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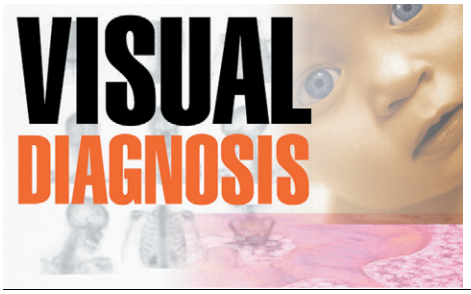
Pediatrics in Review 2014;35;e25
DOI: 10.1542/pir.35-5-e25



Nasal Congestion and Respiratory Distress in a 7-Day-Old Girl

Jamie M. Pinto, MD,* Dorothy Chu, MD,* Sushama Govil, MD,† Samuel Engel, MD, MPH‡

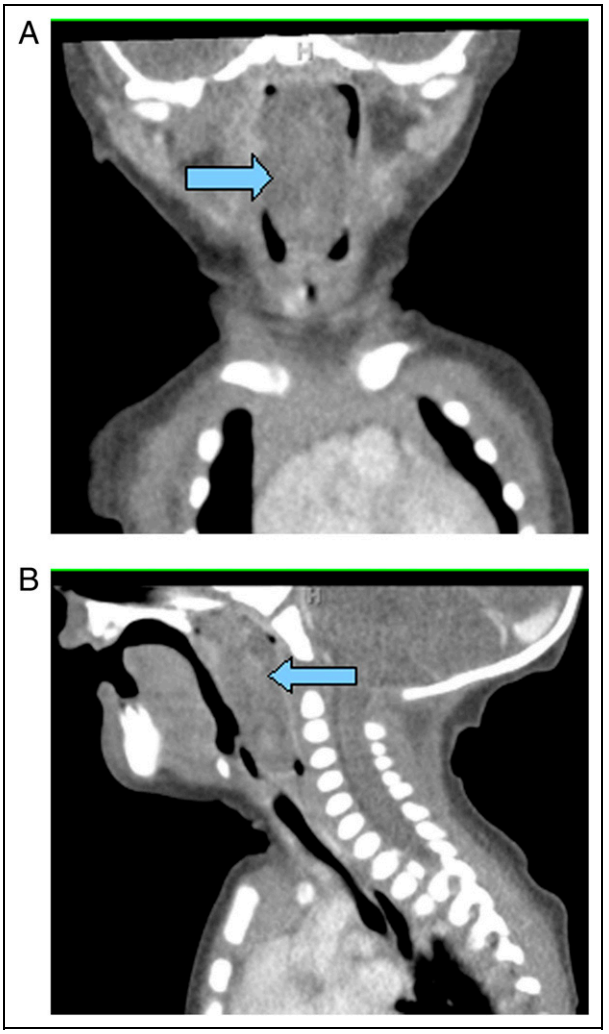


Figure 1. Coronal (A) and sagittal (B) computed tomographic images showing a 1.2 × 1.7 × 4-cm mass in the nasopharynx and oropharynx without intracranial extension.

Author Disclosure

Drs Pinto, Chu, Govil, and Engel have disclosed no financial relationships relevant to this article. This commentary does not contain discussion of unapproved/investigative use of a commercial product/device.

Presentation

A 7-day-old girl presents to the emergency department with a 1-day history of increased work of breathing. She has no associated cough, fever, or cyanosis, but she has had nasal congestion present since birth. She is taking longer to breastfeed, which her mother attributes to her nasal congestion. Her mother has been using nasal saline and suctioning the nares with a bulb syringe without any noted improvement. The girl has had no known sick contacts.

The infant was born full term via cesarean section due to breech presentation. The mother's prenatal laboratory data were within normal limits. No polyhydramnios or other abnormality was noted on prenatal ultrasonograms. Perinatal course was uncomplicated. The child had no episodes of tachypnea or respiratory distress before discharge from the newborn nursery.

