjugated bilirubin in a nonenzym-
atic fashion to a polar, water-soluble form that is more
readily excretable.
- Intravenous immunoglobulin (Gammagard) is indicated in in-
fants who have isoimmune hemolytic disease and bilirubin
levels approaching the threshold for double-volume exchange
transfusion.
- Double-volume exchange transfusion is reserved for infants
who fail phototherapy and intravenous immunoglobulin (if
indicated). It replaces and removes approximately 86% of
the infant’s own blood. In the setting of isoimmune hemolytic
disease, double-volume exchange transfusion has the added
benefit of removing offending maternal antibodies, which con-
tribute to the hemolysis from the infant’s circulation.

Epidemiology

Early-onset hyperbilirubinemia, anemia with or without edema in
the fetus or newborn, was previously synonymous with hemolytic
disease resulting from Rh-isoimmunization. With the onset of
the use of Rh-immunoglobulin (RhIg [RhoGAM]) in pregnant
Rh-negative women in 1968, the landscape of this disorder
has changed dramatically. The differential diagnosis of hemolytic
disease of the fetus and newborn is broad and can be subdi-
vided into isoimmune and nonimmune categories (Box 1). In this
article, we discuss various diseases that result in fetal and neonatal
hemolysis, along with recent improvements in diagnosis and
management.

Isoimmune hemolytic disease in the fetus and newborn
manifests when maternal antibodies cross the placenta and bind
to antigens present on the baby’s red blood cells. These antigens
include Rh factor (D antigen), leading to Rh isoimmunization,
the major blood group antigens (e.g., A, B) leading to ABO incom-
patibility, or minor blood group antigens (e.g., Kell, Kidd, Duffy).
The incidence of Rh isoimmunization has now fallen from nearly
14% of pregnancies in the pre-RhIg era to between 1 and 6 per
1000 live births. Incomplete eradication is due to inadvertent
failures of RhIg administration, poor prenatal care, or earlier sen-
sitization. Rh-isoimmunization can lead to severe complications,
with up to 20% of fetuses having significant anemia and evidence
of hydrops in utero.

ABO incompatibility occurs nearly exclusively in fetuses and
newborns with type A or B blood born to mothers with type O
blood. Although nearly one quarter of pregnancies result in
ABO incompatibility, only approximately 1% to 5% of ABO-
 incompatible infants demonstrate significant hemolytic disease.
The incidence of hemolytic disease from minor antigens is more
difficult to estimate due to the large number of antigen-antibody
reactions that can result in disease. Of the minor antigens, Kell
and Duffy antigens are associated with the most severe disease,
and Lewis and Lutheran are more likely associated with mild or
insignificant hemolysis.

The group of disorders that is nonimmune in nature results in red
blood cell destruction in the absence of an antibody-antigen reaction.
These include red blood cell membrane defects such as hereditary ellip-
tocytosis or spherocytosis, red blood cell enzyme defects such as
glucose-6-phosphate dehydrogenase (G6PD) deficiency and pyruvate
kinase deficiency, and hemoglobinopathies such as α-thalassemia.
With rates up to 1 in 5000 live births, hereditary spherocytosis is
the most common of the RBC membrane defects, occurring most
commonly in infants of Northern European descent.

Of the enzyme defects, G6PD is the most common, especially in
infants of African or Mediterranean descent. It is an X-linked dis-
order that is most commonly seen in male infants, but females can
also manifest the disease. Interestingly, this disease accounts for a
disproportionately large percentage of infants who develop ker-
nicterus. α-Thalassemia is a rare hemoglobinopathy in which all
α-globin chain genes are deleted. It is most common in Asian in-
fants and is nearly uniformly fatal, with severe fetal anemia and
hydrops fetalis, especially when intrauterine transfusions have
not been performed.

Risk Factors

Several elements of the maternal, fetal, and neonatal histories can
assist in determining a fetus’s or infant’s risk of developing one of
these hemolytic processes. The results of the maternal blood type
and antibody screen are useful to evaluate this risk. Infants born to
mothers with type O blood are at risk for ABO incompatibility,
whereas infants born to mothers with Rh-negative blood are at
risk for Rh isoimmunization. The antibody screen that is per-
formed on maternal blood is specifically searching for antibodies
associated with the minor antigen groups that can also be found on
red blood cells. Selected minor antigens are listed in Table 1. The
presence of a positive direct Coombs’ test should raise suspicion
of an isoimmune hemolytic process. This test is not always available
or warranted.

Assessing the risk of nonimmune disease is based almost entirely
on a complete family history. Many of these disorders are associ-
ated with certain ethnic or geographic backgrounds. As examples,
G6PD deficiency is found more commonly in persons of African or
Mediterranean descent, and a family history of persistent anemia
requiring splenectomy is often seen in hereditary spherocytosis.

Pathophysiology

The isoimmune forms of fetal and neonatal hemolysis have a sim-
ilar pathophysiology in that all of them involve the passage of spe-
cific maternal IgG antibodies across the placenta, which then
interact with their corresponding antigens on the fetal red blood
cells. Red cell destruction results when the antibody-coated cells
are scavenged by the mononuclear phagocytic system. The pro-
duction of maternal antibodies is usually the result of previous ex-
posure of the maternal system to fetal red blood cells, which is
common during labor or abortion. The initial response of the ma-
ternal immune system is to produce IgM antibodies, but repeat ex-
posure elicits an IgG response. This is especially true for Rh
isooimmunization, and therefore explains why first-born Rh-positive infants born to Rh-negative mothers are not affected.

In ABO incompatibility, antibodies to A or B antigens already exist, but they are normally IgM antibodies. They do not cross the placenta and therefore do not result in disease. It is only when the antigenicity results in the production of IgG antibodies that passage across the placenta can occur and disease can result. This is exceedingly uncommon in blood type A with B incompatibility (mother is type A, baby is type B), but is more common in mothers with blood type O who have a fetus with either blood type A or B. This can occur in first-born infants. As to hemolysis from antibodies to minor antigens, IgG antibody production may be the result of prior exposure to fetal cells such as during a previous pregnancy or via previous blood transfusion.

The pathophysiology of the nonimmune group of hemolytic disease is unique to the specific disease process. Red blood cell membrane defects, such as hereditary spherocytosis, have specific abnormalities of red blood cell membrane proteins that result in abnormal red blood cell shapes. These cells are more prone to destruction from mechanical forces. The enzyme defects such as G6PD and pyruvate kinase deficiency result in an inability of the red blood cell to protect itself from oxidant stress (G6PD) or to produce energy (pyruvate kinase). This makes the cell more prone to hemolysis. Hemoglobinopathies result in anemia from decreased production of stable hemoglobin chains. Specifically, α-thalassemia major involves the lack of production of the α chain of hemoglobin and leads to early fetal anemia, severe hydrops, and death unless intrauterine transfusions are instituted.

**Clinical Manifestations**

The clinical presentation of hemolytic disease in the fetus and newborn varies according to the timing and severity of the disease. Significant and early hemolysis in utero results in fetal anemia, and, as oncotic pressure decreases in the fetal blood vessels, edema forms in the soft tissues and potential spaces. Hydrops fetalis results when there is edema or fluid accumulation in at least two of these spaces: skin, pleura, pericardium, or peritoneum. If this continues unabated, fetal death can result. Of all the diseases discussed here, Rh-isoimmunization and α-thalassemia are those most commonly associated with fetal anemia and the most severe disease.

Most commonly, hemolytic disease results in early neonatal onset anemia and significant hyperbilirubinemia. Often, infants present with clinical jaundice in the first 24 hours of life and have a significant rate of rise of their serum bilirubin levels or a prolonged course of hyperbilirubinemia. Neonatal anemia with significant hyperbilirubinemia is a common manifestation of ABO incompatibility, hemolysis due to minor antigens, and red blood cell enzyme and membrane defects. The degree of anemia in each, however, is quite variable even within a given diagnosis.

**Diagnosis**

The assessment of maternal blood type and antibody screen can provide valuable insight into the risk of isoimmune hemolytic anemia. Ultrasound techniques and amniocentesis for the antenatal monitoring of fetal anemia are reviewed later.

In the neonate, concern for hemolytic anemia results from a rapidly rising bilirubin level, especially in the first 24 hours of life, a positive direct Coombs’ test, hemolysis detected on a blood smear with anemia detected on a complete blood count (CBC), or prolonged hyperbilirubinemia, individually or in combination. In addition to following serial bilirubin levels, in this setting the practitioner should include a neonatal blood type, Coombs’ (DAT) test, and complete blood count with reticulocyte count to determine whether hemolysis is occurring. A positive DAT in the appropriate clinical setting suggests isoimmune hemolysis, and a negative DAT nearly rules it out. However, in the setting of ABO incompatibility a significant number of infants can have a positive Coombs’ test and not have significant hemolysis.

A G6PD level can be helpful in establishing a diagnosis in infants with the appropriate ethnic background or geographic location. Many states have adopted universal newborn screening for G6PD deficiency. Serum albumin, the primary protein transporter for bilirubin in the blood, can also be measured. Low serum levels of albumin increase the risk of developing neurologic sequelae from the subsequent increased amount of free, unbound bilirubin crossing the blood-brain barrier.

**Differential Diagnosis**

The differential diagnosis of hemolytic disease starts with determining whether or not the hemolysis is antibody-mediated (see Box 1).

Isoimmune hemolytic disease involves the production of maternal IgG antibodies against antigens on fetal red blood cells,

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**TABLE 1** Selected Minor Antigens Associated with Fetal or Neonatal Hemolytic Disease

<table>
<thead>
<tr>
<th>BLOOD GROUP</th>
<th>SEVERE DISEASE</th>
<th>RARELY SEVERE DISEASE</th>
<th>MILD DISEASE</th>
<th>USUALLY NO DISEASE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rh</td>
<td>D, C</td>
<td>C, E, f, Evans, G, Rh29, Rh32, Rh42, Rh46, and others</td>
<td>E, e, f</td>
<td></td>
</tr>
<tr>
<td>Lutheran</td>
<td></td>
<td></td>
<td>Lu&quot; Lu&quot;</td>
<td></td>
</tr>
<tr>
<td>Kell</td>
<td>K</td>
<td>k, Kp&quot;, Kp&quot;b, Ku, Js&quot;, Js&quot;b, K11, K22</td>
<td>Ku, Js&quot;, K11</td>
<td>K23, K24</td>
</tr>
<tr>
<td>Lewis</td>
<td></td>
<td></td>
<td>Le&quot; Le&quot;</td>
<td></td>
</tr>
<tr>
<td>Duffy</td>
<td>Fy&quot;a</td>
<td>Fy&quot;b, Fy3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kidd</td>
<td>Jk&quot;a</td>
<td>Jk&quot;b, Jk3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heme is degraded in a rate-limiting, oxygen (O₂) and energy-requiring process. This leads to accumulation of bilirubin because it must be produced from the high heme load resulting from significant hemolysis. The glucuronyl-transferase enzyme that conjugates bilirubin to bilirubin-3-sulfate is expressed at a lower level in the newborn and must now take on this task. However, in the first days of life, some infants have neurologic manifestations of bilirubin toxicity despite bilirubin levels lower than suggested by the exchange transfusion level. This dose may be repeated in 12 hours.

For some infants, the use of phototherapy and IVIg, if indicated, is not sufficient to control the rising bilirubin level. Alternatively, some infants have neurologic manifestations of bilirubin toxicity despite bilirubin levels lower than suggested by the exchange transfusion level. In these instances, a double-volume exchange transfusion is indicated. This procedure involves removing double the infant’s blood volume with simultaneous isovolemic replacement of reconstituted whole blood. This process achieves two separate but related goals. First, it removes bilirubin and, second, in the setting of isoimmune hemolytic disease, it removes offending maternal antibodies. Criteria for performing a double-volume exchange transfusion are clearly outlined in the guidelines from the AAP published in 2004, but some experts suggest performing a double-volume exchange transfusion at even lower levels when significant antibody-mediated hemolysis is occurring owing to the added benefit provided by removing maternal antibodies.

Two pharmacologic therapies have been proposed in the treatment of neonatal hyperbilirubinemia. Phenobarbital, when given to mothers just before birth, has been shown to decrease the rate of exchange transfusion in their newborn infants. Synthetic metalloporphyrins (e.g., tin-mesoporphyrin, stannsoporfin [Stanato]) decrease the production of bilirubin by inhibiting heme oxygenase, the rate-limiting enzyme in the degradation of heme to biliverdin (which is then converted to bilirubin by biliverdin reductase). Both of these therapies are still considered experimental because the safety profile of both remains in question.

