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Pulmonary Hypertension

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Objectives After completing this article, readers should be able to:

1. Describe the presentation of and treatment for persistent pulmonary hypertension (PH) of the newborn.
2. Identify causes for PH in the pediatric age group.
3. Discuss how congenital heart disease causes PH.
4. Explain how PH is potentially reversible.
5. Recognize that changes associated with sleep may cause PH and cor pulmonale.

Introduction

PH occurs when a disease elevates pulmonary arterial pressure above normal. Pulmonary artery pressure=left atrial pressure+(pulmonary flow×pulmonary vascular resistance). Any single factor or combination of factors that increases left atrial pressure, pulmonary flow, or resistance can cause PH.

PH often is progressive, and if untreated, the right ventricle eventually becomes unable to support the circulation, resulting in significant morbidity and mortality. Pulmonary arterial pressure exceeding 25 mm Hg is abnormal and requires evaluation. Early treatment aimed at the underlying disease process may prevent progression. The prognosis is determined by the reversibility of the underlying disease process.

The World Health Organization (WHO) classification, initially proposed in 1998 and revised in 2003, categorizes different forms of PH based on similarities in pathophysiology, clinical presentation, and treatment (Table 1). Discussing all of the conditions listed in the WHO classification is beyond the scope of this review. Rather, we concentrate on a few select, but highly representative, forms of PH.

Persistent Pulmonary Hypertension of the Newborn

In the newborn, the most common cause of PH is persistent pulmonary hypertension of the newborn (PPHN). PPHN may be associated with acute neonatal respiratory conditions that result in persistently elevated pulmonary vascular resistance, with right-to-left shunting of blood across the foramen ovale, ductus arteriosus, or both, causing significant hypoxemia. Table 2 lists conditions during pregnancy and in the neonate that may predispose a newborn to PPHN. Alternatively, PPHN can occur without parenchymal lung disease (idiopathic). Overall, the incidence of PPHN is approximately 0.2% of term infants.

In the fetus, the highly vascular placenta serves as the organ for gas exchange and contributes to a lowered fetal systemic arterial pressure. Concurrently, the pulmonary vessels are constricted, making pulmonary and systemic arterial pressures nearly equal. This pressure state, in combination with an open ductus arteriosus and foramen ovale, results in 90% to 95% of cardiac output bypassing the fetal lungs.

At birth, the pulmonary artery pressure decreases to 50% of systemic artery pressure, and pulmonary blood flow in-
creases almost tenfold, primarily due to increased arterial pH and oxygen tension; the physical pulling open of capillaries accompanying lung inflation; local endogenous vasoregulatory mediators, especially vasodilatory prostaglandins and nitric oxide; and removal of the low-systemic vascular resistance placenta following clamping of the umbilical cord. The decline in pulmonary vascular resistance is greatest in the first 24 hours after birth and continues to fall over the first 2 postnatal weeks. Many processes, both pulmonary and systemic, may interrupt this normal transition and result in PPHN.

Most newborns who have PPHN have maladaptation, a term describing newborns who, despite normal pulmonary arterial number and muscularization, encounter a disruption in the decrease in pulmonary vascular resistance normally observed during transition. Maladaptation may be associated with perinatal asphyxia, sepsis, meconium aspiration, and acidosis. Maladaptation appears to be mediated by a complex imbalance in local vasodilatory and vasoconstrictor metabolites, including nitric oxide, prostaglandins, thromboxanes, leukotrienes, bradykinin, and inflammatory cytokines. Alternatively, PPHN may accompany chronic intrauterine hypoxia, marked by an increase and extension of medial muscle thickness; obstruction accompanying polycythemia or total anomalous pulmonary venous connection; pulmonary overflow following ductal narrowing; and a decrease in the number of pulmonary arteries, as seen in pulmonary hypoplasia, congenital diaphragmatic hernia,

### Table 1. World Health Organization Diagnostic Classification of Pulmonary Hypertension

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<th>1. Pulmonary Artery Hypertension</th>
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<tr>
<td>4.1 Thrombotic obstruction of proximal pulmonary arteries</td>
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| 5. Miscellaneous |

### Table 2. Conditions Predisposing to Persistent Pulmonary Hypertension of the Newborn

**Conditions in Pregnancy**
- Abnormal fetal heart rate
- Absent prenatal care
- Diabetes
- High altitude
- Illicit drug use
- Low Apgar score
- Meconium-stained amniotic fluid
- Nonsteroidal anti-inflammatory drugs
- Post-date gestation
- Tobacco

**Conditions in the Newborn**
- Acute respiratory distress syndrome
- Asphyxia
- Congenital diaphragmatic hernia
- Hypoglycemia
- Hypothermia
- Meconium aspiration syndrome
- Pneumothorax
- Polycythemia
- Pulmonary hypoplasia
- Respiratory distress syndrome
- Sepsis/pneumonia
- Retained fetal lung liquid syndrome (transient tachypnea of newborn)
or the oligohydramnios sequence. A reduced number of pulmonary arteries and capillaries, accompanied by abnormal arterial muscularization and a thickened alveolar septum, characterizes alveolar capillary dysplasia, a rare and often lethal form of PPHN.

Presentation
In the newborn, profound and labile hypoxemia, often out of proportion to the severity of parenchymal disease, as evidenced by radiography, is suggestive, but not diagnostic, of PPHN. Depending on the underlying cause, newborns may be acutely ill in the delivery room or may exhibit gradually escalating signs, including cyanosis, grunting, flaring, retractions, tachypnea, tachycardia, and shock. Clinically distinguishing the PH component from the underlying disease may be difficult. This dilemma is illustrated in meconium aspiration syndrome, in which atelectasis, hyperinflation, surfactant inactivation, and inflammation may be exacerbated by PH. In PH, the precordium usually is normoactive, whereas hyperactivity is more consistent with structural heart disease. In PH, the second heart sound by auscultation may appear single and loud, and there may be an accompanying systolic murmur from tricuspid insufficiency. Blood pressure and perfusion may be normal or there may be cardiogenic shock. The combination of hypoxemia and acidosis constrains the pulmonary vascular smooth muscle further, increases the PH, and creates a vicious cycle.

If the shunting associated with PPHN occurs exclusively at the ductus arteriosus, there is a gradient in the Pao₂ (the amount of oxygen dissolved in plasma) of greater than 20 mm Hg preductally and postductally, as measured at the right radial artery and left radial or umbilical artery, respectively. A similar gradient in oxygen saturation (the percentage of hemoglobin binding saturated with oxygen) may be observed, with a decrease in postductal oxygen saturation of greater than 5%. The absence of a gradient does not preclude the diagnosis of PPHN because shunting may be intermittent or at the atrial level.

Radiographic findings may reflect the underlying illness precipitating the PH (Table 2) or the images may appear remarkably clear, with diminished vascular markings and a slightly dilated heart suggestive of idiopathic PPHN. Electrocardiographic findings usually are normal. Echocardiography is essential to exclude cyanotic heart disease as the cause of hypoxemia and acidosis. Characteristic findings of PPHN include right-to-left shunting across the foramen ovale or ductus arteriosus, deviation of the atrial septum from right-to-left, right atrial enlargement, and tricuspid regurgitation.

Treatment
Treatment of PPHN is aimed at preventing end-organ injury from hypoxia, ischemia, and barotrauma. This goal is accomplished by correcting any contributing disturbances, including hypoglycemia, polycythemia, hypothermia, or pneumothorax, while maintaining systemic resistance and selectively lowering pulmonary vascular resistance.

Systemic vascular resistance is maintained with volume (crystalloid or colloid) and inotropic (dopamine and dobutamine) support, aiming at a mid- to high-normal systemic blood pressure. Such therapy decreases the pulmonary-to-systemic pressure gradient, reduces the shunt across fetal channels, and improves tissue oxygenation. Pulmonary vascular resistance is lowered by administering generous concentrations of oxygen. For refractory hypoxemia, inhaled nitric oxide (iNO) may be administered, which activates soluble guanylate cyclase, increases cyclic guanosine monophosphate (cGMP) production, and activates a cascade causing calcium efflux, with resultant vascular smooth muscle relaxation. By nature of its rapid binding and deactivation by reduced hemoglobin, iNO exhibits virtually no systemic vasodilatory affects. Although several clinical trials in newborns who had PPHN have shown that iNO improves oxygenation and decreases the need for extracorporeal membrane oxygenation (ECMO) by approximately 40%, this therapy has not reduced mortality. Between 25% and 33% of newborns who have PPHN, particularly those who have poor lung inflation, pulmonary hypoplasia/dysplasia, myocardial dysfunction, and pulmonary vascular structural disease, fail to show a sustained response to iNO. This lack of response is particularly evident in newborns who have congenital diaphragmatic hernia, in which iNO has not decreased ECMO use or mortality rate.

For infants whose hearts or lungs are unable to support them despite these therapies, ECMO provides cardiorespiratory support while the heart, lungs, and vasculature recover. With new therapies, particularly iNO, high-frequency ventilation, and the administration of surfactant, the use of ECMO in newborns suffering PPHN has declined. At the same time, such adjunctive therapies have changed the profile of newborns requiring ECMO such that only the sickest patients not responding to these alternative treatment modalities eventually receive ECMO. Similarly, delays in referral to ECMO centers, longer ECMO run times, increased age at initiation of ECMO, and increased rates of ECMO complications have been observed since the introduction of these adjunctive therapies. Cumulatively, these factors...
may have a negative impact on the mortality associated with ECMO. Although overall survival with ECMO is approximately 80%, survival varies with disease, ranging from as low as 50% in congenital diaphragmatic hernia to as high as 95% in meconium aspiration syndrome. Several studies have demonstrated improved survival for patients who have PPHN and receive ECMO, but the procedure is invasive and is associated with complications that include intraventricular hemorrhage, bleeding, stroke, emboli, and infection.

Outcomes
Survival in PPHN varies with the underlying disorder, severity of hypoxemia, and resultant encephalopathy. Generally, newborns whose parenchymal lung disease is reversible have the best prognosis; those who have primary maldevelopment of the pulmonary parenchyma and vasculature have the worst, despite modern therapies. Survivors of PPHN have an increased incidence of neurodevelopmental impairment, neurosensory hearing loss, behavioral problems (including hyperactivity and conduct disabilities), and respiratory difficulties (including reactive airway disease and rehospitalizations due to respiratory complications). It is believed that the cerebral hypoxia resulting from the underlying condition, such as birth asphyxia, perinatal hypoxia, and systemic hypotension, rather than from the treatment itself, is responsible for the neurodevelopmental handicaps observed in survivors of PPHN.

PH in Infants and Children
The underlying disease resulting in PH varies with age. The most common causes of PH in children are congenital heart disease and pulmonary disease.

Presentation
In infants and children, the signs and symptoms of PH initially are subtle, are nonspecific, and may be overshadowed by the underlying disease process. Dyspnea on exertion and fatigue may be observed initially because the right heart is unable to increase cardiac output with activity. Such right heart impairment may manifest as tiring with feedings and failure to thrive. With disease progression, symptoms may occur at rest. Eventually, signs of overt right-sided heart failure occur, such as peripheral edema, ascites, and hepatomegaly. Syncope on exertion is an ominous sign that warrants a cardiac evaluation because patients who have PH can be prone to sudden death. Death may result from hypoperfusion of the subendocardial tissue due to increased wall stress and increased myocardial demand or from compression of the left main coronary artery by an enlarged pulmonary artery. Cardiac evaluation may reveal jugular venous distention and a palpable right ventricular impulse. In summary, the diagnosis of PH should be considered for any patient who complains of chest pain, dyspnea, or syncope on exertion or who has any of the previously noted physical findings, and the patient should undergo a baseline assessment, including chest radiography and electrocardiography.

Diagnostic Studies
In infants and children, the chest radiograph, although generally not revealing, may demonstrate underlying lung disease and further direct the evaluation. In advanced stages of disease, a prominent right ventricular contour and poorly vascularized lungs (oligemic lung fields) may be evident, but these observations may be subtle and easily missed.

Electrocardiography for infants and children who have PH often shows evidence of right ventricular hypertrophy and perhaps cor pulmonale (Figure). Cor pulmonale is defined as an alteration in the right ventricular
structure and function due to PH caused by disease affecting the lung or its vascular bed. The definition does not include left-sided heart failure. Therefore, congenital heart disease or acquired left-sided heart disease must be excluded prior to diagnosing cor pulmonale. If either chest radiography or electrocardiography indicates the presence of right ventricular hypertrophy, a cardiology evaluation with echocardiography is indicated.

Two-dimensional echocardiography with Doppler evaluation is the confirmatory test and can detect structural heart disease, if present. The tricuspid valve regurgitant jet velocity added to the estimated right atrial pressure allows for estimation of the right ventricular pressure. In the absence of pulmonary valve stenosis, this measurement equals pulmonary arterial pressure and provides the clinician with an estimate of disease severity as well as a response to treatment. Indicators for disease severity and ultimate prognosis include not only the degree of right ventricular pressure elevation, but also the reversibility of the PH. The latter can be determined by demonstrating a decrease in the right ventricular pressure in response to oxygen vasodilator therapy.

**Congenital Heart Disease**

PH occurs as a consequence of congenital heart disease when the pulmonary blood flow is increased, the pulmonary vascular resistance is increased, or some other factor increases downstream resistance to blood flow through the lungs (such as pulmonary venous obstruction, mitral stenosis, or left ventricular dysfunction).

In the pediatric age group, pulmonary arterial hypertension is the most common mechanism. Any congenital heart lesion that creates a significant shunt from the systemic to the pulmonary vascular bed results in PH. These conditions include large intracardiac defects in the atrial or ventricular septa or the endocardial cushion as well as large extracardiac shunts such as a patent ductus arteriosus or aortopulmonary window. Initially, the left-to-right shunt increases flow in the pulmonary vascular bed, creating PH. Such hyperkinetic PH is due to changes in shear stress on the endothelial wall, with resultant pulmonary arteriolar endothelial dysfunction. With time, the smooth muscle of the arteriolar beds proliferates and hypertrophies, and eventually the PH becomes both irreversible and progressive.

Once the pulmonary pressure exceeds the systemic vascular resistance, the left-to-right shunt reverses, and cyanosis develops due to the presence of a right-to-left shunt. This state is known as Eisenmenger syndrome, for which supportive care is the only treatment. Fortunately, with surgical repair of large shunts in the first year after birth, Eisenmenger syndrome now is considered a preventable disease.

PH may accompany obstruction of pulmonary venous flow. Pulmonary venous hypertension can be subcategorized into left-sided atrial or ventricular disease, left-sided valvular disease, and pulmonary venous obstruction. In left-sided ventricular disease, an increase in left ventricular end-diastolic pressure results in primary left ventricular failure. This condition is uncommon in the pediatric age group and usually is related to diseases of the myocardium, such as viral myocarditis. Treatments range from medical support to cardiac transplantation. Left-sided valvular disease and extrinsic compression of the pulmonary veins, by virtue of surgical or catheter intervention, are reversible causes of pulmonary venous obstruction. The same is not true, unfortunately, for pulmonary vein stenosis, for which supportive care is the only treatment.