On physical examination, the patient is afebrile, with a respiratory rate of 58 breaths/min and an oxygen saturation of 84% on room air. Her weight is 2.66 kg, which represents an 11.6% decrease from her birth weight of 3.01 kg. Her head circumference is 35 cm, which is between the 25th and 50th percentiles. She is in moderate respiratory distress with suprasternal and subcostal retractions. No stridor or nasal flaring is appreciated. Her palate is intact. She has nasal congestion without any rhinorrhea or oropharyngeal erythema. An 8F catheter can easily be passed through both nostrils. The heart has a regular rate and rhythm with no murmur, and the lungs are clear to auscultation bilaterally. The remainder of the physical examination findings are within normal limits.

The patient is given blow-by oxygen at 100% and is admitted to the pediatric intensive care unit for further management. Polymerase chain reaction test results for respiratory syncytial virus and influenza are negative. A complete blood cell count reveals a white blood cell count of $19.8 \times 10^3/\mu L$ ($19.8 \times 10^9/L$), with 29% neutrophils, 4% band forms, 44% lymphocytes, and 10% monocytes. Her hemoglobin level is 17.4 g/dL

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(174 g/L), hematocrit is 52.5% (0.525), and platelet count is 457 × $10^3/\mu$L (457 × 10^9/L).

Chest radiographic findings are unremarkable. A barium swallow reveals no evidence of tracheoesophageal fistula or other anatomical abnormality. Otolaryngology consultation is obtained, and bedside laryngoscopy is performed, revealing fullness in the posterior pharyngeal wall. This finding is further evaluated with computed tomography (CT) of the neck without contrast. The study reveals a 1.2 × 1.7 × 4-cm mass in the nasopharynx and oropharynx, extending to the larynx without intracranial extension (Figure 1). The mass is noted to have calcifications. Shortly after, the patient decompensates and is taken immediately to the operating room. The mass is visualized via direct laryngoscopy and partially excised (Figure 2). The infant is intubated and transferred back to the pediatric intensive care unit. Because of the emergency nature of the case, an α-fetoprotein (AFP) level was not measured before excision of the mass. Histologic review of the mass confirms the diagnosis.

Diagnosis: Benign Congenital Nasopharyngeal Teratoma

The clinical presentation and radiographic images are consistent with airway obstruction secondary to a nasopharyngeal mass lesion. Because the CT reveals calcifications within the mass, teratoma is the most likely diagnosis. Partial surgical excision followed by pathologic review confirms the suspected diagnosis. Pathologic analysis reveals elements of all 3 germ layers within the mass, a finding most consistent with congenital nasopharyngeal teratoma. Respiratory mucosa is part of the endoderm, cartilage is part of the mesoderm, and neural tissue is part of the ectoderm (Figure 3). There is no evidence of malignant conversion.

Discussion

Teratomas by definition are derived from the 3 embryonic germ layers: ectoderm, mesoderm, and endoderm. Up to 90% of childhood teratomas contain elements of all 3 layers. Any teratoma not located in the ovary or testis is classified as an extragonadal germ cell tumor. The most accepted hypothesis about their origin is that teratomas are derived from primordial germ cells that do not reach the gonadal ridge during embryonic development, which occurs because of failed or aberrant migration. These cells do not receive the signal to mature and thus are pluripotent. They can then develop into teratomas or other germ cell tumors.

Extragonadal teratomas can be classified based on the types of tissue contained within the mass. Mature teratomas have fully differentiated tissues from various somatic sites. Immature teratomas contain embryonal or incompletely differentiated tissues. The Gonzalez-Crussi grading system describes the amount of immature tissue in the teratoma. Grade 0 is a mature teratoma only, grade 1 has less than 10% of immature tissue, grade 2 has 10% to 50% of immature tissue, and grade 3 has more than 50% of