**Monitoring**

Monitoring of hemolytic anemia may be performed for the fetus in utero and for the infant after birth. Significant advances have improved our ability to determine the degree of fetal anemia in both invasive and noninvasive manners. Initial concern for the presence of significant antibodies against fetal red blood cells begins with the routine antibody screen performed early in gestation. This is normally an indirect Coombs’ test, and most centers consider a titer of 1:16 or 1:32 to be a threshold to suggest significant risk for hemolysis. Liley first described the relationship between bilirubin level in the amniotic fluid and the degree of fetal anemia in infants greater than 27 weeks gestation. Amniotic fluid is analyzed at a wavelength of 450 nm (ΔOD450) to determine the bilirubin level and the value is plotted on known graphs to assess risk. Interventions including delivery or intrauterine transfusion are suggested if the level, when plotted, falls in the upper 20th percentile of zone II or in zone III. An expanded form of the Liley curve as well as the development of the Queenan curve has provided practitioners with tools to determine the risk of Rh isoimmune fetal anemia as early as 14 weeks’ gestation. However, these methods may be less useful when antibodies to the Kell antigens are involved.

The measurement of middle cerebral artery peak systolic velocity (MCA-PSV) by Doppler ultrasonography gives practitioners a noninvasive alternative to amniocentesis for monitoring fetal anemia. Theoretically, as a fetus becomes more anemic, the blood flow velocity increases due to increased cardiac output and vasodilation, resulting in increased MCA-PSV. The measurement is not FDA approved for this indication.
specific for gestational age and can be charted to determine if it is more than 1.5 multiples of the median (MoM), suggesting moderate to severe anemia. The effect of intrauterine transfusions on this measurement is unclear owing to the presence of adult red blood cells, and they can alter the interpretation of MCA-PSV. Large randomized, controlled trials are needed to determine if measurement of MCA-PSV or ΔD450 are equivalent in assessing the risk of anemia. This would give practitioners a noninvasive way to monitor fetuses at risk for severe anemia.

Cordocentesis is the gold standard for measuring fetal anemia but it comes with severe risk including fetal and perinatal death, cord bleeding, hematomas, further maternal sensitization from fetal-maternal hemorrhage, infection, and placental abruption.

After birth, the neonate at risk for hemolytic anemia must be monitored for degree of anemia and for the development of significant hyperbilirubinemia. In utero, bilirubin is transferred to the maternal circulation via the placenta and processed in the maternal liver, which explains why hyperbilirubinemia is a postnatal event. Early and frequent bilirubin levels and complete blood counts allow the practitioner to evaluate the need for intervention. The availability of hour-specific nomograms that plot the risk of severe hyperbilirubinemia based on the level of bilirubin can be used in term infants to guide therapy and timing of outpatient follow-up. These are published in the AAP position statement from 2004.

### Complications

Complications of phototherapy, IVIg, and double-volume exchange transfusions are all possible. Side effects of phototherapy include disruption of mother-baby bonding, increased insensible water loss (less common with modern bilirubin lights), retinal injury from UV light, and, in the setting of an elevated conjugated fraction, a brown discoloration of the skin called “bronze-baby syndrome.” The presence of an elevated conjugated fraction or bronzing of the skin is not a contraindication for phototherapy. This is of cosmetic concern only and is usually reversible after removal of the phototherapy.

Complications involving the use of IVIg are rare but include renal dysfunction, increased incidence of thrombotic events, transfusion reactions, and transmission of infections that can occur with transfusion of any blood product, because blood products are derived from pooled plasma.

Many potential complications are associated with double-volume exchange transfusion. These include electrolyte disturbances, arrhythmias, cardiac arrest, thrombotic or embolic sequelae, metabolic acidosis, thrombocytopenia, disseminated intravascular coagulation, infection, necrotizing enterocolitis, temperature instability, and blood transfusion–related complications such as hepatitis, HIV infection, or transfusion reaction.

### References


The newborn period is defined as birth through the 28th day of life. During this time, newborns primarily feed, grow, and sleep. Therefore, adequate nutrition carries special significance during this phase of life. This chapter focuses on available options for newborn nutrition (e.g., breast milk and commercial formulas), information medical caregivers can use when counseling families, definitions of adequate quality and quantity of nutritional sources, and assessing for appropriate intake in terms of growth.

### Breast-feeding and Breast Milk

Breast-feeding is the nutritional source of choice as recommended by the American Academy of Pediatrics (AAP), the Canadian Pediatric Society, and the American Academy of Family Physicians. Caregivers should always respect the choice of the mother and support her during her bonding period with her newborn infant. However, because many misconceptions exist regarding breast-feeding, it is practical for caregivers to inquire about a mother’s reasons if she chooses to use formula to feed her infant. She may have several concerns about breast-feeding including returning to work, the logistics of pumping, or her modesty, or she may consider breast-feeding to be “antiquated.” Breast-feeding may be contrary to cultural and ethnic beliefs of the mother. For example, some Hispanic women are concerned that when breast-feeding they might inadvertently pass on negative emotions to their newborn. Because Somali mothers attribute special powers to Western medicine and infant formulas, they often breast-feed but supplement with formula to ensure their infant gets everything that modern medicine can offer. With proper education and support, many mothers find breast-feeding to be a more reasonable option than they first thought.

Thanks to the efforts of several organizations promoting the health benefits of breast-feeding, even mothers who choose to formula feed recognize breast milk as the best nutritional option for their infant. But even after making the decision to breast-feed, some mothers continue to struggle with the actual undertaking of breast-feeding. There remains in our culture the inaccurate belief that something so “natural” must be easy to do. Many first-time mothers are easily frustrated and discouraged during the first few attempts at breast-feeding because they have unreasonable expectations based on the media and popular culture. With more and more women willing to try breast-feeding after delivery, adequate support and teaching should be provided by the entire medical team.
Healthy People 2010 established a national breast-feeding initiation goal of 75% and in 2003 and 2004 reported rates for all U.S. women were at 70.9% and 70.3%, respectively. These rates are the highest reported since before World War II and are largely the result of improved public knowledge. Unfortunately, other Healthy People 2010 breast-feeding goals fell short. Despite a goal of 50% breast-feeding at 6 months, only 36% of infants were still receiving any human milk at this age and only 14% were exclusively being breast-fed. Only 17% of babies are breast-fed at 1 year, despite a goal of 25%. The biggest disparities in breast-feeding rates are among racial and ethnic minorities. Special attention should be made by medical teams to provide sufficient support and education to these women.

Breast milk is considered the ideal source of nutrition for all newborns, including premature infants, in a large part owing to its contents. There is a greater ratio of whey to casein in breast milk than in formula. Whey is associated with better absorption and digestion as well as faster gastrointestinal transit times. There are also several specific proteins found only in breast milk, such as lactoferrin, lysozyme, and secretory immunoglobulin A, that aid in immune defense in the gut. Breast milk also contains long-chain polyunsaturated fatty acids (PUFAs) that aid in neural and visual development. Infants given formulas that contain long-chain PUFAs have serum concentrations that never match those of breast milk-fed infants, but there is also no known minimum amount needed to achieve benefit.

There is also a difference in the intestinal microflora seen in infants fed breast milk versus those fed formula. Larger percentages of *Lactobacillus* and *Bifidobacterium* species are found in infants fed breast milk, whereas *Bacteroides* spp and enterobacteria are in more abundance in formula-fed counterparts. Newer evidence suggests this difference in the diversity of gut microflora accounts for the stronger immune systems seen in breast-fed infants.

Breast milk has the benefit of containing several nonnutritive substances that are advantageous for young infants including maternal antibodies, growth regulators, digestive enzymes, and hormones. Breast milk has been associated with a reduced risk for many chronic illnesses including asthma, food and environmental allergies, diabetes mellitus, eczema, cardiovascular disease, and obesity. There is a reduction in the number of short-term illnesses of childhood including acute respiratory and gastrointestinal illnesses as well as otitis media.

Newer research shows an association between being fed breast milk and having higher IQ scores later in childhood.

The act of breast-feeding offers several benefits to the infant. There is a sense of security and closeness that comes from skin-to-skin contact and the resultant interaction between infant and mother. Nursing can also reduce the opportunities and risk for bottle-propping and overfeeding. Breast-feeding allows nutrition to be more immediately available with minimal preparation work compared to the mixing and warming of formula. Breast milk is a much cheaper alternative to supplemental formulas. Breast-feeding can also lead to health benefits for the mother such as decreased risk of ovarian and breast cancers as well as diabetes mellitus type II.

There are very few contraindications to breast-feeding. Contraindications include maternal HIV, active herpetic lesions on the breast (herpetic lesions elsewhere are not a contraindication), maternal use of illicit drugs, women undergoing chemotherapy with antimetabolite agents, and mothers with active tuberculosis. Nearly all over-the-counter medications are safe to take during breast-feeding. Some prescription medications are contraindicated, though safe substitutes are usually available. Providers can use the online National Library of Medicine’s Drugs and Lactation Database (LactMed) to check safety and provide up-to-date counseling. Infants with galactosemia should not be breast-fed or bottle fed with milk products.

**Infant Formulas**

Commercially available infant formulas became widely used during World War II when there was a large influx of women into the national workforce. Since that time, infant formulas have been continuously improved upon and contain all the necessary energy and nutrient requirements for full-term infants up to the age of 6 months. According to the AAP there are three indications for the use of formulas:

- An alternative primary nutritional source for infants whose mothers choose not to or are unable to breast-feed
- A supplementary nutritional source for mothers with an inadequate supply of breast milk
- A nutritional source in infants with a medical condition in which breast-feeding is contraindicated (e.g., galactosemia)

Commercial formulas usually come in three distinct preparations including ready-to-feed, concentrated liquid, and powder. All three preparations yield 20 kcal per fluid ounce when prepared correctly, the same amount of energy per volume found in breast milk. Powder preparations are generally the least expensive. An advantage to formulas over breast-feeding is the ability to increase caloric density for an infant with increased metabolic needs (e.g., infants with congenital heart defects). Breast-feeding mothers have the option to breast pump and add a fortifier if needed to achieve similar increases in caloric density.

Formulas carry the risk of improper preparation, whether intentional or accidental. Caregivers might choose to dilute the formula secondary to financial pressures or to concentrate formula preparations in a desire to have a larger infant, because some cultures equate larger infant size and weight with better health. Either change can be dangerous to the infant. Diluting leads to an excess of free water with an insufficient solute load (e.g., hyponatremia) and concentrating can conversely lead to hypernatremia. Nevertheless, formulas remain an appropriate alternative when desired by the infant’s mother or when medically indicated (Table 1).

**Micronutrients**

Both breast milk and formula contain most of the micronutrients needed by infants, calcium and phosphorus are found in lower concentrations in breast milk but are more bioavailable than the minerals present in formulas. Therefore there is no difference in bone mineral concentrations in both sets of infants. Iron, zinc, and copper serum levels are sufficient during the first 6 months of life in breast-fed infants, though tissue stores are gradually depleted. After 6 months breast-feeding should be supplemented with complementary foods to prevent outcomes such as iron deficiency anemia.

Vitamin K, necessary to prevent hemorrhagic disease, is produced by the digestive actions of intestinal flora. For this reason, most infants at the time of birth are given a single intramuscular dose to provide adequate amounts until intestinal flora concentrations are more mature and dietary supplementation with solid food begins at 6 months.

Vitamin D needs historically have been achieved with adequate sunlight exposure. However, with appropriate use of sunscreens and sunlight avoidance, most infants are at risk for vitamin D deficiency. Vitamin D is not passed in sufficient quantities in breast milk, and the content in formulas is so low that the daily recommended amount of 400 IU is only achieved when infants are consuming a volume typical of a 6-month old. Therefore, supplementation should be recommended for all infants regardless of skin color and nutritional source to help prevent rickets. The recommendation is 400 IU of vitamin D for all pediatric age groups beginning after the first 2 weeks of life.

Neither formula-fed nor breast-fed infants usually require supplementation with water. In fact, providing infants with excess free water can lead to hyponatremia, seizures, and death. If there is concern that the infant is constipated or overheated, caregivers can provide up to a tablespoon of water daily to infants younger than 4 months old.

**Defining Adequate Intake**

To determine if a newborn is receiving adequate nutrition physicians should ask the caregiver how often feedings are occurring, for how long (for breast-fed infants), and how much is eaten.
(for formula-fed infants) and should assess the number of wet diapers and stools daily. Initially infants should consume 10 to 15 mL per feeding for the first 24 to 36 hours, gradually increasing to 30 to 45 mL by the fourth day of life. Breast-fed infants should feed 15 to 20 minutes each side. At the time of discharge to home, all newborns should be feeding 8 to 12 times a day, or every 2 to 3 hours. This interval can be increased to every 4 hours at night, and parents should be encouraged to wake any infants who sleep for longer than this duration. If an infant has lost more than 10% of his or her birth weight, the care team should consider delaying discharge to review the infant’s nutritional status and feeding habits. Caregivers should be attentive to infant cues of hunger and satiety to provide an ideal feeding pattern for each infant.