**Idiopathic PH**

The cause of idiopathic PH is, by definition, unknown. This condition is characterized by a progressive elevation in the pulmonary arterial pressure that eventually leads to right ventricular failure and is a primary disorder rather than a secondary response to chronic illness. Idiopathic PH is rare and has a female preponderance in a 1.7:1 ratio. Between 6% and 10% of cases are familial, with an autosomal dominant inheritance pattern as well as an association with a genetic mutation in the BMPR-2 gene. The pathogenesis involves three processes. First, vascular constriction results from an imbalance in mediators of pulmonary vasodilation and vasoconstriction. Second, vascular remodeling occurs due to proliferation of endothelial cells and vascular smooth muscle. Third, thrombosis occurs due to coagulation abnormalities.

Unfortunately, idiopathic PH progresses rapidly without treatment. Current therapies, although not consistently successful, have improved survival. Treating the pulmonary vasculopathy while targeting symptoms of right ventricular failure and thrombosis is the primary approach. Conventional therapy includes administration of digoxin, furosemide, and warfarin, and if chronic hypoxemia is present, oxygen therapy.

Catheterization of the right heart is indicated if targeted vasodilator therapy is being considered. At the time of catheterization, an atrial septostomy may be performed for patients who have severe right ventricular failure or recurrent syncope. By creating a right-to-left shunt across the atrial septum, the obstructed pulmonary vascular bed may be bypassed, thereby increasing cardiac
output. In addition, the patient’s response to iNO directs vasodilator therapy. Responders are treated with conventional therapy, including calcium channel blockers, which have been found to improve 5-year survival rates. Nonresponders are treated with prostacyclin analogs, such as iloprost, rather than with calcium channel blockers because the latter drugs have been associated with systemic hypotension and right ventricular failure in nonresponders. All patients, regardless of their initial response to vasodilator therapy, require ongoing monitoring to assess their responses to medical therapy and to determine if additional therapies are needed.

For patients who do not respond to conventional therapy or demonstrate no response to iNO, newer therapies are available. These treatments often are used in combination and target different mechanisms of action, including inhibition of the potent endogenous vasoconstrictor endothelin (bosentan) and the breakdown by phosphodiesterase of the vasodilator cGMP generated in the NO pathway (sildenafil).

**Respiratory Disorders**

Disorders of the respiratory system and hypoxemia are common causes of PH. Signs and symptoms relate to the underlying disease. The prognosis is determined by the underlying respiratory disease, with the presence of PH representing an unfavorable sign. Hypoxemia results in remodeling of the vascular wall, with increases in intimal, medial, and adventitial thickness and proliferation of fibroblasts, which leads to increased pulmonary vascular resistance. Right ventricular enlargement with signs of right-sided heart failure may develop. As discussed, pulmonary heart disease, or cor pulmonale, results from acute or chronic PH and manifests as right ventricular enlargement.

Chronic obstructive and interstitial lung diseases, although listed in the WHO classification, primarily are diseases of adults. The mechanisms leading to PH in these disorders include hypoxic vasoconstriction, compression, possibly destruction of blood vessels by fibrosis, and low lung volumes.

More common in the pediatric age group are alveolar hypoventilation syndromes associated with thoracic cage abnormalities such as kyphoscoliosis and neuromuscular diseases. Loss of lung volume causes alveolar hypoventilation and subsequent hypoxemia and hypercapnia. Such gas exchange abnormalities result in pulmonary vasoconstriction and PH. The PH associated with exposure to high altitude is characterized by vascular wall remodeling due to hypoxia. Polycythemia may aggravate PH.

Sleep-disordered breathing, as it relates to obstructive sleep apnea syndrome (OSAS), may cause PH. The incidence of OSAS is estimated to be 2% to 3% in young children. The increasing prevalence in children is largely attributable to the obesity epidemic. OSAS also may accompany adenotonsillar hypertrophy, craniofacial abnormalities, and neurologic disorders affecting upper airway dynamics and patency. Overnight polysomnography provides a definitive diagnostic approach for OSAS. OSAS is characterized by repeated episodes of partial or complete upper airway obstruction during sleep, resulting in abnormalities of gas exchange and disruption of sleep patterns. The changes in respiratory mechanics and homeostasis during sleep are magnified further by upper airway obstruction and manifested as increased work of breathing, sleep fragmentation, episodic hypoxemia, and hypercapnia. Frequent oxygen desaturations during sleep occur in children who have OSAS. Hypoxia-induced pulmonary vasoconstriction results in elevation of pulmonary artery pressure and can lead to cor pulmonale. Episodic nocturnal hypoxia also is speculated to result in changes in the physical properties of resistance vessels and may lead to systemic hypertension.

Treatment of OSAS, although beyond the scope of this article, is aimed at preventing the complication of PH and cor pulmonale. Reversal of hypoxemia is intimately linked to normalization of pulmonary artery pressures.

In general, treatment of patients who have secondary PH rests on correcting the underlying respiratory system abnormality and relieving the hypoxemia and hypercapnia that contribute to pulmonary vasoconstriction. Supplemental oxygen can correct arterial hypoxemia and reduce pulmonary artery pressure. Therapies, including pulmonary vasodilation with prostacyclin and NO and calcium-channel blockers, also have been used.

**Thrombotic or Embolic Disease**

PH caused by chronic thrombotic or embolic disease occurs when pulmonary artery pressure is elevated due to obstruction of blood flow through large pulmonary arteries by a venous clot. The mainstay of management is anticoagulation therapy.

**Disorders of Pulmonary Vasculature**

PH resulting from disorders directly affecting the pulmonary vasculature is uncommon in the pediatric age group. Examples include pulmonary histiocytosis X and sarcoidosis. Pulmonary histiocytosis X is an interstitial pulmonary disease complicated by severe PH from fibrosis of pulmonary arteries and veins. Sarcoidosis, a multiorgan granulomatous disorder, results in destructive vasculitis involving the muscular layers of arteries and veins.
Summary

- PPHN causes profound hypoxemia that is labile and varies pre- and postductally and may exacerbate newborn illnesses such as meconium aspiration.
- Treatment and possible reversal of PH often begins with correction of the underlying disorder that is causing hypoxemia.
- Diagnostic electrocardiographic criteria for cor pulmonale include right ventricular hypertrophy, right axis deviation, right atrial enlargement, and incomplete right bundle branch block.
- For children who have OSAS, early diagnostic evaluation (including polysomnography) and treatment may reverse the hypoxemia that is causing PH or exacerbating existing cor pulmonale.

Suggested Reading


Rubin LJ. Diagnosis and management of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. *Chest*. 2004;126:7s–10s


PIR Quiz

Quiz also available online at www.pedsinreview.aappublications.org.

1. All of the following conditions are associated with a difference in pre- and postductal oxygen saturation except:
   A. Atrial septal defect.
   B. D-transposition of the great arteries.
   C. D-transposition of the great arteries and coarctation of the aorta.
   D. Interrupted aortic arch type-B.
   E. PPHN.

2. All of the following treatments are valuable in the treatment of PPHN except:
   A. Blood transfusion.
   B. ECMO.
   C. iNO.
   D. Oxygen.
   E. Sodium nitroprusside

3. A 6-year-old girl complains of exertional fatigue, and examination reveals a precordial bulge and a loud second heart sound. You consider the diagnosis of idiopathic PH. The first laboratory test to obtain is:
   A. Cardiac magnetic resonance imaging.
   B. Chest radiography.
   C. Echocardiography.
   D. Electrocardiography.
   E. Electrocardiography and chest radiography.

4. Electrocardiography for a 4-year-old boy who has Down syndrome shows right ventricular hypertrophy with strain, right axis deviation, right atrial enlargement, and right bundle branch block. Previous echocardiography demonstrated a large atrial septal defect. The best next step is to:
   A. Begin nighttime oxygen therapy.
   B. Obtain a sleep study.
   C. Order chest radiography.
   D. Perform a tonsillectomy and adenoidectomy.
   E. Perform cardiac catheterization.

5. Which of the following patients is most likely to suffer from irreversible PH?
   A. A 3-month-old boy who has Down syndrome, an atrioventricular septal defect, high pulmonary vascular resistance, and decreased pulmonary blood flow.
   B. A 3-year-old girl who has a structurally normal heart, normal pulmonary blood flow, and high pulmonary resistance.
   C. A 3-year-old girl who has a large ventricular septal defect, systemic pulmonary artery pressure, and increased pulmonary blood flow.
   D. A 3-year-old girl who has pulmonary hypertension and severe mitral stenosis.
   E. A 30-year-old man who has a large atrial septal defect and increased pulmonary blood flow.
Adolescent Immunizations

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Author Disclosure
Drs Brigham and Goldstein have disclosed no financial relationships relevant to this article. This commentary does contain a discussion of an unapproved/investigative use of a commercial product/device.

Objectives After completing this article, readers should be able to:
1. Discuss the rationale for the recent additions to the adolescent vaccination schedule.
2. Describe the indications for vaccines in adolescents.

Introduction
In the past 5 years, the immunization schedule for adolescents has undergone numerous changes. Several new vaccines have been licensed for use in adolescents. The human papillomavirus (HPV) vaccine is expected to decrease the incidence of genital warts, abnormal cervical cytology, and cervical cancer, thereby reducing significant medical, psychological, and economic burdens for patients and society. A new vaccine against meningococcal disease aims to lower the incidence of that rare infection and its associated significant mortality and morbidity. Although diphtheria and tetanus are very rare occurrences in adolescents, the incidence of pertussis has been increasing in this age group. Fortunately, two new vaccines against pertussis for adolescents should lower the incidence of that illness in this population as well as help to reduce pertussis in the high-risk infant and elderly populations. Finally, although influenza generally is a mild illness in adolescents, new recommendations to immunize all adolescents with an influenza vaccine has the objective of reducing the incidence of the disease and its associated morbidity and mortality in high-risk populations. In addition, for some older vaccines, indications and dosing recommendations have been modified.

Clinicians who provide care for adolescents should be knowledgeable about immunization recommendations because immunizing adolescents with age-appropriate vaccines reduces their disease burden. The recommendations for vaccines in individuals who are immunocompromised are beyond the scope of this article. The Figure shows the current adolescent immunization schedule. Contraindications for vaccines are listed in Table 1, and some adverse effects of vaccines are listed in Table 2.

Human Papillomavirus
HPV is the cause of one of the most common sexually transmitted infections in the United States, with an estimated 6.2 million new infections per year. It infects more than 40% of sexually active adolescent females. HPV infections can cause warts, cervical cancer, anogenital dysplasia, and more rarely, respiratory tract papillomatosis and epidermodysplasia verruciformis. Most of the infections are self-limited and asymptomatic, with 70% of new infections cleared within 1 year and 90% within 2 years.

More than 40 HPV types are known to infect the genital area; they vary in their association with cervical neoplasia. High-risk types are detected in 99% of cervical...
cancers; types 16 and 18 cause an estimated 70% of cervical cancers worldwide. Infection with a high-risk HPV type appears to be necessary but not sufficient for the development of cervical cancer because most women infected with high-risk HPV types do not develop cervical cancer. HPV also is associated with 90% of anal squamous cancers, which have increased in incidence in the past 3 decades, especially in men who have sex with men. Low-risk types 6 and 11 can cause benign or low-grade cervical cell changes, genital warts, and anogenital cancers.

In June 2006, the United States Food and Drug Administration (FDA) licensed Gardasil® (Merck & Co, Inc, West Point, Pa.), a quadrivalent vaccine against HPV types 6, 11, 16, and 18, for use in females ages 9 through 26 years (Table 3). Based on international pre-licensure studies in females ages 16 through 26 years, the vaccine had high efficacy in preventing HPV-related cervical intraepithelial neoplasia (CIN) 2 or 3 or adeno-carcinoma in situ. Combined analysis of the studies showed an efficacy of 95.2% in protection against any CIN and 98.9% against external genital warts from HPV 6, 11, 16, or 18. Gardasil® currently is indicated for the prevention of cervical, vulvar, and vaginal cancers caused by HPV 16 and 18 and genital warts caused by HPV 6 and 11.

Cervarix™, a bivalent vaccine against HPV types 16 and 18, is produced by GlaxoSmithKline Biologicals (Research Triangle Park, NC) (Table 3), but it has not yet been approved for use in the United States. This vaccine does not cover HPV types that primarily cause genital warts.

The HPV vaccine ideally should be administered to girls prior to the onset of sexual activity because it does not have any therapeutic effect on existing HPV infections. The 2002 National Survey of Family Growth showed that 24% of females in the United States are sexually active by 15 years of age. In addition, a prospective study of college women in the United States showed that the cumulative probability of infection by HPV was 38.9% by 24 months after first sexual intercourse. Given the early onset of sexual activity and high likelihood of acquiring HPV soon after onset, it is recommended for females ages 11 to 12 years. The Gardasil® series can be initiated in girls as young as 9 years of age or women younger than age 27 years who have not yet received or completed the vaccine series. In addition, it may be given to those already sexually active or those who have abnormal cervical cytology because it protects females who are not yet infected and protects against the remaining types of HPV in those already infected with one or more type.

As of June 2008, 31 cases of Guillain-Barré syndrome
(GBS) occurring after Gardasil® vaccination in the United States were reported to the Vaccine Adverse Events Reporting System (VAERS). Of these, 10 cases have been confirmed, 7 did not meet the definition of GBS, 1 had symptoms of GBS prior to vaccination, 4 were unconfirmed, and 9 were being investigated further. The total number of cases reported is within the range of the expected number of cases that could occur regardless of vaccination.

**Neisseria meningitidis**

*N meningitidis*, a gram-negative diplococcus that has at least 13 serogroups, causes 1,000 to 2,600 cases of meningococcal disease annually in the United States. Since the early 1990s, outbreaks in the United States have been occurring with greater frequency. The three major presentations of *N meningitidis* disease are meningitis (49%), bacteremia (53%), and pneumonia.
Approximately 10% to 15% of those affected die, even with appropriate treatment. Of those who survive, 11% to 19% have serious sequelae, such as loss of a limb or a neurologic disability. Although disease is most common in children younger than 1 year of age, the rate of 1.2 cases per 100,000 in individuals 11 to 19 years of age still is higher than that of the general public. Serogroups B, C, and Y are the three major causes of disease in the United States, with each causing approximately 33% of the cases. In those ages 11 years or older, 75% are caused by serogroups C, Y, or W-135.

Two vaccines against *N meningitidis* are available: the polysaccharide vaccine MPSV4 (Menomune® A/C/Y/W-135, Sanofi Pasteur, Swiftwater, Pa.), and the conjugated polysaccharide vaccine MCV4 (Menactra®, Sanofi Pasteur) (Table 4). Both vaccines are tetravalent, providing protection against serotypes A, C, Y, and W-135. At present, there is no vaccine against serogroup B because the serogroup B polysaccharide is poorly immunogenic in humans, a finding believed to be due to structural similarity to a glycoprotein found in human tissues.

The MPSV4 vaccine does not elicit long-lasting immunity or an anamnestic response after subsequent challenge and does not lead to a reduction in nasopharyngeal carriage. The efficacy of serogroups A and C polysaccharide vaccines are estimated to be 85% to 100% among older children and adults; efficacy data for serogroups Y and W-135 polysaccharide vaccines are not available. The duration of clinical protection is approximately 3 years or more in school-age children and in adults.