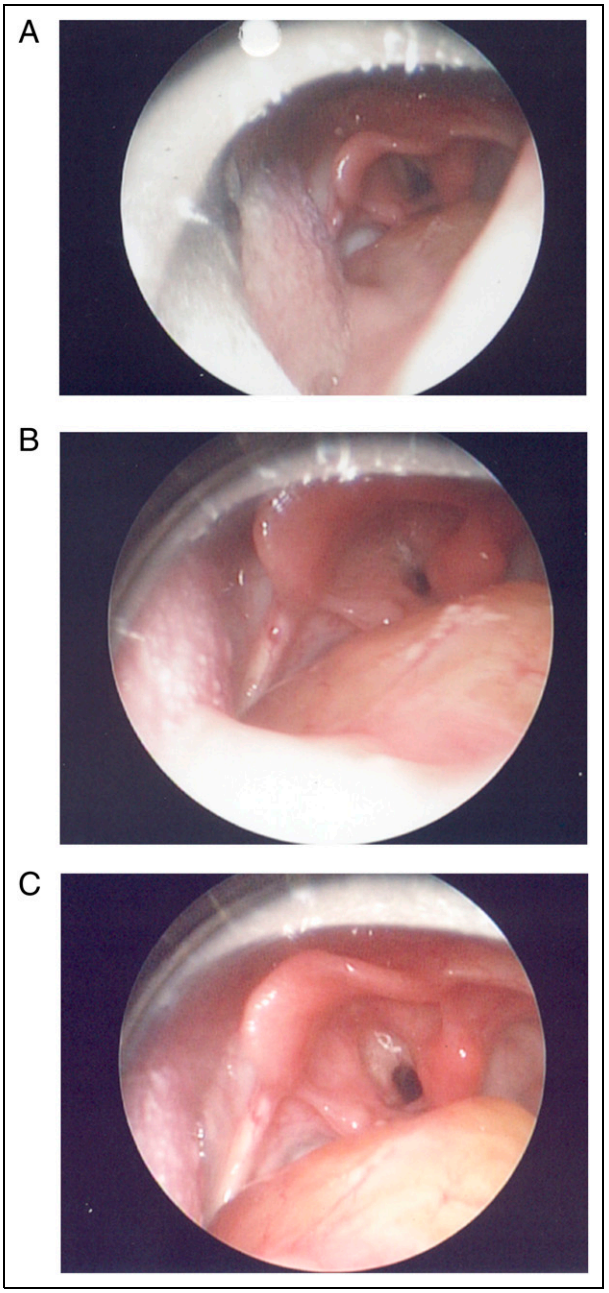

Figure 2. Images from a direct laryngoscopy showing fullness of the posterior pharyngeal wall, which is consistent with a mass lesion.