Voiding and stooling patterns change with age and can also be influenced by the infant’s diet. All newborns should have at least one wet diaper and one stool within the first 24 hours of life. If this does not occur, close observation and further work-up is indicated to rule out structural or metabolic abnormalities. During the first week of life, infants usually void and stool with every feeding or even more often. Beyond the first week, infants should have at least 4 to 6 voids daily regardless of diet. Formula-fed infants might have one stool every other day up to 2 to 3 stools daily. Because of the higher percentage of protein that is absorbed in breast milk, breast-fed infants can go up to 10 days between stools. Physicians should review with families the signs and symptoms (emesis, refusal to feed, lethargy, inconsolability, and abdominal distention) that indicate an infant with infrequent stooling should be medically evaluated. Breast-fed infants also have stools that are described as loose, yellow, and seedy. Caregivers should be educated that this is a normal stool color and consistency and is not considered diarrhea.

Medical providers can also calculate an infant’s nutritional needs and compare to the actual intake. Nutritional needs are represented as kcal/kg per day (KKD). The following formula can be used:

$$KKD = \frac{Volume \ in \ mL \ consumed \ in \ 24h}{Weight \ in \ kg} \times \frac{20 \ kcal/oz}{30}$$

During the first 3 months of life, infants should consume an intake that equals 90 to 135 kcal/kg per day. This intake goal should lead to a weight gain of approximately 25 to 30 g daily. From 3 to 6 months of age, infants gain at a slightly slower rate of approximately 15 to 20 g per day (Table 2). For example, a 2-month-old who weighs 6 kg should consume between 810 mL to 1215 mL daily.

At subsequent visits an infant can be assessed for adequate growth using standardized, gender-specific growth curves. Attention should be paid to growth parameters including weight, length, head circumference, and weight-for-length. Weight-for-length charts are used during the first 2 years of life as a gross equivalent to body-mass-index charts used for children older than 2 years. For years, practices defined adequate weight gain using growth charts as designed by the National Center for Health Statistics (NCHS), a branch of the Centers for Disease Control and Prevention (CDC). These charts were last

### TABLE 1: Infant Formulas and their Indications

<table>
<thead>
<tr>
<th>CLASS</th>
<th>BRAND NAMES</th>
<th>CALORIES (KCAL PER OZ)</th>
<th>CARBOHYDRATE SOURCE</th>
<th>PROTEIN SOURCE</th>
<th>INDICATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast milk</td>
<td>—</td>
<td>20</td>
<td>Lactose</td>
<td>Human milk</td>
<td>Preferred for all infants</td>
</tr>
<tr>
<td>Term formula</td>
<td>Gerber Good Start Gentle</td>
<td>20</td>
<td>Lactose</td>
<td>Cow’s milk</td>
<td>Appropriate for most infants</td>
</tr>
<tr>
<td>Term formula</td>
<td>Enfamil Premium Infant; Good Start Protect; Similac Advanced</td>
<td>20</td>
<td>Lactose</td>
<td>Cow’s milk</td>
<td>Marketed to promote eye and brain development</td>
</tr>
<tr>
<td>Preterm formula</td>
<td>Enfamil Premature; Similac Special Care 24 with Iron</td>
<td>24</td>
<td>Lactose</td>
<td>Cow’s milk</td>
<td>&lt; 34 wk gestational age Weight &lt; 1800 g</td>
</tr>
<tr>
<td>Enriched formula</td>
<td>Enfacare; Similac Neosure</td>
<td>22</td>
<td>Lactose</td>
<td>Cow’s milk</td>
<td>34–36 wk gestational age Weight ≥ 1800 g</td>
</tr>
<tr>
<td>Soy formula</td>
<td>Enfamil Prosobee; Good Start Soy; Similac Isomil</td>
<td>20</td>
<td>Corn-based</td>
<td>Soy</td>
<td>Congenital lactase deficiency, galactosemia</td>
</tr>
<tr>
<td>Lactose-free formula</td>
<td>Similac Sensitive</td>
<td>20</td>
<td>Corn-based</td>
<td>Cow’s milk</td>
<td>Congenital lactase deficiency, primary lactase deficiency, galactosemia</td>
</tr>
<tr>
<td>Hypoallergenic formula</td>
<td>Similac Alimentum; Enfamil Nutramigen; Enfamil Pregestimil</td>
<td>20</td>
<td>Corn or Sucrose</td>
<td>Hydrolyzed proteins</td>
<td>Milk protein allergy</td>
</tr>
<tr>
<td>Nonallergic formula</td>
<td>Elecare; Neocate Infant; Nutramigen AA</td>
<td>20</td>
<td>Corn or Sucrose</td>
<td>Amino acids</td>
<td>Milk protein allergy</td>
</tr>
<tr>
<td>Antireflex formula</td>
<td>Enfamil AR; Similac Sensitive for Spit-Up</td>
<td>20</td>
<td>Lactose (thickened with rice starch)</td>
<td>Cow’s milk</td>
<td>Gastroesophageal reflux</td>
</tr>
</tbody>
</table>

Adapted from O’Connor NR. Infant formula. Am Fam Physician 2009;79:565–70. Abbreviations: ARA = arachidonic acid; DHA = docosahexaenoic acid.

### TABLE 2: Expected Growth Velocities during Infancy

<table>
<thead>
<tr>
<th>AGE</th>
<th>WEIGHT GAIN (g/d)</th>
<th>LENGTH (cm/mo)</th>
<th>HEAD CIRCUMFERENCE (cm/wk)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–3 mo</td>
<td>25–30</td>
<td>2.5</td>
<td>0.5</td>
</tr>
<tr>
<td>3–6 mo</td>
<td>15–20</td>
<td>2.5</td>
<td>0.5</td>
</tr>
<tr>
<td>6–12 mo</td>
<td>10</td>
<td>1.25</td>
<td>0.25</td>
</tr>
</tbody>
</table>
updated in 2000 and unfortunately still reflect means for a population with a predominance of formula-fed infants. The World Health Organization (WHO) has since completed the Multi-Centre Growth Reference Study to better establish growth norms for infants and children who are breast-fed throughout the first year of life. A provider who is uncertain if an exclusively breast-fed infant is meeting minimum growth requirements should refer to these charts before automatically encouraging caregivers to begin formula supplementation. Growth failure: Growth failure is usually considered a weight less than the third percentile or a drop of two or more percentiles in a short time.

Overfeeding of newborns is unfortunately common, though bottle-fed infants are at a greater risk compared to breast-fed infants. Several factors can contribute to overfeeding including lack of caregiver experience and support, as well as cultural biases such as the desire to have a chubbier infant. Many caregivers are unable to recognize infant cues for hunger and satiety and misinterpret cries or other vocalizations as a request for food. Medical providers should teach families about the rooting and sucking reflex and explain that some forms of sucking provide the infant with a means for self-soothing and are not signals that the infant is hungry (nonnutritive versus nutritive sucking).

Introduction of Complementary Foods
It remains controversial when solid foods should be added to the diet of an infant. The WHO recommends waiting until 6 months old. The AAP encourages waiting until an infant is 4 months old before adding solids and encourages continued breast-feeding until at least 1 year of age. However, some families want to start solids sooner than 4 months of age for a variety of reasons. A common explanation is “helping the baby sleep better at night.” Only by 4 months will infants have attained sufficient muscle strength and coordination to keep their head upright when seated and to protect their own airway during feedings that contain solid foods. Families should be encouraged to wait at least until 4 months old before introducing solids, usually starting with rice cereal. Introduction of solids should not be delayed for much longer than 6 months, especially for breast-fed infants, because this is typically when micronutrient stores have been depleted and dietary supplementation with solid foods is needed. Only one new solid should be introduced every 3 to 5 days so infants can be monitored for adverse food reactions.

Either formula or breast milk should continue to be offered until 12 months old, at which time infants can be transitioned to whole-fat cow’s milk. Low-fat milk does not provide toddlers with sufficient lipid concentrations for adequate brain development or the required caloric density for general growth. Large quantities of fruit juices should be avoided throughout infancy and childhood because they provide little nutritional value.

Summary
The majority of term infants are born ready and able to begin feeding, but it is up to providers to know available nutritional options, normal feeding patterns, and means for measuring adequate intake and growth. Providers and other members of the care team also need to be able to counsel caregivers about best practices when feeding infants. When infants are suspected to be overfed or underfed, it may take a multidisciplinary approach by physicians, nurses, dieticians, speech therapists, lactation counselors, and social workers to help patients and their families.

References


CURRENT DIAGNOSIS

- Maintenance fluid therapy is designed to replace the next 24 hours’ anticipated losses from sensible and insensible losses in an otherwise healthy, euvolemic patient with normal kidney function.
- In a patient with extracellular volume loss, the percentage of body weight lost should be used as a guide to the volume needed for restoration.
- Serum sodium in patients with dehydration should be measured at the time of presentation and also after restoration fluid has been provided. The further correction of serum sodium will be much easier in a patient with a normalized extracellular volume.

CURRENT THERAPY

- Maintenance fluid therapy should not be used as a restoration or replacement fluid.
- Restoration fluid therapy can be given over short periods with a plan for complete restoration, in the majority of patients, within 24 hours.
- When treating hyponatremia or hypernatremia, the goal should be to change the serum sodium by no more than 10 mmol/L in a 24-hour period.
- When calculating how much water (in the case of hypernatremia) or how much sodium (in the case of hyponatremia) to provide in order to restore sodium into the normal range, remember the calculation is based on the total body water, which is 60% of body weight, and the aim is to get to the closest serum sodium considered normal; for example, sodium 135 mmol/L for hyponatremia and sodium 145 mmol/L for hypernatremia.
- Replacement fluid therapy for patients with normal losses—gastrointestinal or urinary losses—should be based on measurement of the lost fluid volume and fluid electrolyte content.

Children receive three types of parenteral fluid therapy: maintenance therapy, restoration therapy, and replacement therapy. Maintenance fluid therapy provides the typical anticipated fluid and electrolyte losses seen in otherwise normal, euvolemic children. Restoration fluid therapy restores fluid volume previously lost. Replacement fluid therapy keeps up with ongoing abnormal fluid losses, such as ongoing losses from the gastrointestinal tract or abnormal urinary losses.

Maintenance Fluid Therapy
In 1957, Holliday and Segar proposed an approach to providing parenteral fluids and electrolytes to hospitalized children who are not permitted to eat or drink. The formulation was based on
calories expended, presumed the patient did not have previous fluid losses (was euvolemic), and had normal kidney function. The surrogate for calories is weight because calories expended correlates to weight in grams. Therefore, the anticipated fluid losses for the upcoming 24 hours would come from urine excreted, water lost during breathing, and fluids lost from sweating. The prescription includes two components: water and electrolytes. Table 1 describes the approach recommended by Holliday and Segar to determine parenteral fluids and electrolytes for a 24-hour period. It includes determining the amount of water to be provided based on weight as a surrogate for calories expended and it includes electrolytes to be provided. The electrolytes are sodium and potassium. Sodium is given at 2 to 3 mmol per 100 mL water provided, and potassium is given at 2 mmol per 100 mL water provided, with each provided as the chloride salt. Once the amount is calculated, the hourly rate can be determined by dividing the final calculation by 24.

The prepared solution that most closely resembles this maintenance prescription is 0.2 NS (0.2 normal saline, or 154 mmol sodium and chloride per liter) with 20 mEq KCl/L of fluid. Often glucose is added at 50 g/L (D5W) or 5 g/100 mL. This provides some readily available calories to reduce catabolism. Note also that D5W has an osmolality of nearly 300 mOsm/kg H2O, essentially the same as plasma. This allows safe administration of the electrolytes to be provided. The electrolytes are sodium and potassium. Sodium is given at 2 to 3 mmol per 100 mL water provided, and potassium is given at 2 mmol per 100 mL water provided, with each provided as the chloride salt. Once the amount is calculated, the hourly rate can be determined by dividing the final calculation by 24.

Another approach for calculating the water with the appropriate electrolytes to be provided is 1500 mL/m2/24 hours. This approach requires measuring the child’s height and weight to determine square meters and is less convenient. The volume provided by the approach in Table 1 and the 1500 mL/m² calculation are equivalent.