The MCV4 vaccine is formulated to produce a strong anamnestic response at re-exposure and a reduction in nasal carriage, which can lead to herd immunity, thus protecting the unimmunized. At 28 days after immunization with either MPSV4 or MCV4, both vaccines showed high immunogenicity in humans. However, at 3 years after immunization, antibody titers against all four serogroups were higher in those immunized with MCV4 than in those who received MPSV4.

In June 2007, the Advisory Committee on Immunization Practices (ACIP) recommended that all 11- to 18-year-old children receive one dose of MCV4 at the earliest opportunity. Health-care practitioners also should vaccinate individuals ages 19 to 55 years of age who are at increased risk of meningococcal disease, which includes college freshmen in dormitories, microbiologists routinely exposed to *N meningitidis*, military recruits, travelers to or those living in countries afflicted with hyperendemic or epidemic *N meningitidis*, patients who have terminal complement component deficiencies, and individuals who have anatomic or functional asplenia.

As of February 2008, 24 confirmed cases of GBS that occurred within 6 weeks of receipt of MCV4 in persons

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### Table 3. Human Papillomavirus Vaccines

<table>
<thead>
<tr>
<th>Serotypes covered</th>
<th>Gardasil®</th>
<th>Cervarix™</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composition</td>
<td>Recombinant viruslike particles</td>
<td>Recombinant viruslike particles</td>
</tr>
<tr>
<td>Patient age range</td>
<td>Females 9 to 26 years</td>
<td>Not currently approved</td>
</tr>
<tr>
<td>Vaccination schedule</td>
<td>0, 2, 6 months</td>
<td>0, 1, 6 months</td>
</tr>
<tr>
<td>Route</td>
<td>Intramuscularly</td>
<td>Intramuscularly</td>
</tr>
<tr>
<td>Private sector cost/dose</td>
<td>$125.29</td>
<td>Not currently available</td>
</tr>
</tbody>
</table>

Gardasil® (Merck & Co., Inc); Cervarix™ (GlaxoSmithKline Biologicals)

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### Table 4. Meningococcal Vaccines

<table>
<thead>
<tr>
<th>Serotypes covered</th>
<th>MPSV4 (Menomune®)</th>
<th>MCV4 (Menactra®)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composition</td>
<td>Tetravalent polysaccharides</td>
<td>Tetravalent meningococcal conjugate</td>
</tr>
<tr>
<td>Patient age range</td>
<td>2+ years</td>
<td>11 to 55 years</td>
</tr>
<tr>
<td>Vaccination schedule</td>
<td>Single dose</td>
<td>Single dose</td>
</tr>
<tr>
<td>Route</td>
<td>Subcutaneously</td>
<td>Intramuscularly</td>
</tr>
<tr>
<td>Private sector cost/dose</td>
<td>$95.68 (2008)*</td>
<td>$93.87</td>
</tr>
</tbody>
</table>

*Massachusetts General Hospital Pharmacy
Menomune® (Sanofi Pasteur); Menactra® (Sanofi Pasteur)
ages 11 to 19 years were reported to VAERS. These data suggest a small increased risk of GBS after MCV4, but there are a number of limitations to the data. The findings must be viewed with caution until they can be evaluated and clarified.

Tetanus, Pertussis, and Diphtheria

* Bordetella pertussis*, the fastidious gram-negative coccobacillus that causes pertussis, is endemic in the United States. In adolescents, pertussis can range from an asymptomatic state to a mild cough to the classic pertussis course of catarrhal, paroxysmal, and convalescent phases. Adolescents can transmit the disease to infants, who are more likely to have complications requiring hospitalization and are at the highest risk of dying. The number of reported pertussis cases has been increasing since the 1980s, likely due to both an increased number of cases and better detection. Studies of recent pertussis outbreaks show that adolescents have among the highest incidence of any age group. In 2006, 15,632 cases of pertussis were reported, of which 42% were in children and young persons ages 5 to 24 years. Immunity to pertussis wanes approximately 5 to 10 years after completion of the childhood pertussis immunization schedule.

Tetanus is caused by the spores of the ubiquitous *Clostridium tetani*, an anaerobic bacterium, which enters the body through breaks in the skin and germinates into bacilli that produce tetanospasmin, a neurotoxin that causes contractions of skeletal muscles. The muscle spasms lead to trismus, then to generalized rigidity that can impair respiratory function and autonomic instability that can result in death. Since a tetanus toxoid-containing vaccine was introduced in the United States in the 1940s, tetanus has been uncommon, with only 624 cases reported from 1990 through 2004. Of those cases, 19 (3%) were in individuals ages 11 through 18 years.

Diphtheria is an acute and communicable infectious illness caused predominantly by toxigenic strains of *Corynebacterium diphtheriae*. Infection produces a grayish-colored membrane in the pharynx, palate, or nasal mucosa, which can obstruct the airway. Fortunately, respiratory diphtheria is rare in the United States, with only seven cases reported to the Centers for Disease Control and Prevention between 1998 and 2004.

In 2005, two tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccines, Boostrix® (GlaxoSmithKline Biologicals) and Adacel® (Sanofi Pasteur), were licensed in the United States for use in adolescents (Table 5). Boostrix® may be used only in adolescents up to age 18 years.

In June 2006, the ACIP recommended that Tdap be used routinely in place of tetanus toxoid and reduced diphtheria toxoid (Td) vaccines in those 11 to 18 years of age. Adolescents ages 11 to 18 years of age should receive a single dose of Tdap instead of a Td booster, assuming they have completed the recommended childhood diphtheria toxoid, tetanus toxoid, and whole-cell pertussis (DTP)/diphtheria toxoid, tetanus toxoid, and acellular pertussis (DTaP)/Td immunization series. If the adolescent is between the ages of 11 and 18 years and already has received a Td booster, waiting 5 years after the last Td before giving Tdap is suggested to reduce the risk of local and systemic reactions. However, Tdap can be given sooner if the individual is at increased risk of pertussis or increased risk of complications from pertussis and the benefits of pertussis protection outweigh the risks of possible increased local and systemic reactions. The American Academy of Pediatrics (AAP) recommends that the Tdap and MCV4 be given at the same visit, if both are indicated. If they are not given on the same day, the AAP recommends that MCV4 be given at least 1 month after Tdap due to concerns of possible increased local reactions.

### Table 5. Tetanus, Diphtheria, Pertussis Vaccines

<table>
<thead>
<tr>
<th>Composition</th>
<th>Boostrix®</th>
<th>Adacel®</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT, FHA, pertactin</td>
<td>PT, FHA, pertactin Fimbriae types 2 and 3</td>
<td></td>
</tr>
<tr>
<td>Patient age range</td>
<td>10 to 18 years</td>
<td>11 to 64 years</td>
</tr>
<tr>
<td>Vaccination schedule</td>
<td>Single dose at 11 to 12 years</td>
<td>Single dose at 11 to 12 years</td>
</tr>
<tr>
<td>Catch-up schedule</td>
<td>Tdap time 0 Td at 1 and 6 months</td>
<td>Tdap time 0 Td at 1 and 6 months</td>
</tr>
<tr>
<td>Route</td>
<td>Intramuscularly</td>
<td>Intramuscularly</td>
</tr>
<tr>
<td>Private sector cost/dose</td>
<td>$36.25</td>
<td>$37.43</td>
</tr>
</tbody>
</table>

PT = pertussis toxoid, FHA = filamentous hemagglutinin
Boostrix® (GlaxoSmithKline Biologicals), Adacel® (Sanofi Pasteur)
Influenza

Influenza, an RNA virus, can cause an abrupt onset of constitutional and respiratory signs and symptoms, including fever, myalgias, headache, malaise, cough, sore throat, and rhinitis. Influenza also can cause a primary viral pneumonia, exacerbate underlying medical conditions, contribute to coinfections with other pathogens, and lead to secondary bacterial infections. In the United States from 1990 through 1999, influenza annually caused an average 36,000 deaths and 226,000 hospitalizations.

Human epidemics are caused by influenza A and B. Influenza A subtypes are based on the two surface antigens hemagglutinin and neuraminidase. Influenza B has two distinct genetic lineages but is not categorized into subtypes. Influenza A (H1N1), influenza A (H3N2), and influenza B viruses circulate globally; more recently, influenza A (H1N2) virus also has been circulating. New influenza virus variants arise due to point mutations during viral replication, leading to antigenic drift. Immunity to the surface antigen, particularly hemagglutinin, reduces the likelihood of infection. Unfortunately, antibody against one virus type or subtype provides little or no protection against a different type or subtype.

Two types of influenza vaccines are available (Table 6). Both are multivalent vaccines that contain three virus strains: one each of influenza A (H1N1), influenza A (H3N2), and influenza B.

The estimated efficacy of the trivalent inactivated influenza vaccine (TIV) (Fluzone® [Sanofi Pasteur], Fluvirin® [Novartis], FluLaval® [GlaxoSmithKline Biologicals], FluMist® [MedImmune], which is administered intranasally, has an efficacy estimated to be 86% to 89% against virologically confirmed influenza A (H3N2). This vaccine may produce mild signs and symptoms related to an attenuated live influenza virus infection. LAIV is approved only for healthy individuals who have no chronic conditions that put them at higher risk for complications from influenza, such as asthma, chronic heart or lung disease, kidney disease, or diabetes, or individuals who are immunocompromised (Table 1). Because nasal congestion present prior to administration could decrease delivery to the nasopharyngeal mucosa, the clinician could consider deferring administration until resolution of illness or giving the TIV instead.

The TIV is preferred in those who have underlying medical conditions predisposing them to complications from influenza. In addition, close contacts of severely immunosuppressed people and pregnant women should receive TIV.

In 2008, the ACIP and AAP recommended that all children ages 6 months to 18 years receive an influenza vaccine annually. If possible, health-care practitioners should offer the influenza vaccine to all children ages 6 months to 18 years during the 2008 to 2009 influenza season, and all children should begin to receive annual influenza vaccines no later than the 2009 to 2010 influenza season. Data comparing the efficacy of TIV and the LAIV are limited, with one study showing no statistically significant difference in efficacy and another showing increased protection provided by the LAIV. Comparative efficacy likely is related, in part, to the extent of vaccine homology to the circulating strains in a given year. Advantages of the LAIV include the potential to induce both mucosal and systemic immune responses and its ease of administration, which can lead to increased acceptability by both the recipient and parents.

Table 6. Influenza Vaccines

<table>
<thead>
<tr>
<th>Inactivated Vaccines</th>
<th>Live Attenuated Vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Fluzone®, Fluvirin®, FluLaval®)</td>
<td>(FluMist®)</td>
</tr>
<tr>
<td>Viral strains</td>
<td>A(H3N2), A(H1N1), B</td>
</tr>
<tr>
<td>Composition</td>
<td>Subvirion or purified surface antigen</td>
</tr>
<tr>
<td>Patient age range</td>
<td>Cold-adapted strains</td>
</tr>
<tr>
<td>6 months +</td>
<td>5 to 49 years</td>
</tr>
<tr>
<td>Vaccination schedule for adolescents</td>
<td>1 dose annually</td>
</tr>
<tr>
<td>Route</td>
<td>Intramuscularly</td>
</tr>
<tr>
<td>1 dose annually</td>
<td>Intranasally</td>
</tr>
<tr>
<td>Private sector cost/dose</td>
<td>$16.09/$12.48/$11.10</td>
</tr>
</tbody>
</table>

Price Source: http://www.cdc.gov/vaccines/programs/vfc/cdc-vac-price-list.htm
Fluzone® (Sanofi Pasteur), Fluvirin® (Novartis), FluLaval® (GlaxoSmithKline Biologicals), FluMist® (MedImmune)
Hepatitis A
Hepatitis A virus (HAV), an RNA virus, can cause an acute self-limited illness accompanied by fever, anorexia, malaise, nausea, abdominal discomfort, and jaundice.

Three vaccines are available: two monovalent hepatitis A vaccines and one combination vaccine against hepatitis A and hepatitis B. Havrix® (GlaxoSmithKline Biologicals) and VAQTA® (Merck & Co, Inc, West Point, Pa.) are monovalent vaccines against HAV. Both monovalent vaccines are made from inactivated HAV and are given in a two-dose series licensed for individuals 12 months of age and older. They are offered in two different formulations: one designed for children 12 months through 18 years of age, the other for patients 19 years and older. Both vaccines demonstrated 100% seroconversion 1 month after the second dose when given 6 months after the first dose. Protective efficacy in preventing clinical illness in randomized, controlled, double-blind trials is 94% to 100%.

TWINRIX® (GlaxoSmithKline Biologicals) is the combination HAV and hepatitis B virus (HBV) vaccine; the HAV component is one half of a HAVRIX® dose and the HBV component is the same as Engerix-B® (GlaxoSmithKline Biologicals), a monovalent vaccine against hepatitis B. TWINRIX® is licensed for those 18 years of age or older and can be given in either a three- or four-dose series.

The ACIP currently recommends that immunization against HAV begin at 12 months of age, with the second dose given at a minimum interval of 6 months. In addition, those who are either at increased risk for hepatitis A or increased risk of a fulminant course from hepatitis A should receive the vaccine. This includes travelers to or those living in areas with intermediate or high endemicity, adolescent or adult males who have sex with men, individuals who use injectable or noninjectable illicit drugs, patients who receive clotting factors, and those who work with HAV in a laboratory setting.

Hepatitis B
HBV, a DNA virus, can cause a spectrum of disorders, including a subacute illness that has nonspecific findings, clinical hepatitis with jaundice, or fulminant fatal hepatitis. Chronic infections may lead to hepatocellular carcinoma or cirrhosis.

The vaccines available in the United States for protection against HBV are produced by recombinant DNA technology; the hepatitis B surface antigen (HBsAg) is expressed in yeast and purified. Plasma-derived HBV vaccines no longer are available in the United States. There are two single-antigen vaccines: Recombivax HB® (Merck & Co, Inc) and Engerix-B® (GlaxoSmithKline Biologicals). As noted previously, TWINRIX® (GlaxoSmithKline Biologicals), a combination of recombinant HBsAg and inactivated HAV, is licensed for individuals ages 18 years or older.

Both monovalent vaccines have age-specific dose formulations, with higher doses required in those 20 years of age or older and the highest dose in dialysis and predialysis patients or those who are immunocompromised. For those younger than age 20 years, three doses of the pediatric/adolescent formulation should be given. The second dose should be given 1 month after the first dose, and the third dose should be given 4 to 6 months after the first dose. Alternatively, the vaccine can be given at 0, 1, and 6 months; at 0, 2, and 4 months; or at 0, 12, and 24 months, with equal resultant immunogenicity.

The Recombivax HB® vaccine (Merck & Co, Inc) has an alternative two-dose schedule for adolescents ages 11 through 15 years. However, the adult formulation must be used, which has a higher quantity of HBsAg. The second dose of the two-dose schedule should be given 4 to 6 months after the first dose.

In those found not to have a sufficient serum hepatitis B surface antibody response to vaccination, the three-dose series should be repeated, unless the individual is found to be positive for HBsAg, which reflects HBV infection. If the serum antibody response still is insufficient following the second series, it is unlikely that an additional series will lead to a response.