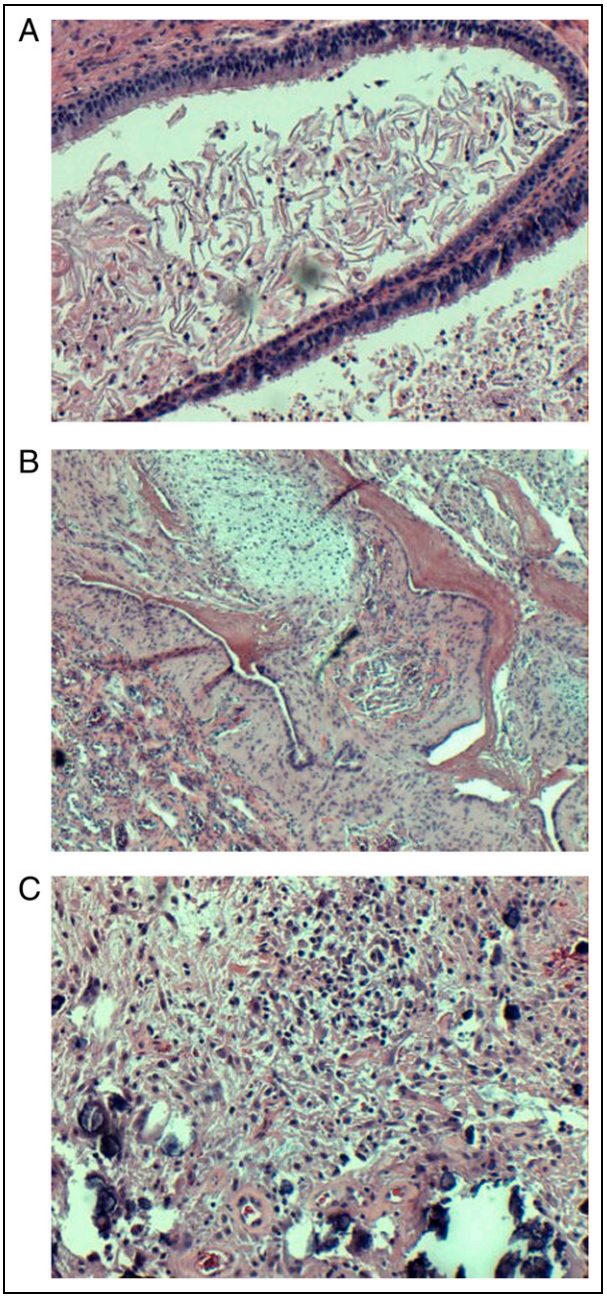

Figure 3. Pathology images showing all 3 germ layers within the mass. Respiratory mucosa (A) is part of the endoderm, cartilage (B) is part of the mesoderm, and neural tissue with calcifications (C) is part of the ectoderm.

immature tissue. Any teratoma with malignant elements is considered a malignant teratoma. The most common malignant element is a yolk sac component, which produces AFP.

Extragonadal teratomas most commonly occur in the sacrococcygeal region but can occur anywhere along the midline. Neonatal head and neck teratomas account for less than 10% of cases, and 75% to 85% of these contain neuroectodermal elements. The incidence of congenital nasopharyngeal teratomas is 1 in 4000 live births, with a female predominance. There are some reports of associated anomalies, including palatal clefts, cardiac anomalies, and microcephaly.

Nasopharyngeal masses are usually diagnosed prenatally via ultrasonography or present shortly after birth as large, visible masses. A history of polyhydramnios is usually present because the mass interferes with the fetus' ability to swallow amniotic fluid. Maternal AFP levels can be elevated if the lesion is a malignant teratoma. In rare cases when a visible mass is not identified, the neonate may have nonspecific findings, such as nasal congestion, respiratory distress, and poor feeding. Respiratory distress results from airway obstruction and can progress to airway occlusion, apnea, and death.

In most cases, nasopharyngeal masses are large and can be detected with the naked eye. However, when there is no visible mass, identification can be a diagnostic dilemma. Often radiography is the first imaging modality used to rule out other more common causes of respiratory distress that stem from the upper or lower airway. The imaging of choice for nasopharyngeal mass is CT or magnetic resonance imaging (MRI), which reveals a soft tissue mass in the nasopharynx that may extend to the oropharynx and possibly the hypopharynx. A nasopharyngeal teratoma is suspected on imaging when the mass contains calcifications or a fatty component. CT or MRI is important before surgical excision to rule out intracranial involvement.

Differential Diagnosis

When a neonate presents with respiratory distress, well-known causes should be in the differential diagnosis. Diagnoses to entertain include laryngomalacia, pneumonia, reflux pneumonitis, heart failure, tracheoesophageal fistula, and choanal atresia. When a nasopharyngeal mass is identified, congenital lesions are most likely. In addition to teratoma, physicians should consider encephalocele, glioma, and nasal dermoid. An encephalocele is a neural tube defect where part of the brain and/or meninges protrudes through a defect in the skull. Gliomas, which are central nervous system tumors made of neuroglial cells, can extend to the dura mater. Dermoids are congenital cystic tumors lined by epithelium that can have sinus tracts and intracranial extension. Surgical excision of a mass with intracranial extension or involvement can lead to complications such as meningitis and brain abscess. CT or MRI should be used to assess for intracranial extension or involvement before excision to avoid morbidity.

Management

Congenital nasopharyngeal teratomas are benign in 80% of cases, and full surgical excision is usually curative. Even with malignant lesions, metastasis is rare. The timing of surgery should be decided on a case-by-case basis, taking into account the size of the mass and the patient's clinical symptoms.

For benign congenital nasopharyngeal teratomas, major morbidity and mortality stem from the location of the mass in relation to the airway and the degree of obstruction present. Surgical excision can alleviate obstructive symptoms and establish a patent airway.