Another approach is to determine the hourly need of water bearing the electrolytes to be provided, the same as Holliday and Segar. The hourly approach to determining volume is shown in Table 2. Using this approach, maintenance fluid therapy for a 15-kg child would be infused at a rate of 50 mL/hour:

\[
(4 \text{ mL/kg/h} \times 10 \text{ kg}) + (2 \text{ mL/kg/h} \times 5 \text{ kg})
\]

Maintenance fluid therapy was designed to provide water and electrolytes to cover future (anticipated) loss, particularly from urine, expired air, and sweat. Unfortunately, since the publication of maintenance fluid therapy guidelines by Holliday and Segar, the formulation has often been misused. Maintenance fluid therapy should not be used as a fluid prescription for restoring extracellular fluid volume previously lost, for example, as a result of vomiting, diarrhea, or burns. It is almost always not an appropriate solution for replacing abnormal losses from the gastrointestinal tract, urinary tract, and so on. The volume calculation and the electrolyte concentrations are not appropriate to calculate a restoration solution or replacement solution.

The primary reason that a hypotonic solution such as maintenance fluids, as described by Holliday and Segar, is problematic for use as a restoration solution is the nonosmotic release of anti-diuretic hormone (ADH, also called AVP [arginine vasopressin]). Since the mid 1950s it has been known that ADH is released from the hypothalamus under two different physiologic stimuli. One is an increase in serum and extracellular osmolality, usually greater than 290 mOsm/kg H2O, termed osmotic stimulus. The other is a nonosmotic stimulus, usually the result of a fall in extracellular fluid volume or the perception of such a fall by volume receptors mainly in the thorax.

Since the 1950s we have come to learn that a large number of other stimuli can act as a nonosmotic stimulus to ADH release. These include, but are not limited to, a wide range of medications (antihypertensives, some antineoplastics, barbiturates), stress, central nervous system (CNS) injury or surgery, positive pressure ventilation, malignancy, and intrathoracic infection or malignancy. Under these conditions, ADH levels will be high and the administration of a hypotonic solution even at calculated maintenance doses could result in a fall in serum sodium and serum osmolality, on occasion to levels that might cause serious CNS injury, seizures, and even CNS herniation and death. Even in the early 1960s, when the precise reasons for the nonosmotic release of ADH were not well known, the risk of developing hyponatremia when providing the full volume prescribed in maintenance fluid therapy in the face of a concentrated urine and low urine volumes (signaling ADH release) was well known. The recommendation was to reduce the volume of fluid provided to approximately 50% of the standard calculated amount.

More recently, some have recommended, to prevent the development of hyponatremia, that all maintenance fluid therapy should be delivered as isotonic (normal) saline. The volume portion of the Holliday–Segar formulation is not altered, but the solution recommended in this approach is isotonic saline. The full impact of this approach on all types of hospitalized children is still unknown. It seems clear that patients in the perioperative period should receive normal saline in anticipation of the potential need for extracellular volume restoration. This approach does not guarantee that hyponatremia or hypernatremia will be totally prevented.

**Restoration Fluid Therapy**

Many children require parenteral fluids because of an inability to take fluids by mouth or due to abnormal fluid losses, such as from vomiting and diarrhea, excessive urinary losses, burns (excessive fluid losses from skin), or third spacing (the extravasation of fluid from the extracellular spaces such as the abdominal or thoracic cavity). In these situations, patients are at risk for serious

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Approach to Determine Parenteral Fluids and Electrolytes for a 24-Hour Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>WEIGHT (kg)</td>
<td>WATER (ml)</td>
</tr>
<tr>
<td>0–10</td>
<td>100/kg</td>
</tr>
<tr>
<td>11–20</td>
<td>1000 + 50/kg 11–20 kg</td>
</tr>
<tr>
<td>&gt;20</td>
<td>1500 + 20/kg &gt;20 kg</td>
</tr>
<tr>
<td><strong>Examples</strong></td>
<td></td>
</tr>
<tr>
<td>15-kg child</td>
<td>1250</td>
</tr>
<tr>
<td>30-kg child</td>
<td>1700</td>
</tr>
</tbody>
</table>

*Note: For sodium, potassium, and chloride, milliequivalents (mEq) and milliosmoles (mOsm) are the same.*

<table>
<thead>
<tr>
<th>TABLE 2</th>
<th>Hourly Administration of Fluids</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHILD’S WEIGHT (kg)</td>
<td>VOLUME OF WATER PER HOUR</td>
</tr>
<tr>
<td>≤10</td>
<td>4 mL/kg</td>
</tr>
<tr>
<td>11–20</td>
<td>40 mL + 2 mL/kg for every kilogram 11–20</td>
</tr>
<tr>
<td>&gt;20</td>
<td>60 mL + 1 mL/kg for every kilogram &gt;20</td>
</tr>
</tbody>
</table>

20) Children’s Health
extracellular volume depletion and even plasma volume depletion, which, left untreated, can result in hypotension or shock.

The parenteral fluid therapy for volume depletion should aim to first replace extracellular volume depletion. How much fluid to provide can be estimated by a long-standing approach using clinical signs to estimate the percentage of reduction in body weight associated with fluid losses (Table 3). In general, these losses can be replaced with a solution that restores extracellular fluid (isotonic saline or lactated Ringer’s solution). In situations of prolonged fluid losses (more than 7 days), partial replacement with isotonic saline followed by a slower replacement with a more hypertonic solution with added potassium may be warranted. Table 3 outlines the clinical approach to assessing a patient’s degree of volume depletion as a percentage of body weight.

Once the percentage of volume depletion is determined and the decision is made to use parenteral fluids based on moderate to severe volume depletion and ongoing vomiting, thus decreasing the effectiveness of oral rehydration, then rapid parenteral volume repletion is usually safe and effective. Replacing 50% of the determined volume depletion in 1 to 4 hours is appropriate, with the remaining replacement in the subsequent 4 to 16 hours. This should result in restored volume and improvement in the signs and symptoms demonstrated or reported by the patient. Often, partial restoration of extracellular volume depletion improves gastrointestinal symptoms and allows a switch to the oral route for completing volume restoration.

Example: A 15-kg patient presents with a 3-day history of vomiting and diarrhea. Physical examination suggests 5% volume depletion. The patient has ongoing vomiting, and parenteral fluids will be started. Volume depletion of 5% is 750 mL of fluid:

\[
0.5 \times 15 \text{ kg (body weight)}
\]

A commonly used volume expansion technique is to provide isotonic saline, 20 mL/kg, in a bolus (over 30 minutes to 1 hour). This amount of 300 mL (15 kg \times 20 mL/kg) is approximately 2% of body weight and in this example is less than 50% of the determined volume depletion. The plan, therefore, is 375 mL (50%) over 1 to 2 hours of isotonic saline (or lactated Ringer’s solution) parenterally, then 375 mL of the same solution over the next 4 to 6 hours.

**Replacement Fluids**

As a general rule of thumb, unusual losses—gastrointestinal or renal, for example—should be replaced with a solution of comparable electrolyte concentration and of comparable volume. The most precise way to determine the needed solution is to measure the concentration of solutes such as sodium, potassium, chloride, or bicarbonate lost in emesis, diarrhea, or urine. Emesis contains sodium at 10 to 40 mmol/L and even less potassium (<20 mmol/L) but large amounts of chloride (90–130 mmol/L). Diarrheal fluid typically contains sodium at 40 to 90 mmol/L, potassium at 10 to 50 mmol/L, and up to 40 or 50 mmol/L of bicarbonate. Cholera patients can excrete sodium up to 140 mmol/L. When possible, the volume of loss should be measured so a replacement fluid solution volume can be planned.

The safe approach to the patient with ongoing losses is first to restore extracellular volume to normal using normal saline or lactated Ringer’s solution as noted earlier. During extracellular volume restoration, measure the output and electrolyte concentration of abnormal losses, preferably over a 12- to 24-hour period. Once this is known, then replacement of ongoing losses should be provided as a separate solution, the volume and electrolyte concentration determined by the measurements of each. Provide the replacement solution over the next 12 to 24 hours. For example, a patient with diarrhea is found to be producing 300 mL of diarrheal fluid over 12 hours. The measured sodium concentration is 80 mmol/L, potassium is 20 mmol/L, and bicarbonate is 40 mmol/L. The solution that will nearly approximate the losses is 0.2 NS (34 mmol/L of sodium and of chloride) with 20 mmol/L of potassium and 40 mmol/L of sodium bicarbonate. The solution will contain 74 mmol/L of Na, 20 mmol/L of K and 40 mmol/L of bicarbonate. The solution would be infused at a rate of 25 mL/hour. The advantage of providing this separately from maintenance or restoration fluids is that the rate of infusion or even the electrolyte content can be changed to address just the replacement needs without having to change all the intravenous solutions.

**Hyponatremia and Hypernatremia**

Hyponatremia (serum sodium <135 mmol/L) and hypernatremia (serum sodium >145 mmol/L) are often associated with volume depletion. Hypernatremia is nearly exclusively associated with volume depletion, and hyponatremia can be seen in situations of volume expansion such as vasopressin excess (syndrome of inappropriate antidiuretic hormone [SIADH]) or congestive heart failure, kidney failure, or liver failure. At times, the need to normalize the serum sodium concentration requires parenteral intervention.

**Approach to Hyponatremia**

Symptomatic hyponatremia can occur if the serum sodium falls rapidly, but usually not until the serum sodium falls below 125 mmol/L. The symptoms associated with hyponatremia include anorexia, anxiety, agitation, ataxia, weakness, lethargy, disorientation, depressed deep tendon reflexes, seizures, coma, and death (usually the result of CNS herniation).

In situations where hyponatremia is associated with volume depletion, restoration of volume with isotonic saline often raises the serum sodium. When extracellular fluid volume is normal or expanded (such as situations when SIADH is at play), a four-fold approach to hyponatremia should be considered:

1. Treat the underlying condition.
2. Reduce water intake. In particular, if parenteral fluids are being provided, reduce or eliminate the use of hypotonic fluids.
3. Increase water excretion. This is usually done with loop diuretics such as furosemide (Lasix 0.5–1 mg/kg IV) to achieve a more rapid response.
4. Hypertonic saline IV is a step reserved for symptomatic patients. The most readily available hypertonic saline solution is 3% normal saline (sodium concentration of 513 mmol/L or approximately 0.5 mmol/mL). The desired outcome is to raise the serum sodium sufficiently to improve symptoms, but never more than 10 mmol/L in a 24-hour period. There is no need to raise the serum sodium beyond the lower limit of normal or 135 mmol/L. The desired increase in the serum sodium concentration should not exceed a maximum of 10 mmol/L.
The addition of sodium into the extracellular space will result in a shift of water from the intracellular to the extracellular space. Thus, the entire water space will be affected. The following example demonstrates how to calculate the amount of hypertonic saline to infuse in the face of severe hyponatremia: A patient weighing 15 kg has a serum sodium of 125 mmol/L and experiences a seizure. The patient is felt to be euovolemic. Thus, hypertonic saline infusion is being considered. How should this be prescribed? Raise the serum sodium to 135 mmol/L from 125 mmol/L:

\[
\text{Change in serum sodium (mmol/L) \times \text{body weight (kg)}} \\
= 0.6(\text{total body water space}) \\
= 10 \times 15 \times 0.6 = 90 \text{ mmol}
\]

Because hypertonic saline is approximately 0.5 mmol/mL, if 90 mmol is the amount of sodium calculated to raise the serum sodium and osmolality, then 180 mL of 3% saline is needed. An alternative way to calculate the maximum 3% saline to use is: The maximum change in serum sodium is 10, the body weight is 15 kg, the water space is 1.2 (0.6 \times 2 = 1.2); i.e., 2 mL/mmol sodium in 3% saline, so:

\[
10 \times 15 \times 1.2 = 180 \text{ mL of 3% saline}
\]

Once the amount is calculated, the rate of administration should be no more than 2 to 4 mL/kg/hour, with measurements of the serum sodium at 2-hour intervals. Usually symptoms improve before there is a full 10-mmol rise in serum sodium. This rate should not result in a change of greater than 1 to 2 mmol/hour. If a change faster than this is seen, slow or stop the infusion immediately.

Approach to Hypernatremia

Hypernatremia (serum sodium >145 mmol/L) is seen with volume depletion. The extremely rare situation of pure salt overload is seen in babies receiving improperly mixed formula or intensive care patients receiving concentrated blood products and IV solutions. In these situations the patients do not show evidence of volume depletion, and urinary sodium excretion (and fractional excretion of sodium) is very high. In the overwhelming majority of patients who are volume depleted, hypernatremia signals volume losses of at least 10% of body weight. The classic teaching is that hypernatremic patients appear less-severely volume depleted than they actually are. This is attributed to the increased osmolality protecting the extracellular space at the cost of intracellular space. Intracellular volume contains two thirds of total body water, and the decreased volume in the intracellular space means nearly all cells in the body (importantly, including in the brain) are smaller than normal.