The ACIP recommends that all unvaccinated children and adolescents younger than age 19 years receive a complete hepatitis B vaccine series. The vaccines licensed in the United States have an efficacy of 90% to 95% for prevention of HBV infection in susceptible children and adults. Long-term studies have shown that immune memory is present for 15 years or more and protects against both acute and chronic infections.

Measles, Mumps, Rubella, and Varicella
Current recommendations are for children to receive two immunizations against measles, mumps, rubella, and varicella. The second dose provides improved protection to the small percentage of individuals who do not respond adequately to the first dose. If the appropriate vaccines were not given in childhood, they should be given as a catch-up vaccination, unless the patient has evidence of immunity.

Vaccines against these viruses consist of live attenuated strains of viruses. The combination measles, mumps, rubella, and varicella vaccination (ProQuad® [Merck & Co, Inc]) can be given to those 12 months to
12 years of age. However, ProQuad® currently is unavailable. Adolescents 13 years of age or older should be given the single-antigen varicella vaccine (VARIVAX® [Merck & Co, Inc]) and the measles, mumps, and rubella combination vaccine (M-M-R® II [Merck & Co, Inc]), if both are necessary. The measles, mumps, and rubella components in the ProQuad® vaccine are identical to the components in the M-M-R® II. The varicella component in the ProQuad® and VARIVAX® vaccines is Oka/Merck varicella-zoster virus, but the titer is higher in the ProQuad®. The ProQuad® was licensed on the basis of immunologic noninferiority of its vaccine antigenic components, rather than on clinical efficacy, because the clinical efficacy of the individual parts had been established previously. The trivalent measles, mumps, and rubella vaccine is the preparation of choice unless one of the components is contraindicated. In that case, a monovalent preparation of measles, rubella, or mumps may be used.

For patients ages 12 months to 12 years of age, the recommended minimum interval between doses of ProQuad® is 3 months, but if the second dose is given at least 28 days following the first dose, this interval is considered valid, and the dose does not need to be repeated. The recommended minimum interval between doses of both VARIVAX® and M-M-R® II for those 13 years of age or older is 4 weeks.

**Streptococcus pneumoniae**

*S. pneumoniae* is the leading cause of bacterial pneumonia, bacteremia, sinusitis, and acute otitis media worldwide. Individuals who have anatomic or functional asplenia, such as those who have sickle cell disease, are at the highest risk of invasive disease in any group due to decreased clearance of encapsulated bacteria. Children younger than age 2 years and adults ages 65 years or older also are at high risk of invasive disease, as are individuals who have underlying chronic medical conditions such as cardiovascular disease, pulmonary disease (excluding asthma), or liver disease. Others at increased risk of invasive disease include those who have either decreased responsiveness to polysaccharide antigens or increased rate of decline of serum antibodies, which can be due to immunosuppressive conditions such as human immunodeficiency virus infection; malignancies; organ or bone marrow transplants; therapy with alkylating agents, antimetabolics, or systemic corticosteroids; chronic renal failure; or nephrotic syndrome. Finally, certain ethnic and racial populations are known to have higher rates of invasive pneumococcal disease, including African Americans, Native Alaskans, and specific Native American populations.

Two types of vaccines against pneumococcus are available in the United States. The 7-valent pneumococcal conjugated vaccine (PCV7) Prevnar® (Wyeth Pharmaceuticals, Philadelphia, Pa.) is licensed by the FDA for children 9 years of age and younger. The 23-valent pneumococcal polysaccharide vaccine (PPV23) Pneumovax® 23 (Merck & Co, Inc) is licensed for individuals ages 2 years and older. PPV23 is made from purified capsular polysaccharides from the 23 most common pneumococcal serotypes in the United States, which account for 85% to 90% of invasive pneumococcal infections in the United States. The antigen-specific antibody response develops 2 to 3 weeks following vaccination in more than 80% of healthy young adults, but may be diminished or absent in individuals who have cirrhosis, type 1 diabetes, or chronic obstructive pulmonary disease or those who are immunocompromised. The concentrations of antibody remain elevated for at least 5 years in healthy individuals, but may decline within 3 to 5 years in children who have sickle cell disease or nephrotic syndrome or who have undergone a splenectomy. Serotype-specific antibodies are known to decrease after 5 to 10 years, with some serotypes declining more rapidly than others.

A single dose of the PPV23 vaccine is recommended for those who are at least 2 years of age and are at an increased risk for invasive disease or complications from pneumococcal infections.
repeat vaccine if it has been more than 5 years since the previous dose. If the vaccine status in those individuals is unknown, they should receive the vaccine, as well.

**Polio**

Immunization against the poliovirus is one of the great successes of vaccination, with no indigenously acquired wild-type polio infections reported in the United States since 1979. Poliovirus, a member of the enterovirus family, perhaps is best known for causing a rapid onset of symmetric acute flaccid paralysis with areflexia.

In the United States, the inactivated poliovirus vaccine (IPV) is the only available polio vaccine. This vaccine, administered intramuscularly or subcutaneously, contains three types of inactivated poliovirus. Four doses should be administered in childhood, and catch-up is recommended for all adolescents not completely immunized. If an adolescent received a combination of IPV and oral poliovirus vaccine (OPV) previously, he or she requires four doses total of polio vaccine. However, if the previous doses were either all IPV or all OPV and the third dose was given at age 4 years or older, only three doses total are required. The seroconversion after two doses of IPV is greater than 95%; after three doses, it is 99% to 100%. Immunity is prolonged, perhaps life-long.

**Conclusions**

Since the development of the smallpox vaccine in the late 18th century, millions of lives have been saved from serious infection by vaccinations. Immunizations today have the potential to continue to decrease both morbidity and mortality from a multitude of diseases. New vaccines provide new opportunities for prevention. Therefore, it is vital for clinicians to stay up-to-date regarding the latest additions to the vaccination schedule.

**ACKNOWLEDGMENTS.** The authors would like to express their gratitude to Dr Mark Pasternack for his careful review of this article.

**Suggested Reading**


PIR Quiz
Quiz also available online at www.pedsinreview.aappublications.org.

6. The currently available HPV vaccine:
   A. Attenuates carcinogenic risk related to pre-existing HPV infections.
   B. Is a live virus vaccine.
   C. Is contraindicated if the patient has a history of anaphylaxis to eggs.
   D. May be given to sexually active females.
   E. Protects against acquisition of all known HPV virus types.

7. The two available vaccines against *N meningitidis*, MPSV4 and MCV4, differ in:
   A. Acceptability for use among adolescents during outbreaks of serogroup A disease.
   B. Short-term immunity they produce.
   C. The degree of herd immunity they offer.
   D. The nonserogroup B strains of *N meningitidis* they cover.
   E. Their coverage of *N meningitidis* serogroup B.

8. In place of a Td booster dose, Tdap vaccine now is recommended routinely for children 11 years of age and older because:
   A. Added acellular pertussis components induce more reliable levels of immunity against respiratory diphtheria.
   B. Added acellular pertussis components induce more reliable levels of immunity against tetanus.
   C. It enhances the immune response to concomitantly administered MCV4.
   D. Pertussis outbreaks are common among adolescents.
   E. Unlike DTaP, it can be administered to individuals who have pertussis vaccine-related encephalopathy.

9. Influenza vaccine now is recommended for routine administration in adolescents. The inactivated and live virus influenza vaccines differ with respect to:
   A. Suitability for patients who have a history of anaphylaxis to eggs.
   B. The need for annual immunization.
   C. The number of doses required for adolescents.
   D. The strains of influenza they cover.
   E. Their use in high-risk groups.

10. Contraindications to immunization exist for all of the available live attenuated vaccines (influenza, measles, mumps, rubella, and varicella). Which of the following contraindications to immunization is shared by all of the live attenuated vaccines?
    A. History of allergy to latex.
    B. History of anaphylaxis to eggs.
    C. History of anaphylaxis to neomycin or gelatin.
    D. History of Guillain–Barré syndrome.
    E. Possible or known immunodeficiency.
Objectives  After completing this article, readers should be able to:
1. Define cultural competence.
2. Explain the need for cultural competence.
3. Describe the changing child demographics of the United States.
4. Discuss the process of becoming a more culturally competent clinician.
5. Review tools and techniques that help achieve cultural competence.

Introduction
Some have suggested that cultural competence cannot be taught or learned and that some clinicians are just more sensitive than others when it comes to issues of cultural differences. Indeed, in some instances, we preach to the choir, if you will, regarding attitudes toward cultural competence. However, certain skills can be imparted to help all clinicians, regardless of their attitudes. As Dr Joseph Betancourt concludes, we would not accept substandard competence in other areas of clinical medicine, and cultural competence should not be an exception. (1)

Certain skills can be acquired, practiced, and honed on the journey of becoming a more culturally competent clinician. This article reviews the evolution and benefits of cultural competence in pediatric practice and gives examples of questions that can be asked to provide more comprehensive care to the patient and his or her family.

Cultural competence can be assessed via several methods. For example, evaluations or satisfaction surveys from patients, families, and staff, otherwise known as 360-degree evaluations, in a busy pediatric practice can provide useful feedback that prompts change in behavior. Observation, one of the best tools for evaluating clinician behavior, can be performed by using either standardized or real patients. Observed role-playing with standardized patients can provide clinicians with formative feedback to improve their interviewing skills. Observation of interactions with actual patients or unidentified standardized patients, similar to the observation model used in education, captures actual clinician behavior when functioning under pressure.

The Landscape
The Institute of Medicine issued its landmark report about health disparities in 2002, referencing inequities in adult health-care services. Pediatrics is a part of the health disparities landscape, with many health outcomes being complicated by childhood poverty. Classic examples of pediatric health disparities include differences in immunization status, care of asthma, and prevalence of teen pregnancy. Although the terms “health disparities” and “cultural competence” often are used interchangeably, cultural competence is one vehicle, along with increased access, insurance coverage, and others, that can improve health outcomes through improved communication and increased trust and understanding between patient and clinician.

What is Cultural Competence?
Culture is defined as patterns of human behavior inherent in the lives of a racial, ethnic, religious, or social group. Some social groups can be defined by age, generation, ability, body image, and mental illness, for example. Characteristic behaviors can include...
thoughts, language, customs, beliefs, and institutions. For example, adolescents are their own culture (subculture), characterized by how they communicate, how they wear their clothes, the types of music to which they listen, and what they value.

Some of the variance across cultural groups can be affected by immigration, family structure, educational attainment, and socioeconomic status. The importance of educational attainment as an influence on socioeconomic status cannot be overstated and is highly predictive of health outcomes for children.

Cultural competence, therefore, is an acknowledgment and incorporation of the importance of culture, assessment of cross-cultural relations, vigilance toward the dynamics that result from cultural differences, expansion of cultural knowledge, and adaptation of services to meet culturally unique needs on the part of clinicians and health-care systems. Some clinicians state that they interact with all patients in the same manner. Indeed, being culturally competent implies that clinicians not treat patients the same, given the cultural dynamics each brings to the encounter.

Cultural competence is a concept that has come to medicine slowly, although it has been discussed in the nursing and psychology literature extensively. Cultural competence terminologies have evolved over the past 2 decades from cultural awareness to cultural sensitivity to cultural competence. Other terms, such as cultural effectiveness and cultural humility, are used currently. Regardless of the term used, the principles of cultural competence may be recognized most often when they are absent. These principles include empathy, curiosity, and respect, with which comes a heightened understanding and appreciation of the social context of the patient.

The term cultural competence is used in this article because it is a familiar term to most clinicians, although it falsely implies that some endpoint can be reached. The exact opposite is true, however; no one ever becomes “competent.” Cultural competence is a process, built upon by asking questions of the patient, family, and oneself.

**Why is Cultural Competence Timely and Crucial?**

Clinicians today are practicing in the midst of a rapid change in the demographics of the pediatric population of the United States. New York is one of several states that has stood apart in terms of patterns of immigration over the past century. The immigrant child population is the fastest growing portion of the child population. In contrast to the white European and English-speaking immigrant populations that migrated to the United States in the early 20th century, families from the Caribbean, Africa, and Asia constitute significant immigrant groups today.

Noteworthy is the growing Hispanic population. Immigrants from Mexico and Central America who are settling and raising their families in the United States, similar to other immigrants, are looking for greater economic opportunities or seeking safety from the conflict of war. It is estimated that by the year 2020, Hispanic adolescents will constitute the largest minority youth population and that approximately 40% of all youth will belong to a minority group.

Given the change in the cultural makeup of the United States, clinicians are being challenged as never before to provide cross-cultural care that is sensitive, effective, and able to meet the needs of the patient and family. Cross-cultural care requires that clinicians be open and seek to understand the various dynamics of the patient-clinician encounter, such as variations in the perception of illness, diverse belief systems around health, differences in help-seeking behaviors, and preferences in approaches to health care. Therefore, cultural competence is not a question of “doing the right thing.” Rather, it is an important vehicle for achieving patient satisfaction, patient safety, and improved health outcomes.

**The Cultural Divide**

One of the first challenges in achieving culturally competent practice is acknowledgment that medicine is its own culture, often at odds with the cultural orientation of patients. Western medicine puts a high priority on concepts such as individualism, emphasizing that the individual has control over his or her health. Western medicine also endorses the following: diseases have specific causes, there is one system of care to address the disease, and patients adapt to the system. Pediatric clinicians may have particular assumptions about family dynamics and how families mobilize on behalf of their children to make health-care decisions.

In contrast to the culture of Western medicine, patients’ cultural norms may demonstrate more community than individual orientation, conceptualize circumstances as being beyond their control, see disease as a result of misfortune or imbalance, and use other treatments in combination with or to the exclusion of Western medicine. To bridge this gap, the onus is on the clinician to ask questions that uncover such orientations to health and illness so they can be integrated into the
c caretaking of the patient and family and negotiated, if possible, when making health-care decisions.

What Does It Take to be a Culturally Competent Clinician?
As mentioned, cultural competence involves empathy, curiosity, and respect. Although being aware of the history, health beliefs, and practices of a particular cultural group can provide a foundation for understanding, such knowledge must be balanced carefully to avoid stereotyping and to accommodate diversity within groups. Resources such as Working with an Interpreter: Stronger Outcomes Tips at www.massgeneral.org/interpreters/working.asp and additional sites (listed at the end of the article) cover general information regarding various racial and ethnic groups. In addition to these broad guidelines, there is an important role for asking questions to acknowledge and create deeper understanding of how the many layers of culture interact within the individual patient and family to influence health care.

Before beginning the process of engaging with the patient, clinicians must have an idea of their own sensibilities, an awareness that comes with self-reflection. Five key goals should be sought in this process of becoming culturally competent:

- The first is the capacity for being self-aware. In other words, are we aware and mindful of our own cultural beliefs, values, and behaviors? How do these factors affect our interactions with patients? If we cannot manage our biases for the sake of the patient, do we recognize that limitation and defer to a colleague? A classic example is counseling about reproductive health choices, including abortion. If such counseling is not congruent with a clinician’s beliefs, he or she should help direct the patient to someone who can do such counseling.