If a large nasopharyngeal mass is identified prenatally, a multidisciplinary team, including an anesthesiologist and an otolaryngologist, should attend the delivery to stabilize the airway and to determine whether immediate surgery is necessary. These neonates should be delivered by cesarean section because vaginal delivery can compromise the airway. After delivery, close monitoring of respiratory status is important because the patient may acutely decompensate, in which case emergency surgery would be necessary.

After full excision of benign congenital nasopharyngeal teratoma, the recurrence rate is low, and no adjuvant therapy is recommended. Following up AFP levels can be helpful because an elevation in this marker can signal malignancy. A baseline AFP level should be measured before surgery. AFP can be trended postoperatively to monitor for malignant conversion when there is incomplete resection of a mass and to monitor for rare cases of malignant recurrence after full excision. AFP levels are predictably elevated in the neonatal period and may be less useful for this age group.

Patient Course

Postoperatively, the patient's respiratory status improved, and she was extubated after 2 days. After extubation, the patient was noted to have mild respiratory distress when breastfeeding. Most notably, she had poor interval weight gain, and after 7 days of admission, she was still at her admission weight. Breastfeeding was supplemented with formula given via a slow-flow nipple, with less than optimal weight gain. She eventually underwent a second surgery for full excision of the lesion at a nearby quaternary center and is doing well, with the exception of eustachian tube dysfunction due to nasopharyngeal scarring.

Summary

Respiratory distress in a neonate always requires further evaluation. The differential diagnosis includes anatomical abnormalities, mass lesions, and infectious conditions from prenatal or postnatal exposure. Congenital nasopharyngeal teratomas are rare but life-threatening causes of respiratory distress and nasal congestion. They are most commonly diagnosed by prenatal ultrasonography or as a large visible mass present at birth. CT or MRI can help to further delineate the lesion and to rule out intracranial involvement before surgical excision. Surgical resection with histologic review is the only way to confirm the diagnosis of benign congenital nasopharyngeal teratoma. A teratoma will include all 3 germ layers. For benign lesions, surgery is usually curative, and there is a low recurrence rate.

Key points to remember about congenital nasopharyngeal teratomas are as follows:

- Congenital nasopharyngeal teratomas are rare but life-threatening causes of respiratory distress and nasal congestion in neonates.
- Rare mass lesions of the upper airway should be considered when more common causes of respiratory distress have been ruled out in the neonatal period.
- CT or MRI should be performed to evaluate for intracranial involvement before surgery.
- Surgical excision with histologic review is necessary to confirm the diagnosis of congenital nasopharyngeal teratoma.
- On histologic review, congenital nasopharyngeal teratomas have elements of all 3 embryonal germ layers: ectoderm, mesoderm, and endoderm.
- Complete surgical resection is usually curative, and no adjuvant therapy is needed for benign lesions.

Suggested Reading

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Cleft Lip and Palate

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Pediatrics in Review 2014;35;177
DOI: 10.1542/pir.35-5-177

Cleft Lip and Palate

Mary-Alice Abbott, MD, PhD*

Author Disclosure
Dr Abbott has 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.

Editor's Note: In the recently published article "Causal Attributions of Cleft Lip and Palate Across Cultures" (Cleft Palate Craniofac J. 2013;50[6]:655–661), the authors state that, across the world, culturally held beliefs concerning cleft lip and palate can have deleterious social effects on children and their families. Our readers should keep this in mind as they read the following article.

Joseph A. Zenel, MD
Editor-in-Chief

Educational Gap

Physicians should be aware of the potential associated medical problems with orofacial clefts, including airway obstruction, feeding difficulties, speech and language abnormalities, otitis media, and underlying genetic syndromes.