The approach to hypernatremia is first to restore volume using isotonic saline. Providing 40 to 50 mL/kg of isotonic saline over 4 hours will improve extracellular volume and is unlikely to markedly reduce the serum sodium. Restoring extracellular volume will improve organ perfusion, especially perfusion of the gut and the kidney. This will improve the likelihood of being able to use the gut for fluid replacement and improve glomerular filtration rate and overall kidney function so as to be able to restore volume and safely return serum sodium and osmolality to normal. The major consequence of a too-rapid fall in serum sodium or osmolality is cerebral edema, the result of smaller-than-normal cell volume too rapidly expanded by IV (especially hypotonic) fluids.

Following the first infusion, as noted earlier, consider providing 30 to 40 mL/kg of isotonic fluid over the next 20 hours (to complete a 24-hour treatment plan) to continue replenishing extracellular volume. Check the serum sodium and serum osmolality frequently, at 2- to 4-hour intervals in the first 24 to 48 hours if the serum sodium is greater than 155 mmol/L at presentation. As with hyponatremia, it is important not to change (in this case, drop) the serum sodium by more than 10 mmol/L in 24 hours or to change the serum osmolality by more than 20 mOsm/kg H₂O in 24 hours. To determine how much water is necessary to lower the serum sodium, the following formula is often used:

\[
\text{Actual serum sodium} - \text{desired serum sodium (not to exceed 10)} \times \text{body weight in kg} \times 4 \text{ mL}
\]

For a 15-kg child with a serum sodium of 155:

\[
10 \times 15 \times 4 = 600 \text{ mL of water}
\]

The safe approach to reducing the water deficit is to provide no more than half of the water deficit in the first 24 hours as a solution of 5% dextrose (D₅W) with potassium of 20 to 30 mmol/L. The intracellular fluid compartment is rich in potassium, and patients with hypernatremic dehydration have had considerable intracellular volume loss and have lost potassium, usually through urinary losses. The same approach may be considered in day 2 and following. Certain caveats are important here. First, as noted earlier, frequent measurements of serum sodium and serum osmolality are necessary to prevent too rapid a decline. Because the maintenance prescription is very hypotonic in the first 24 hours, at least, replacing volume loss should be the first priority. Once the patient approaches a normal volume status and serum sodium, providing maintenance may be appropriate. Patients with hypernatremic dehydration are very thirsty. Any fluid they consume by mouth must be measured and monitored lest their oral consumption along with parenteral fluids exceed the safe amount recommended.

**Intravenous Electrolyte Replacements**

At times, IV replacement of other electrolytes may be necessary. The IV replacement of potassium, in situations where the serum potassium concentration falls below 2.5 mmol/L or where oral replacement cannot be used, can be given as potassium chloride or potassium phosphate at a dose of no more than 0.5 mmol/kg/hour. The concentration of potassium in the solution infused should not exceed 40 mmol/L in a peripheral vein because potassium infusions are painful and sclerosing. Higher concentrations under the appropriate circumstances could be given through a central vein.

On occasion, IV administration of calcium or phosphate (or both) is clinically indicated. IV calcium is considered in patients with tetany, usually a serum calcium <6.5 mg/dL with a normal serum albumin. For IV calcium administration to correct symptomatic hypocalcemia, in older children the recommendation is 10 to 20 mL of a 10% calcium gluconate solution over 15 minutes to reduce or stop symptoms such as tetany or seizures. In neonates and young children, 10 to 20 mg/kg or 1 to 2 mL/kg of a 10% calcium gluconate solution administered at a rate of 1 mL/min with cardiac monitoring is recommended. For more chronic administration, 50 to 75 mg/kg/24 hours of calcium gluconate is recommended. Rapid calcium administration temporarily lowers the serum phosphate and can lead to arrhythmia, hence the cardiac monitoring.

**Hypophosphatemia** might require parenteral administration of phosphate. This approach is usually reserved for patients with a serum phosphate less than 1 mg/dL. The recommended dosage of elemental phosphorus is 2.5 to 5 mg/kg (0.08 to 0.16 mmol/kg) over 6 to 8 hours. This administration can lower serum calcium so frequent testing of both the serum phosphorus and calcium is appropriate.

Finally, bicarbonate may be given intravenously. Usually the IV solution of bicarbonate should not exceed a concentration of 45 mmol/L. For example, in certain clinical conditions alkalinization of the urine is desired to prevent crystal or stone formation. The usual prescription is 1 to 2 mmol/kg body weight in 24 hours. Higher infused concentrations of bicarbonate (seen in patients with proximal tubule disease or injury as noted with certain chemotherapeutic agents) should be given into a central vein under careful monitoring. Calcium and bicarbonate should not be given in the same solution.
RESUSCITATION OF THE NEWBORN

Method of
Stacey Hinderliter, MD, and David Gregory, MD

CURRENT DIAGNOSIS

- The transition from intrauterine to extraterine life at birth requires effective breathing by the infant to expand the lungs and oxygenate the blood. All newborn infants are at risk for delays in this process, prompting a need for resuscitation.
- The fetal and newborn response to hypoxia is to develop apnea. If primary apnea is diagnosed, it can be corrected by gentle stimulation and oxygen delivery. If hypoxia persists, secondary apnea will occur. It is not readily apparent whether a newborn has primary or secondary apnea, and the approach to resuscitation therefore requires that any apneic event be treated using the same sequence of interventions.
- The initial steps of newborn resuscitation include drying the infant, providing warmth, suctioning the airway, and providing gentle stimulation. Infants who do not respond to these interventions need more assistance. Establishment of effective ventilation spontaneously by the newborn or with assistance by positive-pressure ventilation is the most important step in newborn resuscitation.
- Reassessment of the infant's heart rate, respiratory effort, color, and tone every 30 seconds during resuscitation is crucial to determine the next appropriate intervention. Apgar scoring should not be used to guide newborn resuscitation. Pulse oximetry in the delivery room may be used to guide oxygen therapy.
- If application of positive-pressure ventilation does not improve the infant's heart rate, chest compressions or drug therapy, or both, may be required. A team approach is needed to coordinate these interventions, and ongoing reassessment is necessary to determine cardiorespiratory and hemodynamic status. Subsequent assessment and treatment should be performed in an intensive care setting.

CURRENT THERAPY

- Term gestation infants who are breathing and crying with good muscle tone do not need newborn resuscitation.
- Initial resuscitation includes drying the infant, providing warmth, suctioning the nose and mouth, and giving gentle stimulation.
- If the infant is breathing vigorously but has central cyanosis, oxygen should be administered. Pulse oximetry can be used to guide oxygen therapy.
- If the infant is apneic, breathing slowly, or gasping, positive-pressure ventilation (PPV) with a mask and bag should be administered. Infants with meconium-stained amniotic fluid who are apneic should receive suctioning of the trachea by endotracheal intubation before PPV.
- If the infant's heart rate drops below 60 beats/min, chest compressions should be initiated using the thumb or two-finger technique.
- If the heart rate remains less than 60 beats/min despite PPV and chest compressions, IV epinephrine (Adrenalin) should be given using an umbilical venous catheter.
- Reassessment of the newborn every 30 seconds during resuscitation is required to adjust therapy as indicated.

The changes that occur in the transition from fetus to newborn are unmatched in any other time of life. Most newborns manage to make this transition on their own, but about 10% require some assistance. Approximately 1% of newborns require extensive resuscitative measures to survive. The approach to resuscitation in infants is similar to that in adults, consisting of evaluation and intervention when needed for the infant's airway, breathing, and circulation. Every birth should be attended by personnel trained in neonatal resuscitation. Specific training and certification are offered by the American Heart Association's Neonatal Resuscitation Provider (NRP) course.

Transition from Fetal to Extraterine Life

The environment of the fetus differs greatly from that of the infant after birth. The fetus depends on receiving oxygen and nutrients from the mother through the placental circulation. The fetus experiences relative hypoxia and almost constant body temperature in the amniotic fluid. The fetal lungs are filled with fluid and do not participate in the exchange of oxygen and carbon dioxide. Several adaptations in the fetus permit survival in this environment.

Oxygenated blood from the mother enters the fetus by means of the placenta through the umbilical vein. Most of this oxygenated blood bypasses the liver through the ductus venous and enters the inferior vena cava. On entering the right atrium, this oxygenated blood is directed toward the patent foramen ovale into the left atrium, bypassing the fetal lungs. Fetal blood also passes through the right atrium into the right ventricle and then into the pulmonary artery. The vascular resistance and blood pressure of the pulmonary vessels in the fetal lung are higher than in the aorta and systemic circulation; most of the blood is therefore shunted away from the lungs through the ductus arteriosus into the ascending aorta. Only a small amount of fetal blood passes through the lungs to the left atrium and then to the left ventricle. The umbilical arteries branch off from the internal iliac arteries and return fetal blood to the placenta. The functional organ for gas exchange of oxygen and carbon dioxide in the fetus is the placenta.

At birth, the newborn is no longer connected to the placenta, and the lungs become the only source of oxygen. The first breaths of the infant cause the fluid in the lung alveoli to be replaced with air. The umbilical arteries and veins constrict at birth and are eventually clamped. This increases the vascular resistance and blood pressure of the systemic circulation. As the oxygen level in the alveoli increases, the blood vessels in the lung start to relax, decreasing pulmonary vascular resistance. Blood in the pulmonary artery travels toward the lung and away from the ductus arteriosus because the blood pressure in the systemic circulation is higher than that in the pulmonary circulation. Increased blood flow to the lungs allows the oxygen from the alveoli to enter the infant's blood, increasing the $PO_2$. Oxygenated blood enters the left heart through the pulmonary vein and is delivered to the rest of the infant's tissues through the aorta.

Although the initial steps in this transition occur within a few minutes of birth, the entire process may not be completed for several hours to days. The ductus venosus, foramen ovale, and ductus arteriosus remain potentially patent and do not completely

References


Press; 2010. p. 3–47.


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involve for days or weeks. Changes in the infant’s systemic and pulmonary pressures can result in blood flow through these channels in the infant.

Transition can be prevented or delayed in several circumstances. The infant may not breathe adequately, in which case the lung fluid is not forced out of the alveoli. Material such as meconium may block air from entering the alveoli. If the lungs do not fill with air, hypoxia will quickly develop. Systemic hypotension due to excessive blood loss, poor cardiac function, or bradycardia prevents the change in the direction of blood flow that is necessary to promote blood flow into the lungs. Failure of the lungs to expand or hypoxia can prevent relaxation of the pulmonary blood vessels, resulting in a high pulmonary vascular resistance. This leads to decreased blood flow to the lungs and worsening of hypoxia.

**Risk Factors for Newborn Resuscitation**

A number of prenatal and intrapartum factors are associated with a higher chance that the infant will have a delay in transition and require resuscitation (Table 1). However, some infants with no risk factors need resuscitation; therefore, preparations for neonatal resuscitation should be made during all deliveries.

**Reaction to Hypoxia and Asphyxia**

Normally at birth, the newborn makes vigorous efforts to breathe. The process of leaving the warm, dark, and liquid environment in utero is replaced by cold air, dryness, and bright lights. Drying the infant with towels and wiping the mouth and nose are all the assistance that most newborns require. The end result of any mechanism that delays transition is a period of hypoxia for the fetus or newborn infant. Laboratory studies have shown that the first sign of oxygen deprivation in the newborn is a change in the breathing pattern. After an initial period of rapid breathing attempts, cessation of breathing occurs. This is called primary apnea. Stimulation by drying the infant or slapping the feet can cause breathing to resume. If hypoxia continues after primary apnea has occurred, the infant will make attempts at gasping and then stop breathing. This is called secondary apnea. Stimulation does not affect secondary apnea. Assisted ventilation is necessary to provide breaths to the newborn to reverse the hypoxia. The infant’s heart rate starts to decrease when primary apnea occurs. The heart rate increases with stimulation if the infant has primary apnea, and blood pressure is maintained. With continued hypoxia, the heart rate continues to drop, and hypotension develops. If assisted ventilation is not adequate to increase the infant’s heart rate, chest compressions will be required.

When a newborn becomes apneic, it is not readily apparent whether the infant has primary or secondary apnea. The approach to resuscitation therefore requires that any apneic event in a newborn be treated using the same sequence of interventions. If the apneic infant responds to simple stimulation, the diagnosis is primary apnea, and no further intervention is required. If the infant does not improve with stimulation, secondary apnea has occurred, and more intensive intervention is needed.