- The second goal is being aware and accepting of cultural differences. This mindset is self-explanatory and implies developing a value for diversity.

- The third goal is understanding the dynamics of difference. This is particularly important for physicians, given the power bestowed on them by titles, white coats, and other attributes. If we believe in a particular treatment for a patient and the patient does not agree, based on cultural difference, because of our sense of power, we may not respect and work with that difference.

- The fourth goal is assessing our own cultural knowledge. Such knowledge is shaped by interacting and integrating lessons learned from colleagues and patients with whom we interact. We also should be aware of our limits and know when to ask for help with particular populations with whom we may be less familiar to determine core principles for a particular culture.

- Finally, a culturally competent clinician must be able to adapt to diversity. How do we adapt to the needs and preferences of our patients? Are we open to different approaches to the same problem?

The Surprises and Challenges of Cross-Cultural Communication
Cultural competence is not only an orientation to employ when the patient speaks a different language or looks different from the clinician; it should be engaged with every patient. Some of the most surprising instances of cultural “disconnects” occur with patients and families who look like their clinicians. Regardless of shared race, ethnicity, or cultural identification, we may not have the same values, perspectives, or choices as our patients.

Given the challenges in everyday practices, how do clinicians negotiate across cultures with families? First steps are to recognize individual biases in a particular situation. Are we able to sidestep the bias or do we need to refer? If we can sidestep the bias, how do we create time and space to reassess that bias and its origin? How do we organize these efforts for the office team? With self-reflection, can we change how we engage with patients and families?

What are the Key Questions We Need to Ask?
Exploring the Meaning of Illness
Patients may hesitate to offer their beliefs and fears, which can be overcome through respectful questioning (Table 1). Clinicians can save time during the encounter by having the patient help set the agenda for the visit and, therefore, meet his or her needs. Bridging a gap by recognizing the role of complementary and alternative medicine may shed more light on a patient’s explanatory model for health or illness. The next three examples, all of which are real, are designed to highlight how asking or not asking such questions can help or hinder a patient-clinician interaction.

A 17-year-old African American girl comes in for a scheduled health supervision visit. While performing a psychosocial assessment, you note that she appears agitated. After some time, she states that she wants oral contraceptives.

This is a case of asynchronous agendas. The patient’s agenda was very well-defined, basically to avoid becoming...
Table 1. Exploring the Meaning of Illness

Explanatory Model

- What do you think has caused your problem? What do you call it?
- Why do you think it started when it did?
- How does it affect your life?
- How severe is it? What worries you the most?
- What kind of treatment do you think would work?

The Patient’s Agenda

- How can I be most helpful to you?
- What is most important for you?

Illness Behavior

- Have you seen anyone else about this problem besides a “physician”?
- Have you used nonmedical remedies or treatment for your problem?
- Who advises you about your health?


*Note: Any clinician can be referenced here, that is, nurse practitioner, physician’s assistant, nurse, etc.

open the door to a comprehensive conversation about how patients help themselves.

Such an approach also gave the clinician a sense of the family’s interest in complementary and alternative medicines, demonstrated the clinician’s openness to such considerations, and allowed the clinician to steer them toward appropriate alternative treatments. Some of the therapies that were proposed and accepted by the family included melatonin=valerian root for sleep disturbance, peppermint for stomach upset, and yoga for general conditioning. Also, continued biofeedback therapy, in which the family already was engaged, was encouraged. Asking about and coordinating care with complementary and alternative medicine clinicians or traditional healers in the community can be validating to a family and encourage a nonmutually exclusive approach to a health condition.

A Chinese father brings in his 9-month-old son for a health supervision visit. The baby has been doing well, but the baby’s grandparents have been pressuring the father to start feeding the child eggs. The clinician summarily tells the father that eggs are not recommended until 12 months of age because of the risk of food allergies. She suggests that the father use her as the scapegoat with the grandparents for adhering to this recommendation.

This case encompasses the issue of who advises parents about their child’s health. Although pediatric clinicians see themselves as the pillars of prevention and health, many other influences affect the daily lives of children, such as grandparents. In this case, the clinician missed an opportunity to inquire about the cultural importance of eggs to this Chinese family’s diet. Questions such as “Tell me why this is important to you and your family” open a dialogue to increase understanding of a family’s explanatory model for health. Instead, this clinician closed the conversation with no guarantee that the father is in agreement with the recommendation or that the father will disclose the family’s health beliefs in the future.

Social Context “Review of Systems”

The social context of patients can affect their health and presentations. Poverty is one of the most significant barriers to health and access to health care. Table 2 highlights questions regarding resources, change in environment, social supports, and literacy, which can open the dialogue. Understanding of such social factors can increase the clinician’s appreciation of the challenges encountered by patients and compensate for them in counseling and treatment. The following four actual patient cases demonstrate this focus.
A 7-year-old boy has just been diagnosed as having attention-deficit/hyperactivity disorder. His mother is eager to have him on medication because of the pressure she is getting from his school. Unfortunately, she has switched jobs and is in between insurance plans. The out-of-pocket cost for a 30-day supply of stimulant medication would be $200 for the month between this visit and when the mother might have her new insurance plan.

The clinician in this case was able to determine that finances were an issue for this family and would affect the family’s ability to purchase medication. In light of this situation, frank discussion of how much the family could afford was possible. The mother agreed to the idea of purchasing the medication for 2 weeks until she met her next pay period. The ability to consult social workers or community health workers who can perform outreach to a family can increase access to services as well as increase understanding of the challenges families may face.

A 12-year-old girl who has sickle cell disease and emigrated from Jamaica is having adjustment reaction issues and conflict with her mother. The mother, who now is an illegal alien, has had a dramatic change in her earning potential compared with their middle class lifestyle in Jamaica. The family emigrated for better health care for the girl.

As is common for many immigrant children, this patient was between two worlds. She was mourning the loss of the life she had in Jamaica while being confronted daily with the unpredictability of her family life in a new country. Her mother had to work jobs that paid “under the table,” which sometimes meant that her mother needed to move away for months at a time, leaving the patient with other family members. Questions such as “Tell me what brought you to this country” and “What was life like for you in your country?” elicit information about place and family of origin, changes in socioeconomic status, and acculturation. As in this case, just letting the patient/family tell their story can answer many critical questions.

A 19-year-old African American man is dealing with the second recurrence of his cancer. He is admitted to the hospital. Both parents are vigilant and at the bedside. Various family and church members come to pray for him. The number of visitors becomes more of an issue as the patient develops neutropenia and requires isolation.

It was clear that this family’s spirituality was very important. They were connected to their church and appreciated the prayers that the congregation had said for them. Spirituality also was important to this young man. He had taken on many active roles in the church, including maintaining the church property and helping some of the more elderly parishioners. These parishioners, in turn, visited him for the sake of laying on of hands to facilitate prayer and healing of the patient. Questions such as “Who is your support?” would uncover this family’s religious beliefs and connectedness to their church community. This understanding also would help anticipate the expectations of the patient and family about visitation.

An 8-year-old boy and his 6-year-old sister are brought to the doctor’s office for rashes. Their mother is from Puerto Rico; the family moved to the United States several years ago for better economic opportunities. The mother speaks Spanish only. There is no interpreter, but the clinician attempts to communicate with the patient.

Every patient has the right to be understood. This was

<table>
<thead>
<tr>
<th>Table 2. Social Context “Review of Systems”</th>
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</thead>
<tbody>
<tr>
<td><strong>Control Over Environment</strong></td>
</tr>
<tr>
<td>• Is money a big problem in your life? Are you ever short of food or clothing?</td>
</tr>
<tr>
<td>• How do you keep track of appointments? Are you more concerned about how your health affects you right now or how it might affect you in the future?</td>
</tr>
<tr>
<td><strong>Change in Environment</strong></td>
</tr>
<tr>
<td>• What is your country (city, town) of origin?</td>
</tr>
<tr>
<td>• What made you decide to come to this country (city, town)? When did you come?</td>
</tr>
<tr>
<td>• How have you found life here compared with life in your country (city, town)? What was medical care like there compared with here?</td>
</tr>
<tr>
<td><strong>Social Stressors and Support Network</strong></td>
</tr>
<tr>
<td>• What is causing the most difficulty or stress in your life? How do you deal with this?</td>
</tr>
<tr>
<td>• Do you have friends or relatives on whom you can call for help? Who are they? Do they live close to you?</td>
</tr>
<tr>
<td>• Are you very involved in a religious or social group? Do you feel that God (or a higher power) provides a strong source of support in your life?</td>
</tr>
<tr>
<td><strong>Literacy and Language</strong></td>
</tr>
<tr>
<td>• Do you have trouble reading your medication bottles or appointment slips?</td>
</tr>
<tr>
<td>• What language do you speak at home? Do you ever feel that you have difficulty communicating everything you want to say to the doctor or staff?</td>
</tr>
</tbody>
</table>

a very awkward situation, in which the clinician did not speak much Spanish and, instead, was gesticulating and speaking loudly to make his points. The mother was concerned, and it was not clear by the end of the encounter that she understood the diagnosis, the treatments, or how the treatments were to be used. This situation creates the possibility for medical error. Knowing the language the patient speaks, preferably before the visit, allows for planning to have an interpreter present and develops a working scheme with the interpreter. The use of family members as interpreters should be avoided, despite being convenient. Family interpreters may not be able to interpret medical terminology and may hinder open communication knowingly or unknowingly.

This was a case of language being a barrier, but literacy can be a barrier in any language and should be considered when counseling and giving patient instructions. In those cases, use of diagrams and concrete language can help overcome the barrier.

Cross-Cultural Negotiation

Part of a clinician’s responsibility during a patient encounter is negotiation of a treatment plan. This final case exemplifies differences in explanatory models for illness, the influence of family members, and the need to bridge the gap. Table 3 includes action steps to create shared understanding and agreement or, at the very least, an acknowledgment of clinicians’ and families’ boundaries.

A 5-year-old African American boy who has sickle cell disease is not taking his prophylactic medications. His mother thought the medications made him sick because once he stopped taking them, he had no further hospitalizations for his painful crises. When the clinician encourages the mother to reconsider her son’s prophylactic medications, she hesitates to decide without the input of her own mother, the child’s grandmother. A family meeting is arranged.

The mother’s explanatory model was that the prophylactic medications used for sickle cell disease brought on the pain crises. Therefore, the family did not give the patient the medications to avoid this perceived consequence. Fortuitously, the patient did not have pain crises during that period of being off the medication, which reinforced the explanatory model.

The mother was not comfortable making a decision about medications for her child without her own mother’s input and approval. The maternal grandmother had an important role in terms of brokering power around medical decision-making. She also was a caregiver for the child and would be the primary person responsible for administering his medications.

The family meeting gave the medical team a chance to re-explore with the family their conceptualization of how sickle cell disease works and to reorient these concepts within the biomedical framework. All family members present agreed to restart the prophylactic medications. The team would not have made progress with the non-adherence issues without involving the maternal grandmother very early in the negotiation process.

This case was unhindered by real conflict, time pressure, or imminent health risk. Difficult negotiations often are characterized by apparent adherence to absolutes on the part of clinician, patient, family, or all parties. Even what appears to be absolute can be relative and leave room for negotiation and compromise. Involving a family’s traditional healer or religious or community leader also can help broker a difficult negotiation.

At the Systems Level

Cultural competence interventions also can exist at the systems level. Hiring practices of clinicians and office staff can demonstrate value for diversity. Physicians can support cultural competence training of office staff to enhance the quality of care provided at every point of the
patient encounter. Educational materials and posters on display can have diverse models and be in different languages. Techniques such as culturally competent health promotion, interpreter services, training, and accommodations such as allowing time and space for self-reflection by all staff can communicate a value for diversity within the practice or service.

Summary

Cultural competence is needed in pediatrics, especially in light of the ever-changing childhood demographics of the United States. Becoming a culturally competent clinician requires the fundamental attitudes of empathy, curiosity, and respect that are constantly being reshaped by self-reflection. Clinicians can develop their skills in cultural competence by incorporating questions about the meaning of illness, performing a “review of systems” within a social context, and negotiating explanatory models and treatments into their interviews with all patients. Diversifying staff and ensuring that the office environment and protocols are inclusive and respectful of other cultures can solidify a commitment to culturally competent practice.

Reference


Suggested Reading


Web Sites

Culture Clues™ at: http://depts.washington.edu/pfcs/cultureclues.html
CulturedMed at: http://culturedmed.sunyit.edu/
DiversityRx at: www.diversityrx.org/
The Manager’s Electronic Resource Center at: http://ethnomed.org/
National Center for Cultural Competence at: http://www11.georgetown.edu/research/gucchd/nccc/
Resources for Medical Education on the Provision of Culturally Effective Care at: http://www.aap.org/visit/CEPC_resources_COPE_7-16-08.xls
Working with an Interpreter: Stronger Outcomes Tips at: www.massgeneral.org/interpreters/working.asp

Evaluation Tools

Cultural Competence Health Practitioner Assessment at http://www11.georgetown.edu/research/gucchd/nccc/resources/index.html
Cultural Competency Organizational Assessment – 360 (COA 360) at http://apps22.jhsph.edu/coa360/
PIR Quiz

Quiz also available online at www.pedsinreview.aappublications.org.

11. Which of the following is the behavior that best represents cultural competence?
   A. Acknowledging and addressing the importance of patients’ culture in their care.
   B. Interacting with all patients in the same manner despite their culture.
   C. Involving family members in all aspects of a patient’s care.
   D. Knowing all of the cultural beliefs of the patients in one’s practice.
   E. Learning to speak the languages of all the patients in one’s practice.

12. You are seeing a 13-year-old Central American girl for the first time. She has just moved to your area and is in your office for a health supervision visit. Her 18-year-old brother accompanies her. They both speak somewhat limited English, but they seem to be able to communicate with you. She defers most questions to her brother, who denies that she has any past health problems. Which of the following is the most important initial step to ensure treating this girl in a culturally sensitive manner?
   A. Ask her brother to leave the examination room so you can interview her privately.
   B. Consider your own beliefs about yourself and biases toward others’ cultures.
   C. Immediately ask an interpreter to sit in on the interview.
   D. Refer her to a Hispanic colleague in your practice.
   E. Speak primarily to her brother during the interview because she seems to defer to him.

13. You are evaluating an African American adolescent who has asthma. She has come to you because she has had several days of cough and shortness of breath. She stopped taking her inhaled corticosteroid several months ago. She has missed more than 10 days of school this semester for asthma-related complaints. Which of the following questions is the most effective to begin to evaluate the impact of this girl’s culture and beliefs on her asthma?
   A. Do any of your family members also have asthma?
   B. Do you feel more short of breath when you exercise?
   C. Was there a particular reason you stopped taking your medicine?
   D. What kind of grades do you make at school?
   E. Who do you live with at home?