Objectives

After completing this article, readers should be able to:

1. **Understand the role of genetics and environmental factors in the incidence of orofacial clefts.**
2. **Be aware of the availability of special nipples and bottles for feeding some infants with orofacial clefts.**
3. **Recognize the associations between cleft palate and airway issues (Pierre Robin sequence) and palatal dysfunction and otitis media.**

Introduction

Oral-facial clefts are a common birth defect, occurring in approximately 1 in 600 US live births. (1) Epidemiologic studies have found that incidence varies according to sex and ethnic background; clefts occur most commonly in Native American and Asian populations and are least common in those with African heritage. Clefts of the lip are associated with a palatal cleft in approximately two-thirds of affected individuals. Cleft lip with or without cleft palate occurs more often in males, whereas isolated cleft palate is seen more often in females; cleft lip with or without cleft palate is more frequent that cleft palate alone.

Etiology and Pathogenesis

Facial development is a complex process. Five structures are involved in the development of the fetal face: the median frontonasal prominence, the paired maxillary prominences, and the paired mandibular prominences, both derivatives of the fetal first branchial arch. Upper lip formation is essentially complete by the sixth week of gestation and requires accurate fusion between the maxillary prominences and the medial nasal tissues, an outgrowth of the frontonasal prominence. Palatal fusion occurs later, between the 5th to 12th weeks of gestation, and proceeds anteriorly to posteriorly, ending with fusion of the uvula. Palatal development involves primary and secondary palatal structures. The primary palate (medial palatine process) is derived from the fused medial nasal tissues and forms the philtrum, part of the alveolus, and the most anterior segment of the hard palate. The secondary palate is derived from swellings of the maxillary prominence (the lateral palatine processes) and forms the hard palate, the soft palate, and uvula. When the accurate coordination of these

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developmental processes fails, orofacial clefts can result. Understanding of the complex genetic and cellular mechanisms required for normal orofacial development remains limited.

Clinical Characteristics

Orofacial clefts are categorized by their location and by descriptive terms, such as *unilateral*, *bilateral*, or *midline* and *complete*, *incomplete*, or *submucus*. Clefts can involve the nasal tip, philtrum, lip, lip vermillion, alveolus (gum), hard palate, soft palate, or uvula. Less common are facial clefts, such as eyelid coloboma (a feature of craniofacial microsomia syndrome), and oblique facial clefts, which extend from the upper lip to the inner canthus of the eye, following the course of the lacrimal duct. This rare cleft involves the line of fusion along the maxillary process and lacrimal nasal fold tissues.

Differential Diagnosis

Clefts occur in 2 categories: syndromic or isolated. Syndromic clefts are typically accompanied by abnormalities in other developmental fields or organ systems (eg, skeletal, craniofacial, and eye). Syndromes associated with clefts have many origins, including intrauterine exposures and genetic disorders. Prenatal exposure to alcohol, antiepileptic drugs (phenytoin and others), isotretinoin, cigarette smoking, maternal diabetes, and low folic acid have all been linked with the development of oral-facial clefts. Genetic causes of clefts range from aneuploidy (abnormal number of chromosomes, such as trisomy 13) and microdeletion syndromes, including 22q11.2 deletion syndrome or velocardiofacial syndrome, to single-gene disorders, such as van der Woude syndrome, ectodermal dysplasia and clefting syndromes, Stickler syndrome, Smith-Lemli-Opitz syndrome, and Treacher Collins syndrome.

Genes play a role in the formation of isolated clefts, but in contrast to syndromic clefting, the occurrence of isolated clefts is due to complex or multifactorial inheritance. Numerous factors interact to support or disrupt the complex embryologic development of craniofacial structures, and a complex interaction of genetic, environmental, and unidentified factors leads to the expression of a cleft. Genetic syndromes can be a factor in craniofacial clefts; however, the clefting is an isolated finding in two-thirds of individuals with cleft lip with or without cleft palate and in half of individuals with cleft palate only.

Diagnostic Approach

For any infant with an orofacial cleft, the pediatrician must first determine the nature and extent of the cleft and then determine whether the clefting is isolated or syndromic. This evaluation is relatively straightforward but must be rigorous and thorough because it reveals vital information about prognosis and risk of recurrence. Typically, the most effective evaluation is accomplished in consultation with a geneticist and collaboration with a craniofacial team. History should include a careful family history of clefts and other features of clefting syndromes, such as skin disorders, speech abnormalities, or other craniofacial abnormalities. Any history of prenatal exposures should be elicited (alcohol, cigarettes, medicines).