**Sequence of Newborn Resuscitation**

**Initial Steps and Basic Resuscitation**

Resuscitation of the newborn starts the rapid assessment of three characteristics: Is the infant at term gestation, is the infant crying and breathing, and does the infant have good muscle tone? The answers to these questions will affect the approach to care. Resuscitation when fluid is meconium stained is discussed later in this chapter. The information presented here refers to term infants with clear amniotic fluid. More information regarding the care of premature infants is discussed in a later section.

The infant at term who is crying and breathing with good muscle tone does not need resuscitation and should not be separated from the mother. The baby should be dried, placed skin-to-skin with the mother, and covered with dry linen to maintain temperature. Ongoing observation for breathing, activity, and color should continue while the infant is with the mother. If the infant is not term, is not crying and breathing, or does not have good muscle tone, newborn resuscitation should begin with the initial seeps: providing warmth, positioning and clearing (if needed) the airway, drying and stimulating the infant.

The newborn should be placed under a radiant warmer to prevent heat loss and to allow easy observation. Although warm blankets or towels can be used to dry the infant, they should not be left in place to cover the infant. The newborn should be placed on the back with the neck slightly extended in the “sniffing” position (Figure 1). This facilitates air entry into the lungs by lining up the posterior pharynx, larynx, and trachea. Hyperextension or hyperflexion of the neck can obstruct air entry into the lungs.

If the newborn is crying vigorously, secretions can be removed by wiping the nose and the mouth with a towel. Gentle suctioning of the mouth and nose with a bulb syringe or suction catheter is only indicated when there is obvious obstruction to spontaneous breathing.

**Table 1. Risk Factors for Newborn Resuscitation**

<table>
<thead>
<tr>
<th>PRENATAL FACTORS</th>
<th>INTRAPARTUM FACTORS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal</td>
<td>Placental</td>
</tr>
<tr>
<td>Diabetes, preexisting</td>
<td>Placenta previa</td>
</tr>
<tr>
<td>Chronic hypertension</td>
<td>Abruption of the placenta</td>
</tr>
<tr>
<td>Infected</td>
<td>Premature or prolonged rupture of membranes</td>
</tr>
<tr>
<td>Cardiac, renal, pulmonary, thyroid, or neurologic disease</td>
<td>Chorioamnionitis</td>
</tr>
<tr>
<td>Drug therapy</td>
<td>Fetal</td>
</tr>
<tr>
<td>Substance use</td>
<td>Macrosomia</td>
</tr>
<tr>
<td>Lack of prenatal care</td>
<td>Low birth weight</td>
</tr>
<tr>
<td>Age &lt;16 or &gt;35 years</td>
<td>Breech or other abnormal presentation</td>
</tr>
<tr>
<td>Previous fetal or neonatal death</td>
<td>Persistent fetal bradycardia</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Non-reassuring fetal heart rate patterns</td>
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<tr>
<td>Bleeding in second or third trimester</td>
<td>Labor</td>
</tr>
<tr>
<td>Pregnancy-induced hypertension</td>
<td>Premature labor</td>
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<tr>
<td>Toxemia</td>
<td>Precipitous labor</td>
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<td>Gestational diabetes</td>
<td>Prolonged labor (&gt;24 h)</td>
</tr>
<tr>
<td>Fetal anemia or isoimmunization</td>
<td>Prolonged second stage of labor (&gt;2 h)</td>
</tr>
<tr>
<td>Polyhydramnios</td>
<td>Lapsed cord</td>
</tr>
<tr>
<td>Oligohydramnios</td>
<td>Emergency cesarean section</td>
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<tr>
<td>Fetal hydrops</td>
<td>Forceps or vacuum-assisted delivery of membranes</td>
</tr>
<tr>
<td>Postterm gestation</td>
<td>Other</td>
</tr>
<tr>
<td>Multiple gestation</td>
<td>Mecconium-stained amniotic fluid</td>
</tr>
<tr>
<td>Size-date discrepancy</td>
<td>General anesthesis</td>
</tr>
<tr>
<td>Diminished fetal activity</td>
<td>Narcotics given within 4 h of delivery</td>
</tr>
<tr>
<td>Fetal malformation or abnormality</td>
<td>Uterine hyperstimulation</td>
</tr>
<tr>
<td></td>
<td>Severe intrapartum bleeding</td>
</tr>
</tbody>
</table>

**Figure 1.** The sniffing position. Positioning the infant on the back with the neck slightly extended brings the posterior pharynx, larynx, and trachea in line (white line) to facilitate air entry into the lungs.
Respiratory Support and Positive-Pressure Ventilation

If the infant is breathing with a heart rate higher than 100 beats/min but has central cyanosis, free-flowing oxygen delivery is indicated. This can be administered with a facemask or by holding oxygen tubing or a flow-inflating bag and mask close to the infant’s face. A **self-inflating bag and mask cannot be used to give free-flowing oxygen**. If the newborn is apneic, not breathing effectively, or has a heart rate less than 100 beats/min, PPV using a self-inflating bag, flow-inflating (or anesthesia) bag, or a T-piece resuscitator is required. Use of a flow-inflating bag requires a compressed gas source and considerable practice to be used effectively. A T-piece resuscitator needs special equipment and a compressed gas source. Most delivery rooms are equipped with self-inflating bags (Figure 2) because they are easy to use and can be fitted with a pressure-release valve to decrease overinflation. A reservoir must be used with a self-inflating bag to provide 100% oxygen.

**Figure 2.** Self-inflating bag with infant mask and reservoir. This type of device is available in most delivery rooms.

Deep or vigorous suctioning can be detrimental to the infant because of stimulation of the vagus nerve, causing bradycardia or apnea.

Drying the infant, slapping the feet, and rubbing the back are appropriate forms of stimulation. More forceful methods of stimulation can harm the infant. Primary apnea, if present, will respond to stimulation in less than 30 seconds. Prolonged apnea will require positive-pressure ventilation (PPV).

Evaluating the infant’s response to resuscitation is essential. The Apgar score is a traditional method for evaluating newborn status at 1 and 5 minutes after delivery. However, effective resuscitation demands that evaluation of the newborn’s status not be delayed until 1 minute of age, and Apgar scores therefore should not be used to guide resuscitative efforts. Within 30 seconds of delivery, the infant’s need for PPV must be assessed. Establishment of effective ventilation spontaneously by the newborn or with assistance by PPV is the most important step in newborn resuscitation. The respiratory status, heart rate, and color should be determined. The chest wall should move with each breath, and the newborn should be breathing spontaneously. Heart rate can be assessed by feeling for a pulse at the base of the umbilical cord. If this pulse cannot be felt, a stethoscope can be used to listen for the heartbeat. The heart rate should be greater than 100 beats/min. Peripheral cyanosis (i.e., blueness of the hands and feet) is acceptable in the initial period after delivery. Central cyanosis in which the lips and trunk are blue indicates hypoxemia and the need for more resuscitation efforts. A pulse oximeter can provide continuous assessment of the pulse and oxygen saturation and is the optimal method for monitoring the infant’s state of oxygenation. The initial steps of stabilization, reassessment, and establishing ventilation should be completed within the first minute of life (the “Golden Minute”).

**Figure 3.** Facemask. Choose a size that covers the infant’s mouth and nose.

The facemask should cover the infant’s nose, mouth, and tip of chin, but not the eyes (Figure 3). Multiple sizes should be available. A tight seal between the infant’s skin and the facemask is needed, but excessive pressure can bruise the face. The mask can be held in place using the thumb and index finger in a C-shaped position on top of the mask, with the remaining fingers in an E-shaped position below the infant’s chin (Figure 4). Inspiratory pressures of 20 to 30 cm H2O are usually needed when squeezing the bag to make the infant’s chest rise. A pressure gauge can be connected to the self-inflating bag for monitoring inspiratory pressure. The heart rate and color of the infant should rapidly improve if enough pressure is being given. An assistant can also use a stethoscope to listen to breath sounds for air movement. Breaths should be given at a rate of 40 to 60 breaths/min.

Traditionally, 100% oxygen has been used in newborn resuscitation. However, several randomized, controlled studies enrolling term and near-term infants have shown that room air can be used initially with oxygen as a backup if room air fails. A meta-analysis of these trials showed a benefit for the use of room air. Providing oxygen at concentrations between room air and 100% requires the use of compressed air, oxygen, and blenders by experienced personnel. A pulse oximeter with a probe designed for use in newborns can be used to guide oxygen administration during newborn resuscitation. It will take 1 to 2 minutes to apply the pulse oximeter probe to the infant’s right palm or wrist (preductal site) and get a consistent reading. The pulse oximeter may not function during states of very poor cardiac output or perfusion. In these situations, observation for central cyanosis will be necessary. The infant’s oxygen saturation may remain in the 70% to
Children's Health

in and out of the heart and to the body. The direction of the
sternum is depressed to a depth of one third of the infant's antero-

and 30 breaths/min. The thumb or fingers are placed on the lower

this sequence is repeated to give the infant 90 compressions
required. Two people are required to give PPV and chest compres-

ventilation.

air introduced into the infant's stomach during bag and mask

ventilation, it can be continued for longer periods; how-

ly mastered and maintained. If an infant is responding well to bag

tube can be placed in the stomach and left open to air to vent any

respiration. If these steps do not improve the infant's heart rate and
color, endotracheal (ET) intubation may be required.

ET intubation is a technical skill that must be learned and prac-
ticed to maintain competency. Effective ventilation can be given
with a bag and mask approach to most newborns. This skill is eas-
ily mastered and maintained. If an infant is responding well to bag
and mask ventilation, it can be continued for longer periods; how-
ever, some air may escape into the esophagus and into the stomach.
This may cause gastric distention, which can prevent full expa-
sion of the lungs and cause vomiting and aspiration. An orogastric
tube can be placed in the stomach and left open to air to vent any
air introduced into the infant's stomach during bag and mask
ventilation.

Chest Compressions

After 30 seconds of effective PPV, the heart rate should be assessed.
If the heart rate dips below 60 beats/min, chest compressions are
needed to support the circulation. The thumb technique (Figure 5)
is preferred, but the two-finger technique (Figure 6) can be used,
especially when placement of an umbilical venous catheter is
required. Two people are required to give PPV and chest compres-
sions effectively. To coordinate the breaths and chest compressions,
three compressions are given followed by one breath, and this
sequence is repeated to give the infant 90 compressions and 30 breaths/min. The thumb or fingers are placed on the lower
third of the infant's sternum but above the xiphoid process. The
sternum is depressed to a depth of one third of the infant's antero-
posterior chest diameter. The purpose of chest compressions is to
squeeze the heart between the sternum and the spine, forcing blood
in and out of the heart and to the body. The direction of the
compressions should be perpendicular to the chest surface, and
the fingers should not be lifted off of the chest after the correct
placement is obtained. Incorrect methods during chest compres-
sions can cause rib fracture and liver laceration.

After 30 seconds of chest compressions, the infant's heart rate,
color, breathing, and tone are reassessed. If the heart rate is higher
than 60 beats/min, chest compressions can be stopped, although
PPV may still be needed. If the heart rate is not improving, the fol-
lowing problems must considered: ventilation is not adequate,
100% oxygen concentration is not being given, or the compressions
may not be deep enough or well coordinated with the breaths. If the
arrest is suspected to be of primary cardiac etiology, a compression
ratio of 15 compressions to 2 breaths or 30 compressions to
2 breaths may be more effective.

Medications for Newborn Resuscitation

If the newborn heart rate remains below 60 beats/min despite PPV
and chest compressions, epinephrine (Adrenalin) can be used to
stimulate the newborn heart. Fewer than 2 of 1000 infants will re-
quire this step in resuscitation. IV administration of epinephrine is
preferred.

A catheter can be quickly inserted into the umbilical vein for in-
travenous access. A 3.5 or 5 F catheter prefilled with saline and
connected to a 3-way stopcock is inserted about 2 to 4 cm into the
umbilical vein using sterile technique. After blood is aspirated,
insertion of the catheter is stopped, and the epinephrine is given,
followed by a saline flush. The concentration of epinephrine used
in neonatal resuscitation is 1:10,000. The intravenous dose is 0.01
to 0.03 mg/kg (0.1 to 0.3 mL/kg) (Table 2). A dose of epinephrine
may be considered through the ET tube during the umbilical vein
catheterization. The ET dose of epinephrine is 0.03 to 0.1 mg/kg
(0.3 to 1 mL/kg). These higher doses are for ET use only. Because
lung absorption of epinephrine varies, the intravenous route using
the umbilical vein is preferred.