14. A 14-year-old Hispanic girl who has a history of systemic lupus erythematosus (SLE) is admitted to the hospital because of nephritis. She has received multiple medications for the SLE in the past, but she only takes occasional ibuprofen for pain because the other medications “make her sick.” She is fluent in English, but her mother, with whom she lives, only speaks Spanish. Which of the following is the least effective culturally competent approach to this patient?
   A. Ask her what exactly happens when she takes her other medications.
   B. Determine what effect her SLE has on her daily lifestyle.
   C. Explain the consequences of SLE and the importance of being compliant with medications.
   D. Find out whether she has taken complementary or alternative therapies.
   E. Obtain an interpreter for her mother so the girl does not have to act as translator.
The reader is encouraged to write possible diagnoses for each case before turning to the discussion. We invite readers to contribute case presentations and discussions. Please inquire first by contacting Dr. Deepak Kamat at dkamat@med.wayne.edu.

Author Disclosure
Drs Wells Collins, Piebenga, Toth, Fish, Dueker, Sadiq, and Wolff and Ms Shaw have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

**Frequently Used Abbreviations**

- ALT: alanine aminotransferase
- AST: aspartate aminotransferase
- BUN: blood urea nitrogen
- CBC: complete blood count
- CNS: central nervous system
- CSF: cerebrospinal fluid
- CT: computed tomography
- ECG: electrocardiography
- ED: emergency department
- EEG: electroencephalography
- ESR: erythrocyte sedimentation rate
- GI: gastrointestinal
- GU: genitourinary
- Hct: hematocrit
- Hgb: hemoglobin
- MRI: magnetic resonance imaging
- WBC: white blood cell

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**Case 1 Presentation**

A 16-year-old girl presents to the ED with persistent fever and headache for 9 days. She was previously healthy except for a tooth extraction 3 weeks ago, for which she received penicillin. She denies shortness of breath, visual changes, vomiting, diarrhea, palpitations, joint pain, weight loss, cough, or urinary symptoms. She had been seen repeatedly in the ED and had normal examination findings and unremarkable CBC, CSF analysis, and urinalysis. She was given intramuscular ceftriaxone and sent home with a prescription for oral azithromycin. After returning to the ED today, she is admitted.

Physical examination shows a temperature of 102.2°F (39.0°C), heart rate of 120 beats/min, respiratory rate of 18 breaths/min, and blood pressure of 103/71 mm Hg. Auscultation of the heart reveals a mid-systolic click followed by a 2/6 crescendo-decrescendo murmur. Her WBC count is $11.0 \times 10^3/\mu\text{L}$ (11.0 $10^3/\mu\text{L}$) with 27% bands. Chest radiography demonstrates normal findings. A blood culture that had been obtained during a previous ED visit grew *Streptococcus viridans*. Subsequently, multiple blood cultures continued to grow *S viridans*. Trans-thoracic echocardiography showed no evidence of vegetations but did show a small pericardial effusion and mitral valve prolapse.

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**Case 2 Presentation**

A 15-year-old girl presents to a New England ED in early October with a 1-day history of headache. She states that the headache is bitemporal and accompanied by neck pain, myalgias, fever, and vomiting. The teenager relates that her pediatrician recently diagnosed her with migraines, but this headache is worse than any she has had before. She denies any history of trauma, recent illness, or travel. She lives in an urban neighborhood and does not take walks through wooded areas or remember being bitten by a mosquito or tick recently. She has no pets and is an only child.

Physical examination reveals an uncomfortable adolescent girl who has complaints of a headache and photophobia but is cooperative, alert, and answering questions appropriately. Her temperature is 99.2°F (37.4°C), heart rate is 95 beats/min, respiratory rate is 16 breaths/min, and blood pressure is 110/66 mm Hg. There are no signs of trauma, mental status change, or increased intracranial pressure and no lymphadenopathy. A complete neurologic examination shows no focal deficits. She does have nuchal rigidity, but Kernig and Brudzinsky signs are negative. No rashes are apparent.

Laboratory results show a normal CBC and electrolytes. CSF analysis reveals 210 red blood cells/high-power field (hpf) and 780 white blood cells/hpf with 4% neutrophils, 92% lymphocytes, and 4% monocytes. The CSF glucose is 48 mg/dL and protein is 88 mg/dL. Head CT scan is read as normal. Additional history and a subsequent laboratory finding confirm her diagnosis.

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**Case 3 Presentation**

A 6-month-old girl presents to the ED with irritability, vomiting, and a mildly reddened right eye. The infant was well in the morning, and her parents left her unattended in her playpen. However, she developed the manifestations several hours after they left her in the playpen.
Physical examination reveals a right eye hyphema completely filling the anterior chamber and an intraocular pressure (IOP) in the high 70s by portable tonometry (normal IOP for most adult patients is less than 21 and slightly less in pediatric patients). The left eye pressure is normal. External eye examination reveals no evidence of trauma. The right pupil cannot be seen directly; the left pupil shows no relative afferent pupillary defect. Dilated fundus examination is deferred to monitor the patient’s pupillary response in the setting of elevated IOP. The patient is admitted for acute management aimed at treating the hyphema and determining the underlying cause.

Case 1 Discussion
The differential diagnosis for the presenting symptoms of prolonged fever with headache may include bacterial and aseptic meningitis as well as encephalitis. However, the physical findings and the predisposing dental extraction for this patient make infective endocarditis (IE) a likely diagnosis, despite the absence of a previous history of cardiac problems. Myocarditis and pericarditis also could be considered, based on the new murmur and effusion. Despite intravenous antibiotics, the patient continued to exhibit fever and positive blood cultures. Transesophageal echocardiography showed a pedunculated atrial mass between the posterior mitral leaflet and the left atrial appendage. Ultimately, the mass was considered to be an infected vegetation because intralesional culture grew gram-positive cocci, although the organisms never were speciated. Because of its size, cardiothoracic surgery was consulted for its removal. The patient was sent home to complete 6 weeks of intravenous antibiotic therapy.

The Condition
The diagnosis of IE is based on a constellation of clinical findings. The diagnosis can be obvious in the presence of persistently positive blood cultures with a predisposing cardiac lesion. A careful cardiac examination looking for signs of a new regurgitant murmur or heart failure is critical. Other stigmata of endocarditis include evidence of emboli to the fundi, skin, digits, or conjunctivae. Additional organ systems may be affected by emboli, including the kidneys, spleen, and brain.

The Duke criteria are used to diagnose IE. These include demonstration of microorganisms either by culture or histology in a vegetation, a vegetation that has emolized, an intracardiac abscess, or a lesion showing evidence of active endocarditis.

The clinical criteria require two major, one major and three minor, or five minor criteria. The first of the three major criteria is a positive blood culture with typical organisms for IE from two separate blood cultures OR persistently positive blood cultures (cultures drawn more than 12 hours apart) OR three or more positive blood cultures, with the first and last ones drawn at least 1 hour apart, OR a single positive blood culture for Coxiella burnetti or serologic evidence of C burnetti (titer >1:800). The typical organisms for IE include Streptococcus viridans, S bovis, HACEK group (Haemophilus sp, Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella sp, and Kingella kingae), and Staphylococcus aureus. The other two major criteria are positive echocardiography for IE and new valvular regurgitation.

Minor criteria include: 1) predisposition; 2) fever; 3) vascular phenomena (arterial emboli, septic pulmonary infarctions, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, Janeway lesions); 4) immunologic phenomena such as glomerulonephritis, Osler nodes, Roth spots, and rheumatoid factor; and 5) single positive blood culture or serologic evidence of active infection with an organism consistent with IE.

This patient developed IE despite receiving penicillin before her dental procedure. The validity of the underlying principle that antimicrobial prophylaxis is effective in humans for prevention of IE associated with dental, GI, or GU tract procedures is questionable. Although recent studies show that prophylactic amoxicillin reduces the incidence, nature, and duration of bacteremia from dental procedures, no studies have shown that such a reduction decreases the risk of or prevents IE. IE is more likely to be caused by frequent exposure to random bacteremias in everyday life. This is the primary principle guiding the development of revised American Heart Association (AHA) guidelines that no longer suggest prophylaxis for mitral valve prolapse.

The new guidelines limit prophylaxis to cardiac conditions that have the highest risk of poor outcome from IE. The current indications for prophylaxis include only 1) prosthetic heart valves, 2) previous IE, 3) un repaired cyanotic heart disease that includes palliative shunts and conduits, 4) completely repaired congenital heart disease with pros-
Risk.

considered individually in terms of population. Each patient should be of prophylaxis in the moderate-risk will take time, given the previous use nonallergic patients.

cephalosporins are recommended in or first- or second-generation oral new guidelines. In general, ampicillin tions and dosages are provided in the tissue of skin or musculoskeleton.

and surgical procedures on infected nary tract infection or colonization, trhal dilation with enterococcal uri-ceptible than others to developing IE. It is increas-ingly clear that IE may not be due to bacteremia seen after dental or other invasive procedures and, therefore, the routine use of prophylactic antibiot-ics, although possibly reducing the incidence of bacteremia, does not necessarily reduce the risk of IE. Pa-tients who fall into the high-risk cate-gory, however, still must receive prophylactic antibiotics because their cardiac disease makes them more sus-ceptible than others to developing IE during episodes of bacteremia. Fi-nally, given the move toward de creased use of prophylactic antibiot-ics in patients who have cardiac disease, it is imperative that clinicians use good judgment when assessing a patient who has prolonged fever with or without a history of cardiac abnor-malities. (Shelley Wells Collins, MD, The Congenital Heart Center, University of Florida, Gainesville, Fla.)

Prophylactic antibiotic medica-
tions and dosages are provided in the new guidelines. In general, ampicillin or first- or second-generation oral cephalosporins are recommended in nonallergic patients.

Comfort with the new guidelines will take time, given the previous use of prophylaxis in the moderate-risk population. Each patient should be considered individually in terms of risk.

Treatment
Antimicrobial therapy for IE should be administered in a dose designed to provide sustained bactericidal serum concentrations throughout the entire dosing interval. The minimum inhibitory concentration should be determined for all patients. The duration of intravenous antimicrobial therapy is approximately 4 to 6 weeks.

Lessons for the Clinician
A careful examination of this patient would have led to the clinical diagno-sis of mitral valve prolapse that would have raised the index of suspicion regarding endocarditis as a possible diagnosis. Transthoracic echocardiography may not be sufficiently sen-sitive to identify vegetations; trans-esophageal echocardiography may be needed to diagnose IE. It is increas-ingly clear that IE may not be due to bacteremia seen after dental or other invasive procedures and, therefore, the routine use of prophylactic antibiotics, although possibly reducing the incidence of bacteremia, does not necessarily reduce the risk of IE. Pa-
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malities. (Shelley Wells Collins, MD, The Congenital Heart Center, University of Florida, Gainesville, Fla.)

Case 2 Discussion
On admission, ceftriaxone was ad-
ministered for potential bacterial meningitis and a CSF specimen was sent for Gram stain and bacterial cul-
ture. Gram stain was negative for bacteria. On further questioning, she revealed a prior presentation 6 days earlier to a women’s clinic with a bump and some painful sores around her vulva. Viral cultures were positive for herpes simplex virus type 2 (HSV2) on the day of her admission. By then, her vulvar lesions had healed. Additional HSV polymerase chain reaction (PCR) testing was conducted on her CSF. She was started on 1 g valacyclovir by mouth twice daily. Bacterial cultures of her CSF were negative after 48 hours, and the antibiotics were discontin-
ued. The PCR on CSF was positive on hospital day 3 for HSV2, confirm-
ing the diagnosis of HSV2 menin-
gitis. By that time, her neck pain, headache, and fever had resolved completely. Her neurologic exami-
nation results were normal, and she was discharged from the hospital with a prescription for valacyclovir to complete a total of 7 days.

Approach to the Patient
The girl in this case presented with severe headache, photophobia, nu-
chal rigidity, and neck pain. The ini-
tial history taking for this presenta-
tion must include age-appropriate questions, such as sexual history in a teenager, and previous medical and surgical encounters. Herpetic CNS disease may have been suspected ear-
ier in her course had these questions been asked. Also, history and exami-
nation of the patient must focus on differentiating between diseases such as bacterial meningitis or HSV1 en-

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meningitis, which are associated with significant morbidity and mortality and require prompt treatment, and self-limited processes such as the aseptic viral meningitis.

In this case, the patient exhibited no signs of mental status change and had a normal head CT scan, which made the diagnosis of meningitis more likely than one of an encephalitis, mass, or hemorrhage. Initial CSF analysis suggested a viral rather than bacterial source, and she presented at a time of year typical for enteroviral infection, which causes more than 75% of viral meningitis cases. Only a careful later history, including sexual history, and full physical and neurologic examinations pointed the clinician toward HSV2 infection as a possible cause of her symptoms. Although the use of acyclovir may be effective in the treatment of herpetic encephalitis, it may only decrease viral shedding or shorten the duration of symptoms in herpetic meningitis. Thus, treatment for herpes meningitis, like most viral meningitis, is primarily supportive.

The Condition
Although genetically very similar, the two HSVs tend to cause very different diseases. HSV infection in the neonate usually is caused by HSV2 transmitted from mother to child during delivery. It can present with skin, eye, and mouth vesicles; lethargy; poor feeding; or irritability. These findings signify meningitis/encephalitis or multiple organ system failure in the case of disseminated disease. In older children and adults, HSV2 causes oral and genital lesions as well as a self-limited, lymphocytic meningitis. In fact, HSV2 is the second most common cause of viral meningitis in the United States. In contrast, HSV1 is responsible for only a small fraction of neonatal HSV infections and causes severe encephalitis rather than meningitis, as in older children and adults.

The incidence of HSV2 meningitis shows no seasonal variability, but the likelihood that a given case of aseptic meningitis is the result of HSV2 decreases in the summer and early fall, when enteroviruses and arboviruses cause a higher proportion of cases. Although enteroviruses cause most viral meningitides, HSV2 is an important contributor to morbidity. In fact, 36% of women and 16% of men experience symptoms of meningitis with their first outbreak of HSV2 genital herpes. Unfortunately, up to 20% of primary HSV2 meningitis recurs, with latent periods ranging from weeks to decades. When HSV2 meningitis recurs three or more times and is associated with fever, it is termed Mollaret meningitis. Some patients who have Mollaret meningitis experience transient neurologic symptoms such as cranial nerve palsies, seizures, hallucinations, or diplopia.

Risk factors for HSV2 meningitis are similar to those of most sexually transmitted infections, including early onset of sexual activity, multiple sexual partners, and concurrent sexually transmitted infections. The pathogenesis of HSV2 meningitis is not currently known. The three mechanisms that have been proposed include hematogenous spread of HSV2 from dorsal root ganglia to the CNS, neurologic spread of viral particles from the peripheral nervous system to the CNS, and direct seeding of CNS neurons.

Clinically, children and adolescents who have HSV2 meningitis present with nuchal rigidity, severe headache, and photophobia. The characteristic HSV2 genital lesions may accompany such neurologic signs and symptoms. The genital lesions generally precede CNS symptoms by 7 days.

The evaluation of a patient suspected of having a CNS infection involves a complete history and physical examination, looking for possible sick contacts, history of prodromal symptoms, rashes, or lesions. Blood and CSF samples should be collected for Gram stain and culture and CSF analyzed for glucose, protein, and cell count at presentation. Broad-spectrum antibiotics should be administered soon after presentation but preferably after the blood and CSF samples have been obtained. Imaging of the head may be indicated if there is concern for mass effect, hydrocephalus, or hemorrhage and clinical examination cannot exclude these findings.