During umbilical vein cannulation, PPV and chest compressions
are continued. More personnel will be needed to place the catheter
and draw up the medications and saline flushes. After an intrave-
nous dose of epinephrine, the infant's heart rate, respirations,
color, and tone are reevaluated. The heart rate should increase
to more than 60 beats/min. If the heart rate does not respond,
the dose of epinephrine can be repeated every 3 to 5 minutes.
The effectiveness of ventilation and compressions should be reas-
sessed. If the infant appears pale, has delayed capillary refill, or de-
creased pulses, shock may be present. Infant blood loss might have
occurred during delivery from placental problems or other
sources. Administration of an isotonic crystalloid solution such as
normal saline or Ringer's lactate at 10 mL/kg over 5 to 10 mi-

Figure 5. Thumb technique. The hands encircle the torso, and the thumbs
are placed on top of the lower sternum above the xiphoid process and
below a line drawn between the nipples (white line).

Figure 6. Two-finger technique. The index and middle finger are used to
apply pressure on the lower third of the sternum above the xiphoid process
and below a line drawn between the nipples (white line).
Endotracheal Intubation
During neonatal resuscitation, endotracheal intubation may be indicated in the following circumstances: initial endotracheal suctioning of a nonvigorous meconium-stained infant, cases in which bag and mask ventilation is ineffective or prolonged, if chest compressions are performed, and in special situations such as congenital diaphragmatic hernia or extremely low birth weight infants. Intubation of the newborn requires preparation that can be performed while the infant is being ventilated by bag and mask. The ET tube should not be placed unless the glottis is visualized by direct laryngoscopy. To ensure that the tube is in the trachea, a carbon dioxide (CO2) detector should be used. Listening for equal breath sounds and looking for vapor condensation in the ET tube during exhalation can help, but an increase in the infant’s heart rate or a positive detection of CO2 is most reliable. It should be noted that poor or absent pulmonary blood flow may result in the absence of CO2 detection despite tube placement in the trachea.

Intubation should be performed as quickly as possible, with a goal of 20 seconds from insertion of the laryngoscope to the connection of the ET tube to the resuscitation bag. Complications of intubation include worsening of hypoxia and bradycardia, pneumothorax, contusions, perforation of the trachea or esophagus, and infection. After the infant has been intubated, deterioration in the infant’s status should prompt an organized sequence to assess the adequacy of ventilation using the mnemonic DOPE: Dislodged (D): Is the tube obstructed by secretions or blood? Obstructed (O): Is the tube obstructed by secretions or blood? Pneumothorax (P) and esophagus (E): Is the tube in the esophagus?

An alternative to intubation is placement of a laryngeal mask airway. This type of airway does not require laryngoscopy. A soft inflatable mask that is attached to a flexible airway tube is placed in the hypopharynx such that the air in the tube is directed into the larynx and away from the esophagus. However, this type of airway cannot be used to suction meconium from the trachea nor to give endotracheal drugs. Its use has not been evaluated during chest compressions.

Premature Infants
Infants born before 37 weeks’ gestation are at increased risk for complications and the need for resuscitation. Premature lungs may lack surfactant, making ventilation difficult. Very low birth weight (less than 1500 g) infants will need additional warming techniques such as prewarming the delivery room, covering the baby in plastic wrapping, and placing the baby under a radiant warmer and/or an exothermic mattress; however, iatrogenic hyperthermia should be avoided. Immature brain development may decrease the drive to breathe. Weak muscles make respiratory efforts less effective. Thin skin and decreased subcutaneous fat make temperature regulation a challenge. Premature infants often have infections such as pneumonia or sepsis. The blood vessels in their brains are fragile and can easily bleed during periods of blood pressure variation. The lower birth weights of premature newborns also require smaller sizes of equipment for resuscitation such as facemasks, suction catheters, endotracheal tubes, and umbilical catheters. Oxygen concentrations less than 100% are often used to protect the premature infant from oxygen toxicity. The use of continuous positive airway pressure (CPAP) in premature infants who are breathing spontaneously but with difficulty following birth may reduce the need for intubation, mechanical ventilation, and surfactant use. Many personnel trained in newborn resuscitation should be present at the delivery of a high-risk premature infant.

Meconium Staining of the Amniotic Fluid
Meconium is formed in the newborn gastrointestinal system during gestation. Intrauterine stress can cause release of meconium into the amniotic fluid. Aspiration of meconium-stained amniotic fluid into the lungs can result in severe pneumonia and lung injury. The approach to resuscitation for an infant with meconium-stained fluid depends on the condition of the infant immediately after birth. There is no evidence that the consistency of meconium-stained fluid (i.e., thick or thin) should change these approaches.

### TABLE 2
**Drugs for Newborn Resuscitation**

<table>
<thead>
<tr>
<th>DRUG</th>
<th>CONCENTRATION</th>
<th>DOSE</th>
<th>INDICATIONS</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epinephrine</td>
<td>1:10,000</td>
<td>0.01–0.03 mg/kg</td>
<td>Asystole Bradycardia that does not improve with PPV and chest compressions</td>
<td>May repeat every 3–5 min</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IV = 0.1–0.3 mL/kg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>IV route preferred 0.03–0.1 mg/kg ETT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Volume expanders</td>
<td>Normal saline</td>
<td>10 mL/kg IV</td>
<td>Hypovolemia</td>
<td>Crossmatch blood to mother if possible</td>
</tr>
<tr>
<td></td>
<td>Ringer’s lactate</td>
<td></td>
<td></td>
<td>Repeat if needed</td>
</tr>
<tr>
<td></td>
<td>O negative blood</td>
<td></td>
<td>Hypoglycemia</td>
<td>Monitor glucometer or venous glucose levels</td>
</tr>
<tr>
<td>Glucose</td>
<td>10% Dextrose</td>
<td>2–5 mL/kg IV</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** ETT = endotracheal tube; IV = intravenous.

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cautiously because there is evidence from animal studies for poorer outcomes when it is used in the absence of hypovolemia. Rapid infusion of large volumes has been associated with intraventricular hemorrhage in premature infants.

Newborns, especially premature infants, are at risk for hypoglycemia. Blood from the infant’s heel or the umbilical vein can be tested at the bedside and intravenous 10% dextrose (2 to 5 mL/kg) given for low blood glucose. No specific glucose level has been associated with a poorer outcome. There is no evidence that use of sodium bicarbonate benefits the neonate, and its use during resuscitation in the delivery room is not recommended.

After resuscitation, newborns should be monitored in an intensive care setting. These infants are at risk for several complications, such as infection, metabolic abnormalities, and seizures. Infants of 36 weeks’ gestation or older with moderate to severe hypoxic-ischemic encephalopathy may benefit from induced hypothermia.

### Special Considerations
Some newborns do not respond to resuscitation because of specific problems. Infants with upper airway obstruction from micrognathia can be helped by a nasopharyngeal airway and placement of the infant in the prone position. Choanal atresia can be treated by placing an oral airway. Absence of breath sounds on one side of the chest can indicate a pneumothorax, requiring needle aspiration of the chest. An infant with a scaphoid abdomen and decreased breath sounds may have a diaphragmatic hernia. These infants should be intubated, and PPV by mask and bag should not be used. If the mother has received narcotics shortly before the delivery, the narcotic may be the cause of respiratory depression in the infant. These infants need PPV and respiratory support. Naloxone is no longer recommended as part of initial resuscitative efforts in the delivery room. Heart rate and oxygenation should be supported by PPV.

Intubation include worsening of hypoxia and bradycardia, pneumothorax, contusions, perforation of the trachea or esophagus, and infection. After the infant has been intubated, deterioration in the infant’s status should prompt an organized sequence to assess the adequacy of ventilation using the mnemonic DOPE: Dislodged (D): Is the tube obstructed by secretions or blood? Obstructed (O): Is the tube obstructed by secretions or blood? Pneumothorax (P) and esophagus (E): Is the tube in the esophagus?

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Crying and Vigorous Infant
If the newborn with meconium-stained amniotic fluid has normal respiratory effort and muscle tone with a heart rate higher than 100 beats/min, gentle mouth and nose suctioning can be performed using a bulb syringe or suction catheter. Deep and prolonged suctioning should be avoided. ET intubation is not required for vigorous infants with meconium-stained amniotic fluid.

Nonvigorous Infant
Newborns who are gasping or apneic, have poor muscle tone, and have a heart rate less than 100 beats/min may benefit from direct suctioning of the trachea. A laryngoscope is inserted, and a 12- or 14-F catheter is used to suction the mouth and posterior pharynx. After visualizing the glottis, an ET tube is inserted and attached to a suction source. Suction is applied as the ET tube is withdrawn (Figure 7). This maneuver may be repeated until the suctioned fluid is clear unless the infant requires resuscitation (e.g., apneic, heart rate <100 beats/min, decreased muscle tone, cyanotic). After ET suctioning, a bag and mask can be used to provide PPV for the infant if needed. The usual sequence of newborn resuscitation is then followed. If attempted intubation is difficult and prolonged, bag and mask ventilation should be started without tracheal suctioning, especially if there is persistent bradycardia.

Newborn Resuscitation Outside of the Delivery Room
Resuscitation of infants born at home, in an emergency room, in an ambulance, or otherwise outside of a delivery room setting should proceed according to the same principles as in the delivery room. Providing warmth, wiping the airway, and providing stimulation are usually adequate measures. Establishing effective ventilation using a bag and mask is the most important step if the infant fails to breathe on its own. Emergency providers should be familiar with resuscitation of the newborn, and basic equipment (Table 3) should be available.

Withholding and Withdrawing Newborn Resuscitation
Newborns should be offered resuscitation at delivery except in extreme circumstances. Newborn resuscitation should not be used if the infant has a condition that is incompatible with survival, such as a confirmed gestational age of less than 23 completed weeks, birth weight less than 400 g, or congenital anomalies associated with certain death or extreme morbidity.

In most situations, initial resuscitation can provide time to observe the infant’s response to interventions and to discuss the infant’s condition with the parents. Techniques for obstetric dating of pregnancies are accurate only to ±1 to 2 weeks, and estimates of fetal weight are accurate only to ±100 to 200 g. Care must be taken before deciding to withhold resuscitation from a newborn. Ongoing conversation between parents and medical caregivers allows mutual decision making. Withdrawal of care is indicated if continued support is futile. After 10 minutes of asystole (heart rate of 0), newborns are very unlikely to survive.

References

Figure 7. The meconium aspirator is attached to a suction source and connected to the endotracheal (ET) tube inserted into the infant’s trachea. The thumb is used to occlude the suction-control port to apply suction to the ET tube while gradually withdrawing the ET tube from the trachea (arrow).
TRAUMATIC BRAIN INJURY IN CHILDREN

Method of
Stephen R. Deputy, MD

CURRENT DIAGNOSIS

- Children under the age of 2 years with traumatic brain injury (TBI) may require neuroimaging because clinical predictors of intracranial hemorrhage are less reliable in this age group.
- Children under the age of 1 year presenting with lethargy, irritability, apnea, or seizures should be evaluated with computed tomography (CT) imaging and a dilated funduscopic examination to rule out shaking-impact syndrome.

CURRENT THERAPY

- Children with mild TBI and a GCS score of 15 at presentation can usually be observed clinically without the need for neuroimaging.
- The goal of treatment for TBI is to minimize secondary brain injury.
- In the setting of raised ICP, it is important to maintain CPP above 50 to 70 mm Hg.
- Early post-traumatic seizures are relatively frequent in open head injury and in severe TBI. They should be empirically treated in any patient in whom raised ICP is a concern.
- Direct intracranial pressure monitoring should be considered in any TBI patient with a GCS score of 8 or less.

Abbreviations: CPP = cerebral perfusion pressure; ICP = intracranial pressure; GCS = Glasgow Coma Scale; TBI = traumatic brain injury.

Traumatic brain injury (TBI) is one of the leading causes of death and disability among children, adolescents, and young adults. An estimated 185 per 100,000 children (ages 0 to 14 years) and 350 per 100,000 adolescents (ages 15 to 19 years) are hospitalized each year for TBI. The etiology of TBI varies depending on the age of the patient, with younger children more likely to be injured from falls and pedestrian injuries, and adolescents more often injured in motor vehicle accidents and assaults. Inflicted TBI (shaking-impact syndrome of infancy) is the leading cause of injury-related deaths in children younger than 4 years of age and accounts for 80% of deaths from head trauma in children younger than 2 years of age.

Types and Severity of Head Injury

Closed head injury is the most common type of TBI seen in children. Forces from rapid deceleration are applied diffusely throughout the brain and consciousness is frequently impaired. Open head injuries, in which the dura is breached, are caused by focal penetrating forces, and the risk of post-traumatic epilepsy is relatively high.

Primary brain injury is caused by the mechanical forces of the trauma itself. Diffuse axonal injury is an example of primary brain injury. During rapid deceleration, angular forces applied to the head cause the brain to rotate about its center of gravity. Shifting regions of differing densities within the brain result in shearing forces between planes such as the gray-white junction, corpus callosum, and brainstem. The shearing of axons effectively serves to “disconnect” the cortex from the brainstem and consciousness becomes impaired. Translational (straight-line) forces applied to the head produce impact-loading contact phenomena, resulting in focal injuries to the scalp, skull, and brain, such as lacerations, skull fractures, cerebral contusions, and epidural hematomas. Subdural hematomas may occur because of tearing of fragile dural bridging veins during rapid decelerations.

Secondary brain injury follows and is the consequence of primary injury. Examples include hypoxic-ischemic injury (secondary to low cerebral perfusion pressure or anoxia), disrupted cerebral autoregulation, seizures or status epilepticus, diffuse cerebral edema, hydrocephalus, and raised intracranial pressure. The goal of treatment for TBI is to reduce or prevent secondary brain injury from occurring because the primary brain injury has already happened at the time of trauma and cannot be altered.

The severity of TBI can be broken down into mild, moderate, and severe. Mild TBI is defined as head trauma with an initial Glasgow Coma Scale (GCS) score of 13 to 15. Moderate TBI occurs with an initial GCS score of 9 to 12. Severe TBI occurs with an initial GCS score of 8 or less. The GCS is modified for use in infants under the age of 36 months (Table 1).

Special attention should be given to those infants with TBI who do not show evidence of external facial or head trauma and who may not be presented by their caregivers as having a history of head injury. The shaking-impact syndrome is usually found in infants younger than 3 years of age with a peak incidence in infants younger than 1 year of age. Presenting symptoms include irritability, lethargy, or coma, apnea or breathing irregularities, and seizures. Retinal hemorrhages may be found in from 65% to 95% of these patients and should be actively looked for with a dilated funduscopic examination in any case where head trauma is suspected. Computed tomography (CT) imaging most commonly shows evidence of acute or remote subdural hematomas with or without evidence of cerebral infarction. Workup should include a skeletal survey to look for evidence of skull, posterior rib, or long bone fractures of different healing stages. Infants may be more susceptible to shaking-impact syndrome given their relatively large head size compared to their underdeveloped neck musculature. Infants also have thinner skulls, and translational forces may cause more severe contusions. Relatively longer subdural veins that bridge the infant’s enlarged subarachnoid spaces

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Glasgow Coma Scale for Children</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SCORE</strong></td>
<td><strong>EYES OPEN</strong></td>
</tr>
<tr>
<td>6</td>
<td>—</td>
</tr>
<tr>
<td>5</td>
<td>—</td>
</tr>
<tr>
<td>4</td>
<td>Spontaneously</td>
</tr>
<tr>
<td>3</td>
<td>To verbal commands</td>
</tr>
<tr>
<td>2</td>
<td>To painful stimuli</td>
</tr>
<tr>
<td>1</td>
<td>None</td>
</tr>
</tbody>
</table>

"BEST VERBAL RESPONSE:" 
6. Follows命令
5. Oriented and converses
4. Confused
3. Inappropriate words
2. Nonspecific sounds
1. None

"BEST MOTOR RESPONSE (<36 mo):"
6. Normal spontaneous movements
5. Withdraws to touch
4. Withdraws to pain
3. Flexor posturing
2. Extensor posturing
1. No response
can be easily lacerated from angular forces, resulting in subdural hematomas.

**Management of Traumatic Brain Injury in Children**

**Mild Traumatic Brain Injury**

Mild TBI accounts for more than 90% of all pediatric admissions for TBI. Children in this category should have a GCS score of 15 upon arrival to the emergency room, no focal neurologic deficits, and no signs of increased intracranial pressure (ICP). These children may have had a brief loss of consciousness (less than 1 minute), amnesia for the event, an immediate impact seizure, vomiting, or lethargy (as long as the GCS score is 15 during the evaluation). Children without loss of consciousness or amnesia may be observed or sent home with competent caregivers without performing neuroimaging studies. Vigilance for any change in the child’s neurologic status should be maintained for up to 72 hours after the injury. If there has been a brief loss of consciousness or amnesia for the event, the risk of intracranial hemorrhage is still relatively low, and it is up to the discretion of the treating physician whether CT imaging is warranted.

Clinical predictors of intracranial hemorrhage are less reliable for children under the age of 2 years, and nonaccidental trauma also comes into consideration in this age group. Therefore, most children under the age of 2 years with TBI should undergo CT imaging followed by careful observation.

**Moderate Traumatic Brain Injury**

Patients who fall within the moderate category generally need more intensive monitoring and medical management to avoid secondary brain injuries. As with all critical illness, attention should first be paid to following the ABCs (airway, breathing, circulation).

**Airway**

Patients with a GCS score of 9 or greater usually do not require endotracheal intubation for airway protection, although they should be kept NPO (nothing by mouth) in case of clinical deterioration.

**Breathing**

Hypoxemia and hypoventilation may increase ICP, so supplemental oxygen by nasal cannula may be helpful.

**Circulation**

It is important to avoid hypotension to maintain adequate cerebral perfusion pressure (CPP). Isotonic intravenous fluids should be provided with care to avoid fluid overload, hypoglycemia, or hyperglycemia. Careful attention should be paid to fluid and sodium balance because these patients may be at risk for developing diabetes insipidus. Likewise, the head of the bed should be raised to 30 degrees and the patient’s head kept midline to optimize venous return from the cranium to the right side of the heart. Sedation with short-acting sedatives (propofol [Diprivan] or midazolam [Versed]) or opioids may be necessary to avoid agitation, which can also reduce venous return to the heart.

Early post-traumatic seizures are fairly rare in children with moderate TBI. The need for empirical anticonvulsant therapy in this group remains controversial and should be reserved for those patients in whom raised intracranial pressure is of concern. Likewise, empirical use of mannitol has little clinical support for this group.

**Severe Traumatic Brain Injury**

Patients in the severe group are at the highest risk for secondary brain injuries. The following additional interventions are recommended.

**Airway**

By definition, these patients have a GCS score of 8 or lower and require endotracheal intubation for airway protection.

**Breathing**

Hyperventilation with a goal P\(\text{CO}_2\) of 26 to 30 mm Hg should be performed only if there is impending brainstem herniation or to bridge the gap until more definitive neurosurgical intervention can be performed to lower intracranial pressure. The benefit of hyperventilation is generally short lived (1 to 24 hours) and may worsen local ischemia following trauma or acute stroke.

**Circulation**

In the setting of suspected raised intracranial pressure, the goal of fluid and blood pressure management should be to maintain the cerebral perfusion pressure greater than 50 to 70 mm Hg. Recall that CPP equals MAP (mean arterial blood pressure) minus ICP. Because children generally have a lower MAP than adults, it is not always necessary to provide vasopressor therapy to keep the CPP above 70 mm Hg unless there is evidence of raised ICP. Invasive intracranial pressure monitoring should be considered if the GCS score is lower than 8 or in the setting of elevated ICP to optimize CPP.

**Other Techniques to Lower Intracranial Pressure**

**Neurosurgical**

Obvious mass lesions, such as hydrocephalus, subdural and epidural hematomas, and contused cortical tissue should be surgically evacuated whenever feasible. CT scanning is able to identify most of these surgical lesions. Decompressive craniectomy is now used more frequently to relieve pressure when multifocal contusions or diffuse cerebral edema is present. As mentioned earlier, ICP monitoring is usually warranted for all severe TBI patients.

**Osmotherapy**

Mannitol (20% solution) may be given as an initial bolus of 0.5 to 1 g/kg. Repeat doses of 0.25 to 0.5 g/kg are given every 6 to 8 hours as needed to maintain the serum osmolality and sodium levels to less than or equal to 320 mOsm/L and 150 mEq, respectively. Osmotic diuretics should be used with caution in patients with renal insufficiency. The beneficial effects occur within minutes, peak at 1 hour, and last 4 to 24 hours. Potential disadvantages include worsening of focal cerebral edema in areas where the blood-brain barrier is disrupted.

**Barbiturates**

Sedating agents may lower ICP by reducing pain as well as by making the brain metabolically less active. Pentobarbital is given as a loading dose of 5 to 20 mg/kg, followed by a continuous infusion of 1 to 4 mg/kg per hour. Continuous EEG monitoring to maintain a burst suppression pattern is warranted with this therapy. Potential disadvantages include systemic hypotension and a long half-life that may interfere with the declaration of brain death.

**Anticonvulsant Therapy**

Children with severe TBI are at a high risk for early post-traumatic seizures, which can further elevate the ICP. It is generally recommended empirically to load these children with 20 mg/kg of intravenous phenytoin (Cerebyx). Maintenance therapy can be achieved with 5 mg/kg per day divided every 8 hours with target blood levels of 10 to 20 mg/dL.

**Hypothermia**

More centers are including hypothermia as an option for patients with elevated ICP not responsive to medical or surgical management. The best method of cooling (i.e., whole body versus head only) and the optimal core temperature are not established for children.

Of note, apart from neurosurgical interventions, none of the techniques just described are shown definitively to reduce morbidity or mortality in children with severe TBI.
URINARY TRACT INFECTIONS IN INFANTS AND CHILDREN

Method of
Ellen R. Wald, MD

The urinary tract is the most common site for serious bacterial infection in infants and young children. Urinary tract infections (UTIs) are more common than bacterial pneumonia, and bacteremia.

Infection of the urinary tract may involve only the bladder, or only the kidney, or both. In general, infections of the bladder (cystitis), while causing substantial morbidity, are not regarded as serious bacterial infections. In contrast, infections that involve the kidney (pyelonephritis) can cause acute morbidity and lead to scarring with the consequences of hypertension, preeclampsia, and chronic renal disease.

Diagnosis

The diagnosis of UTI may be suggested by certain signs and symptoms, but culture of the urine is the gold standard. Because culture results are not available for at least 24 hours, there has been considerable interest in evaluating tests that may predict the results of urine culture, so that appropriate therapy can be initiated at the first encounter with the symptomatic patient. The tests that have received the most attention are urine microscopy for white cells and bacteria and biochemical analysis of leukocyte esterase and nitrite.

Several studies have concluded that both the presence of any bacteria on Gram staining of an uncentrifuged urine sample and dipstick analysis for leukocyte esterase and nitrite perform similarly in children from birth through 12 years of age and are helpful in identifying individuals with UTI. Other recent studies done involving young infants (<2 months of age) and older infants (<12 months and 1–24 months) concluded that a hemocytometer white blood cell count of 10 or more cells per microliter provides the most valuable cutoff point for identifying infants for whom urine culture is warranted.

The definition of a positive urine culture depends on the method used to collect the specimen. This variable definition reflects the fact that urine which has passed through the urethra may be contaminated by bacteria present in the distal urethra. If the urine is obtained by the clean-catch method, a positive culture is defined as equal to or greater than 10^5 colony-forming units (CFU)/mL. If the specimen is obtained by catheterization of the urethra, a positive culture is defined as equal to or greater than 5 x 10^4 CFU/mL.

Finally, if a urine culture is obtained by suprapubic aspiration, a method that bypasses the potential source of contamination, a positive culture is defined as recovery of any bacteria from the urine.

Imaging

Imaging studies have been the standard of care for young children with a first UTI for the past decade. Commonly, a renal ultrasound study is performed to evaluate the gross anatomy of the urinary tract (size and shape of the kidneys, duplication or dilatation of the ureters). A voiding cystourethrogram (VCUG) is done to determine whether vesicoureteral reflux is present. This practice has

References


1Not FDA approved for this indication.

2Exceeds dosage recommended by the manufacturer.
The latest Cochrane Review of the effectiveness of long-term antibiotics for preventing recurrent UTIs in children indicated that most published studies to date have been poorly designed without proper blinding. There is no question of the biologic plausibility of prophylactic antimicrobial therapy in preventing recurrent UTI; however, adverse effects, emergence of antimicrobial resistance, and difficulties with long-term adherence to prophylactic strategies present barriers to effectiveness.

References
Figure 1. Head circumference for age: boys.

Figure 2. Length for age: boys.
Figure 3. Weight for age: girls.

Figure 4. Weight for length: girls.
Figure 5. Head circumference for age: girls.

Figure 6. Weight for length: boys.
Figure 7. Weight for age: boys.

Figure 8. Length for age: girls.