Treatment and Prognosis
As previously mentioned, supportive care is the mainstay of treatment for aseptic meningitis because these illnesses most often are self-limited. In the case of HSV2 meningitis, treatment with antivirals such as acyclovir may shorten the duration of symptoms and viral shedding.

Lessons for the Clinician
When evaluating a patient who has suspected CNS infection, the clinician should keep in mind a few facts: 1) HSV2 is the second most common cause of viral meningitis in adolescents and adults in the United States, 2) 36% of women and 13% of men experience symptoms of meningismus with primary genital herpes, 3) HSV2 meningitis is a transient meningitis that can recur, and 4) antiviral treatment may shorten the course of symptoms and decrease viral shedding. (Elise C. Piebenga, MD, Emily Shaw, BA, MS-4, Hasbro Children’s Hospital, Brown Alpert Medical School, Providence, RI)
Case 3 Discussion

Hyphema is a common presentation to a children’s hospital that has potentially permanent sequelae of blindness or amblyopia. Typically, hyphema is associated with trauma and often includes periocular signs of trauma, such as bruising, skin abrasion, subconjunctival hemorrhage, corneal abrasion, or even an orbital fracture. The hyphema in this case appeared to be spontaneous and without trauma, which suggests a possible underlying condition. Entities that may present as spontaneous hyphema include leukemia, bleeding diathesis, retinoblastoma, and other intraocular tumors or lesions.

Diagnosis

Appropriate evaluation includes a complete blood count, ultrasonography of the eye (B-scan), and coagulation studies if a bleeding diathesis is suspected. If there is suspicion of nonaccidental trauma, a child abuse team should be notified and the appropriate evaluation initiated, including a skeletal survey and head CT scan. A dilated fundus examination should be performed by an ophthalmologist and remains an important part of the evaluation for nonaccidental trauma. If the patient is African American, a thorough history regarding sickle cell anemia should be obtained, and hemoglobin electrophoresis is recommended if sickle cell disease is considered. Both sickle cell anemia and sickle cell trait can have devastating consequences on an eye that suffers a hyphema. The presence of either condition dramatically changes the treatment plan from noninvasive to surgical on an emergent basis. Patients who have sickle cell anemia have a significantly worse visual prognosis from a hyphema, and the use of acetazolamide is contraindicated.

Treatment and Clinical Course

Acute treatment of hyphema is aimed at lowering the IOP because a high IOP can lead to corneal staining from the iron in hemoglobin, permanent optic nerve damage, and blindness. In this patient, therapy was directed at lowering the IOP with systemic acetazolamide and topical timolol. A beta blocker must be used judiciously in a child who has asthma. Intravenous methylprednisolone was added to control intraocular inflammation (topical prednisolone acetate also could be considered as an anti-inflammatory agent), and atropine eye drops were instilled to fix and dilate the pupil, theoretically lowering the risk of the iris rebleeding. Prostaglandin analogs and alpha-2 agonists are not appropriate choices in the pediatric patient but often are used in adults to control IOP. Bed rest is the standard of care for patients who have hyphema, although difficult to enforce in small children. The vomiting reported for the patient may have been related to the elevated eye pressure. Hospitalization with sedation must be considered if the child’s activities at home cannot be controlled. The goal is for bed rest to lower the risk of rebleeding and to allow the settling and clearing of the red blood cells from the anterior chamber of the eye.

The next day, this patient’s hyphema appeared to have cleared to about 20% to 30% of the anterior chamber involvement (Fig. 1), and her IOP improved. Examination of the right eye revealed a small iris lesion partially obscured by the blood in the anterior chamber. Further physical examination revealed two 2.5-mm yellowish-pink, smooth papules on the left lateral abdomen and right upper back (Fig. 2). Dermatology performed a skin biopsy, and the diagnosis of juvenile xanthogranuloma (JXG) was established on histopathology.

The Condition

JXG is a localized, benign, histiocytic infiltrative lesion that appears to affect the pediatric population most commonly. JXG primarily is a self-limited dermatologic disorder that is associated rarely with systemic manifestations. The nodular lesions typically are cutaneous, arise spontaneously, and typically regress within 2 months. The lesions also may be found in many other locations.
Subcutaneous, intramuscular, and visceral lesions may develop and typically are noted incidentally. The eye, particularly the uveal tract (the iris and ciliary body), is the most frequent site of extracutaneous involvement. Approximately 50% of patients who have ocular involvement have skin lesions. JXG is the most frequent cause of spontaneous hyphema in children and can result in secondary glaucoma and eventual blindness. Ciliary body involvement also may present as a uveitis, with the patient having a painful red eye, photophobia, and tearing.

**Prognosis**
The prognosis for JXG is excellent. Typically, the lesions resolve with topical steroids but may require systemic or periocular steroids if topical treatment fails. Occasionally, low-dose radiation therapy or surgical excision is recommended for otherwise nonresponsive lesions. Patients should be followed closely and all potential eye complications managed by an ophthalmologist until the lesions regress. This patient had new skin lesions develop, but no further eye involvement, and she continues to do well at home.

**Lessons for the Clinician**
A child who has an ophthalmologic emergency, such as hyphema, can present with the vague complaint of irritability. Although hyphemas most commonly are caused by trauma, uncommon causes may be supported by physical findings. A thorough physical examination is critical when making the diagnosis in a child, especially if nonaccidental trauma is part of the differential diagnosis. (Heather Toth, MD, Robert Fish, MD, David Dueker, MD, Raja Sadiq, MD, Yolanda Wolff, MD, Medical College of Wisconsin, Milwaukee, Wis.)

To view Suggested Reading lists for these cases, visit www.pedsinreview.aappublications.org and click on Index of Suspicion.
The Erythrocyte Sedimentation Rate and the C-reactive Protein Test

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Introduction
The erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are two commonly used and widely available diagnostic tools employed by physicians to aid in diagnosing and managing various pathologic states. They both are nonspecific measurements of inflammatory processes.

The ESR
As the name suggests, the ESR measures the distance that red blood cells (RBCs) settle over time. Through various methods, mixed and anticoagulated whole blood is placed in a vertical sedimentation tube for 1 hour, and the ESR is measured (mm/hr) as the distance from the top of the blood column to the top of the RBC layer below.

Numerous factors affect the ESR. In the blood of healthy patients, gravity causes RBCs to settle. However, as they fall, the upward displacement of plasma balances the downward force, resulting in little settling. When RBCs aggregate, forming rouleaux, the downward forces exceed upward forces, and the ESR increases. Plasma proteins have the greatest effect on RBC aggregation, which is directly proportional to the protein’s molecular weight and degree of asymmetry.

Needle-shaped fibrinogen, a large and asymmetric molecule, has the greatest effect on all plasma proteins on ESR. When fibrinogen increases, as in various inflammatory states, the ESR increases concomitantly. For this reason, many clinicians view the ESR as an indirect measure of fibrinogen. Because it is affected by plasma proteins, the ESR tends to rise slowly after the onset of inflammation and can stay elevated for days to weeks after resolution of the inflammation.

Importantly, noninflammatory conditions also affect the ESR. RBCs that have abnormal morphology, as in sickle cell disease, have less of a tendency to form rouleaux, thereby producing lower ESRs. Anemia tends to increase rouleaux formation, and polycythemia decreases it. Understandably, hyperviscosity states slow the ESR, and hypoviscosity states speed the ESR.

The CRP
CRP is an acute-phase reactant synthesized in the liver primarily in response to cytokines interleukin (IL)-1-beta, IL-6, and tumor necrosis factor-alpha. The name derives from the observation that it reacts with C-polysaccharides of pneumococcal cell walls. CRP functions by binding directly to microorganisms as an opsonin for complement, activating neutrophils, inhibiting platelet aggregation, clearing necrotic host tissue, and possibly activating natural killer cells. The concentration of CRP may increase several hundred-fold in extreme inflammatory states. Its synthesis begins within 4 to 6 hours of the onset of inflammation and peaks between 36 and 50 hours; concentrations decline rapidly because of its short 4- to 7-hour half-life. In general, therefore, the CRP

Abbreviations
CRP: C-reactive protein
ESR: erythrocyte sedimentation rate
IL: interleukin
RBC: red blood cell

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both rises and normalizes faster than does the ESR.

Because CRP is a directly measured plasma protein, it is unaffected by the external conditions that alter ESR values. CRP values do increase slightly with age and pregnancy, however. Of note, new technology allows for a relatively rapid and sensitive quantitative measurement.

**Clinical Use**

The nonspecificity of both tests limits their use in diagnosing clinical states or as a sole guide to direct therapy. They are better suited as adjuncts to clinical suspicion and best interpreted with serial measurements. Although they can be monitored in adults to determine risk for cardiovascular events, in pediatrics they are frequently used to help in the management of infectious, rheumatologic, and oncologic disorders.

**Infections**

ESR and CRP most commonly are measured in infectious states. Recent evidence suggests that CRP is an excellent screen for serious bacterial infections in neonates. Because CRP does not cross the placenta, its presence in a neonate indicates de novo production. Thus, some groups advocate measurement of CRP in infants at risk for sepsis. These protocols recommend measuring CRP at the initiation of the “septic evaluation” and subsequently at 24 to 48 hours to determine the trend. Use of the CRP in this situation is limited by the observation that concentrations of this protein also are elevated in noninfectious conditions such as meconium aspiration, respiratory distress, and intraventricular hemorrhage, among others. However, CRP has a high negative predictive value for serious bacterial infections; that is, such infections are ruled out with a high degree of certainty when consecutive normal values are obtained.

Attempts have been made to use ESR and CRP to differentiate viral from bacterial causes in children who have fevers. Although both the ESR and CRP tend to be higher in patients who have more invasive infections, this relationship is not always observed. Most viral infections tend to cause modest elevations, but higher values of both ESR and CRP have been measured during uncomplicated infections with common viruses, including adenovirus, influenza, and cytomegalovirus. Thus, ESR and CRP have variable responses that prohibit their use in differentiating benign from serious disease in a specific patient.

Recently, the concentration of CRP in cerebrospinal fluid was evaluated for its utility in distinguishing bacterial from viral meningitis. Although one study recommended measuring the concentration of cerebrospinal fluid CRP once to help differentiate the cause, follow-up studies showed significant overlap among diverse microbial infections. Therefore, this measurement is not recommended for this purpose.

Both tests also have been used to screen for bacteremia. Numerous studies have failed to show a correlation between either test and the presence of culture-proven bacteremia. Again, serial measurements of CRP may help determine if a child is responding to therapy and, therefore, may allay concerns that a serious bacterial infection may develop. However, these tests do not provide a reliable screen for bacteremia.

ESR and CRP are used together by some clinicians to direct treatment of osteomyelitis and septic arthritis. After diagnosis, patients are treated with appropriate intravenous antibiotics, and baseline measurements are obtained. On day 10 to 14 of treatment, ESR and CRP values are measured again and subsequently at set intervals, usually every few days. Once the CRP has normalized and the ESR value is significantly lower, many clinicians convert therapy to oral antibiotics to complete the 6-week course. After conversion to oral treatment, just one of the tests may be sufficient for follow-up.

An alternative philosophy recommends measuring only the CRP early in the clinical course because it responds more quickly than the ESR, both in rising and falling, making the test useful in judging the initial degree of inflammation and the early response to therapy. When the CRP returns to normal values, switching to the ESR and following that measurement until normal would assure that all inflammatory markers have returned to baseline.

Both markers have been used to evaluate acute rheumatic fever, as well. Neither has been shown to help in the diagnosis of acute rheumatic fever, but CRP values have been shown to decrease in response to corticosteroid treatment and to remain low after discontinuation of corticosteroids if the disease is suppressed adequately. Again, the markers have been shown to be useful adjuncts to determine the response to treatment.

**Inflammatory Disorders**

In addition to infectious diseases, these markers have been used in the management of other inflammatory disorders. In Kawasaki disease, they are used as secondary diagnostic criteria to identify incomplete cases. Numerous studies have attempted to determine a “cut-off” CRP value to predict response to therapy and future development of coronary artery disease. Unfortunately, no definitive CRP values have been found to correlate consistently, although two studies did show that measurements
greater than 150 mg/L were associated with greater treatment failure and development of coronary lesions. Numerous other studies have shown that CRP normalizes rapidly once the child has received adequate treatment with intravenous immune globulin or aspirin.

As with infectious processes, these tests appear to help identify disease flares and complications in certain autoimmune disorders. For example, no reproducible values have been identified to aid in the initial diagnosis in systemic lupus erythematosus and inflammatory bowel disease. However, the inflammatory markers are useful in monitoring for flares and their response to treatment.

Studies also have been undertaken to determine if the markers can help diagnose graft versus host disease in transplant patients. The findings vary by organ, but no cut-off values have been found to correlate consistently.

Importantly, the inflammatory markers have a strong negative predictive value, aiding diagnosis by ruling out diseases. In patients afflicted with periodic fever syndromes, such as familial Mediterranean fever, the inflammatory markers are elevated during acute febrile flares but are normal when the patient is afebrile. Such normalization is not seen with subacute infections from cytomegalovirus or Epstein-Barr viruses that mimic some periodic fever syndromes. Similarly, normal concentrations of inflammatory markers strongly rule out acute rheumatic fever and serious bacterial infections.

Normal Values
Normal values for ESR and CRP vary among clinical laboratories primarily because of different assay methods, and clinicians should learn the values for the laboratories they employ. Commonly accepted values for the ESR are 0 to 15 mm/hr for males and 0 to 20 mm/hr for females, using the traditional Westergren and similar methods. A newer rapid test has different normal values. CRP in healthy people generally is below 1.0 mg/L (0.1 mg/dL). As with the ESR, a newer procedure, called the high-sensitivity CRP, may be used in some laboratories and has different normal values from the traditional method.

Conclusion
The ESR and CRP are excellent tests that aid practitioners greatly but are limited by nonspecificity. Evidence shows that CRP tends to be more accurate and precise when compared with ESR. Such findings are related to the CRP concentration being less affected by other factors and responding more rapidly than the ESR. Routinely obtaining or following both values serially is unnecessary and unhelpful because they are nonspecific reflections of inflammation. It is crucial to remember that these tests never can serve as a substitute for a careful history and physical examination. Their greatest assets are helping to rule out specific disorders and monitoring response to treatment. In general, the most effective use of these tests is to follow only one serially to monitor the trends in a patient’s clinical course.

Suggested Reading
Hilliard NJ, Waites KB. C-reactive protein and ESR: what can one test tell you that the other test can’t? *Contemp Pediatr*. 2002;19:64–74
Complementary, Holistic, and Integrative Medicine: Fever

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Introduction
Fever, commonly defined as a temperature of 99.5°F (37.5°C) or greater (axillary) or 100.4°F (38.0°C) or greater (core), is a common pediatric sign that has many causes (eg, bacterial or viral infection). Some of the causes are self-limiting and do not require treatment; others are serious underlying conditions requiring treatment. In children (particularly infants), seeking medical attention for the evaluation, diagnosis, and treatment of the underlying cause of fever is standard care. (1) Some families seek to alleviate fever and its associated symptoms (eg, discomfort, irritability, crying) through easily accessible, adjunctive self-care techniques and complementary and alternative medicine (CAM) therapies.

This review discusses common CAM therapies that have been used to treat fever in children and is limited to the following modalities, for which published scientific literature is available: physical methods, natural health products (NHPs), and traditional Chinese medicine (TCM).

Physical Methods
Physical methods such as tepid sponging, bathing, fanning, and cooling blankets often are used to treat fever. (2)(3) Although physical methods often are inexpensive and readily available, the efficacy of many of these methods has not been established through rigorous research. (4)

A 2006 systematic review of seven quasi-randomized, controlled trials (RCTs) that included children (n=467) ages 1 month to 15 years who had fever of a “presumed infectious origin” compared physical methods (eg, tepid sponging) with or without a drug treatment (antipyretic) to a drug treatment, placebo, or no treatment. (4) Of the seven studies, three small trials had positive findings and demonstrated that tepid sponging helped to reduce fever in children. However, these findings were observed in children who had already taken acetaminophen, so it is unclear whether the tepid sponging was responsible for the observed reduction in fever. The trials considered in this systematic review had very small numbers and suffered from various methodologic limitations, such as inadequate/unclear methods of subject allocation and high dropout rates or withdrawals. The authors concluded that evidence to either support or discourage the use of physical methods alone to treat fever is limited. (4)

Another systematic of 10 quasi-RCTs, including the seven studies in the previously cited review, also found minimal benefit from sponging in temperate climates and concluded that evidence to support the routine use of sponging is lacking. (5) This review involved studies of febrile children between 3 months and 16 years of age who were not critically ill.

In 2000, a review examining the efficacy of tepid sponging for fever cited results from four pediatric studies and reported little advantage to using tepid sponging in addition to acetaminophen compared with using acetaminophen alone. Furthermore, acetaminophen appeared to be a better tolerated treatment and was preferred by parents. (6)

Common adverse events (AEs) of physical methods of treating fever in general, and
sponging in particular, include shivering, having “goose pimples,” crying, and having discomfort. These AEs are the same fever-associated symptoms that sponging aims to reduce. Thus, the efficacy of sponging in children is arguable. Rare AEs reported after sponging with alcohol include the loss of consciousness.

**Natural Health Products**

**Traditional Herbal Medicine**

Many popular NHPs used to treat fever (eg, gentian, licorice root, peppermint, yarrow) have not been evaluated scientifically through clinical studies. One published RCT assessed the efficacy of a Japanese herbal medicine, Mao-to, to treat fever and influenzalike symptoms in 60 children (ages 5 months to 13 years). (7) Mao-to is a combination of *Ephedra Herba*, *Cinnamomi Cortex*, *Armenicae Semen*, and *Glycyrrhizae Radix* and is reported to have antiviral and autoimmune effects. Children in the study were randomized to take either Mao-to alone orally (0.06 g/kg per dose three times daily); a neuraminidase inhibitor, oseltamivir (2 mg/kg per dose twice daily) alone; or a combination of Mao-to and oseltamivir. (7) The group that received only Mao-to had a shorter duration of fever after starting the medication (15 hours, 95% confidence interval [CI] 13.2 to 22.1, \( P < 0.01 \)) compared with the combination of Mao-to and oseltamivir group (18 hours, 95% CI: 15.2 to 27.7, \( P < 0.05 \)), and the neuraminidase inhibitor-only group (24 hours, 95% CI: 23.5 to 43.0, \( P < 0.01 \)). No AEs were reported. These results suggest that Mao-to may be a cost-effective control for fever due to type A influenza in children because it costs between one tenth and one twentieth that of neuraminidase inhibitors. (7)

Limitations of this study include lack of true randomization because patients younger than 1 year of age were assigned to the Mao-to-only group (they did not meet the criteria for neuraminidase inhibitor treatment in Japan) and small sample size. (7) Study results suggest that Mao-to could be a possible candidate for additional research outside of Japan to assess the generalizability of efficacy and safety of the herb.

**Zinc or Vitamin A Supplementation**

Both zinc and vitamin A are important for human growth and immune function. (8) An RCT examined the effects of zinc acetate and vitamin A supplementation on resolving fever in 153 children (ages 2 to 24 months) hospitalized in India who had severe acute lower respiratory infection (ALRI), including fever. Children received zinc acetate (10 mg twice daily for 5 days) plus vitamin A placebo; vitamin A (10,000 mcg retinol twice daily for 4 days) plus zinc placebo; zinc acetate plus vitamin A; or zinc and vitamin A placebos. For boys supplemented with zinc acetate only, the resolution of fever was 3.1 times more rapid (\( P < 0.003 \)) than seen in children not supplemented with zinc. Reported AEs included death (\( n = 1 \)), diarrhea (\( n = 5 \)), pyopneumothorax (\( n = 4 \)), and bulging fontanelle (\( n = 3 \)). These results suggest that zinc treatment reduces duration of fever due to ALRI for boys, but not for girls, and that vitamin A treatment had no benefit. (8)

Baseline evaluations of zinc or vitamin A status were not reported in this study for the “urban and peri-urban poor” subjects, who may possess deficiencies (ie, suffer from malnutrition) that may make them much more vulnerable to the onset of ALRI and its complications and also might affect the resolution of fever, thereby serving as confounders. Conclusions based on the results, therefore, are not generalizable to other pediatric populations, and research to determine the exact mechanism of action for zinc therapy is needed. Zinc has several AEs. When taken in high doses over long periods, it can decrease immunity and copper absorption, causing copper deficiency that, in turn, increases the risk of anemia. Milder AEs associated with excessive zinc intake include headaches, stomach irritation, nausea, and vomiting.

**Traditional Chinese Medicine**

TCM is an ancient Chinese system of medicine that includes meditation, herbal and nutritional therapy, physical exercises, massage, and acupuncture. A paucity of well-designed RCTs exist that have investigated the effectiveness of TCM remedies to treat fever. Thus, the information presented in this section comes from case reports that have several methodologic limitations. Such findings should be viewed as being preliminary, inconclusive, and requiring additional research.
Cupping
In TCM, cupping involves the application of a vacuum to a localized area of the skin. (9) This procedure is believed to increase circulation in the treated area and theoretically eliminate toxins trapped in the tissue. (10)

Liu assessed the efficacy of cupping therapy in 103 individuals from 17 to 58 years of age who had high fever due to upper respiratory tract infection. (11) The intervention was described as “fire-insertion cupping” for 5 to 15 minutes over three pressure points on the head. The author defined the outcomes as: 1) cured, if the body temperature dropped to the normal range and was still normal after 14 hours or 2) effective, if the body temperature dropped to the “normal range” (not defined) and was no more than 100.4°F (38°C) 14 hours later or if the temperature dropped to between 99.3°F and 100.4°F (37.4°C and 38°C) and rose by no more than 0.4°C 14 hours later. (11) A total of 31 study participants were described as cured, and results in 68 cases were termed effective; the outcomes from the remaining four cases and any AEs were not mentioned.

Although the authors reported a high success rate (96%) with this method, this study suffers from major methodologic inadequacies, including lack of information on the method of diagnosing upper respiratory tract infection, “blinding,” randomization, and a control group. Study results need verification through larger and better designed RCTs. Furthermore, because this research was conducted in a predominantly adult population, the findings may not be generalizable to children.

Several mild AEs from the use of cupping have been reported, including circular ecchymotic lesions (bruising). (10) Occasionally, cupping can cause panniculitis (inflammation of subcutaneous fatty and muscle tissue) or thermal injury. (10)

Acupuncture
Acupuncture is a method of healing developed in China at least 2,000 years ago that describes a family of procedures involving stimulation of anatomic points on the body by a variety of techniques. The acupuncture technique that has been scientifically studied most involves penetrating the skin with thin, solid, metallic needles that are manipulated by the hands or that carry electrical stimulation. (12)

A Chinese study investigated whether fever caused by the common cold could be treated with application of acupuncture needles at three pressure points on the head. (13) Participants (n=57) ages 16 to 68 years suffering from the common cold were recruited from a local hospital. Of these, 45 individuals had received medica-tion more than 4 hours earlier, and 12 had received none. Patients were asked to rest quietly for 10 to 15 minutes before the acupuncture. The author reported statistically significant changes in 11 objective indicators after treatment (eg, body temperature, respirations, heart rate, blood pressure, temperature at the three pressure points on the head where acupuncture needles were applied). The frequency of these measures was not described, and no correlations between them were discussed.

Clinical effects were described as being effective in 46 of 57 cases for a total efficacy rate of 80.7%. (13) Finally, a comparison of morbidity scores before (8.55±0.43) and after (3.85±0.22) treatment showed a statistically significant difference. Although this study observed positive effects of acupuncture in treating fever and associated symptoms in patients suffering from the common cold, influenza, acute tonsillitis, and acute bronchitis, poor study design limits the validity of the findings. Methodologic limitations include lack of a control group, poor reporting of outcomes, and questionable primary outcome measures (due to combining objective and subjective measures into one score). No AEs were reported. Additional research in this area is needed to clarify the efficacy and safety of needle acupuncture to reduce fever.

Acupuncture therapy rarely results in serious AEs. (14) Evidence from 12 prospective studies of more than 1 million treatments estimates the risk of a serious AE occurring from acupuncture therapy to be 0.05 per 10,000 treatments and 0.55 per 10,000 individual patients in the general population. (14) The most common serious AEs included pneumothorax, injury to the central nervous system, transmission of hepatitis B, and skin infections. (14)

Conclusion
Reviews of available evidence have concluded that physical methods of cooling, such as tepid sponging, cannot be considered effective in reducing childhood fever due to the lack of clear and verifiable findings. The rationale for and physiologic mechanisms of the herbal medicine Mao-to and zinc supplementation for treating fever are not well understood; they should be viewed with caution when considered as treatments for children. Preliminary evidence for the efficacy of TCM (cupping and needle acupuncture) in treating fever comes from three inadequately described case series. These studies have methodologic shortcomings and do not provide sufficient evidence to support the use of these CAM therapies. The need for more rigorous studies to evaluate the efficacy of CAM therapies in children suffering from fever is clear.
References

Adherence

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Telephone Reminders Improve Adolescent Clinic Attendance: A Randomized Controlled Trial. Sawyer SM, Zalan A, Bond LM. J Paediatr Child Health. 2002;38:79–83

Adherence to medication regimens by children who have any chronic medical condition is a complex process influenced by multiple factors, including demographics, health status, specific medications, and developmental and psychosocial characteristics of the child and family. Adherence to (or compliance with) a medical regimen is defined as the extent to which a person’s behavior coincides with medical or health advice. The word “adherence” is preferred by many clinicians because “compliance” suggests that a patient is passively following the doctor’s orders, while adherence suggests that the established treatment is based on a therapeutic relationship.

A number of models have been developed to explain patient adherence, including the authoritarian, health belief, and ecological models. The authoritarian model, which is one of the earliest developed, results when the doctor gives an order and the patient follows. Because adherence to a treatment is multifaceted, studies have shown that adherence is not all-or-none, as this model suggests. For example, adherence to one aspect of care does not equate to adherence to all aspects of care. According to the health belief model, adherence is determined by an individual’s perception of the severity of a problem as well as the benefits of a treatment and the presence of cues to take actions, such as pain.

The ecological model takes into consideration most of the factors that may affect adherence. It focuses not only on individual level factors, but on contextual and process factors. Individual factors in this model include self-evaluation or perception of severity of the illness, beliefs, motivation for change, and self-efficacy. Self-efficacy, or the perception of one’s own ability to produce and execute expected outcomes, is necessary for adolescents to adhere to a treatment plan. Contextual factors include family, social support, and perceived support from physicians, culture, and society. Process factors relate to the ability of the clinician to communicate effectively and to provide well-understood, realistic goals to motivate adolescents into action.

Developmental factors that influence adherence include Piaget’s stage of understanding causality and Erikson’s identity formation stage. During early adolescence, adolescents seek to become autonomous from the family, and the adolescent who feels autonomous may view health-promoting influences as being restrictive on autonomy, resulting in reluctance to accept parental advice. Middle adolescence is characterized by an increased feeling of invincibility and risk-taking behavior, with more influence from peers. The influence of peers and limited insight into causality can result in medication nonadherence. Later in adolescence, adolescents may be given more responsibility. Although simultaneously being required to take on greater responsibility in general, many adolescents who have chronic illnesses may be cognitively limited relative to their age, and simply facing normal challenges of adolescence may impair their willingness and ability to assume the important role of managing their illnesses.

Multiple adherence studies focusing on adolescents who have chronic illnesses such as human immunodeficiency virus (HIV) infection, diabetes, or being recipients of organ transplants highlight the importance of family and parental involvement. Direct parental involvement and monitoring of adolescents’ health-related activities are associated with improved adherence. Parental support of health management, which also may result in improved adherence, includes reviewing adherence strategies with the adolescent and discussing steps that the adolescent can take to manage the illness better, as well as praising effective steps already taken.
Many features of a medical regimen might limit adherence. Lack of symptoms, multiple treatments, adverse effects of regimens, multiple daily medication doses, and lack of perceived seriousness all have been associated with poor adherence. Although it is difficult to predict which adolescent is likely not to adhere to a therapeutic plan, those who have not adhered to a treatment plan in the past are likely to continue to do so poorly in the future. Poor adherence should be considered when a patient’s condition is not responding to therapy.

Clinicians should ask the adolescent nonjudgmentally how often he or she misses taking medications. Adolescent patients generally want to please their clinicians and often tell them what they think they want to hear. The simplest solution is to remove the burden from the adolescent by rephrasing the question and asking about any adverse effects associated with the medication, any barriers to taking the medication regularly, and any challenges or problems that may have occurred. Clinicians who acknowledge the challenges of taking daily medications will be more likely to develop a rapport with an adolescent patient that results in more truthful responses. Adolescents should be asked about whether they know the purpose and benefits of their medications. Open communication between the clinician and the adolescent likely can reveal concerns around adherence.

In a recent Cochrane systematic review of randomized controlled trials that measured medication adherence and treatment outcomes in patients of all ages, the authors concluded that several strategies can improve adherence and treatment outcomes. These include a combination of thorough patient instructions and counseling, reminders, close follow-up, supervised self-monitoring, rewards for success, family therapy, psychological therapy, crisis intervention, and manual telephone follow-up.

The most important single strategy, however, appears to be recalling of patients who missed appointments. Adolescent-specific studies are limited, but some have found that telephone reminders to facilitate adherence with appointments, free medication, and vouchers for transportation have been effective in improving short-term adherence. There was not enough evidence in the Cochrane review to recommend the widespread use of patient contracts in health services.

**Comment:** Dr Arrington-Sander’s remarks are very important, and we as clinicians need to understand the morbidity and mortality that follow when patients do not adhere to medication regimens. As the pediatrician of an adolescent patient who died from lack of medication adherence 5 years after she received a heart transplant, I saw how this tragedy affected her family and the numerous specialists who had worked with her following the miracle of her transplant. Taking the time to elicit honest answers, understanding the social and psychological barriers, and working to overcome those barriers is critical. Continued research is necessary to establish strategies to improve adherence and to make medication regimens easier and freer of adverse effects.

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