A careful examination for clefts is essential in all neonates, with consideration for neonatal transfer to a specialty center as needed for respiratory or nutritional support and/or assessment and treatment of other associated anomalies. Careful visualization and palpation of the hard and soft palate are necessary to identify a bifid uvula or submucous cleft of the soft palate. Palatal clefts are more likely to be syndromic than cleft lip or cleft lip and palate. The presence or absence of lip pits, eyelid coloboma, or dysmorphic facial features should be noted. Some palatal clefts are associated with Pierre Robin sequence (the triad of palatal cleft, micrognathia, and airway obstruction or glossoptosis). Pierre Robin sequence is important to identify because affected neonates are at high risk of airway obstruction and need close monitoring. Vision and hearing assessments should be conducted as early as possible.

Management, Therapy, and Follow-up

Most centers use a team-based approach for the management of craniofacial problems. Team members may include specialists in plastic surgery, oral and maxillofacial surgery, dentistry, orthodontics, otolaryngology, neurosurgery, genetics, nutrition, and child development. Multidisciplinary teams are poised to address the clinical problems that accompany clefts, including speech, middle ear disease and hearing, and dental. The challenge faced by the craniofacial team is to achieve optimal outcomes for both function and cosmesis. Lip clefts are usually repaired at approximately 10 weeks of age. Palatal clefts are repaired later; closure is usually completed between ages 9 months and 1 year. The benefits of early closure (speech development) are weighed against the risks of infant and complications related to earlier repair (eg, fistula formation). Because a crucial outcome measure for repair is speech, close attention is paid to the functionality of the levator musculature. There are now excellent online resources available to parents, including preoperative and postoperative photographs that can help them

understand the staged approach to craniofacial cleft repairs and to manage expectations.

Many parents are concerned about feeding their newborn with a cleft. Breastfeeding can be successful in many cases of isolated cleft lip, but direct breastfeeding is rarely successful as the sole means of feeding an infant with cleft palate. The presence of a cleft palate prevents an infant from effectively creating suction, despite having normal suck and swallow reflexes. Access to a high-quality breast pump is important for mothers who want to provide their infants with all the benefits of breast milk. There are a variety of special nipples available to facilitate feeding infants with clefts; some are assisted-delivery bottles, whereas others are not. Because of increased air intake while feeding, infants with a cleft require more frequent burping. It is helpful to place the infant upright for feeding and monitor the pattern of sucking and swallowing, followed by a breath. Nasal regurgitation is common when there is a palatal opening or dysfunction, and this does not herald choking. The treatment of gastroesophageal reflux disease can help prevent airway inflammation in infants with Pierre Robin sequence. Growth and nutrition must be carefully monitored while feeding techniques are established. Detailed information about feeding methods is available in the Cleft Palate Foundation publication "Feeding Your Baby."

Children with palatal clefts are at substantially increased risk for eustachian tube dysfunction, recurrent otitis media, and conductive hearing loss. Serous otitis media with effusion is virtually universal in children with palatal clefts; therefore, tympanostomy tubes are routinely placed at the time of palatal repair. Audiology evaluations should occur on an annual or semiannual basis for any child with a palatal cleft, and referral to an early intervention developmental program for speech therapy should occur as soon as possible. Submucous clefts and velopharyngeal insufficiency are part of the spectrum of palatal clefts and can be associated with syndromes; a bifid uvula can be associated with a submucous cleft palate, velopharyngeal insufficiency, and middle ear effusion. Children with these more subtle palatal problems should receive a complete evaluation so that appropriate speech therapy, and in some cases surgical repair, can be pursued and the best possible outcome ensured.

In addition, children with clefts are at increased risk for the psychosocial problems associated with any atypical physical trait. They often display hypernasal speech or other speech abnormalities that may elicit teasing from peers. Social work intervention and family support groups are an important component of care for both the child with a cleft and the family. A forthright approach by family members, as well as adequate preparation for the child with strategies for dealing with potential negative social interactions, is important for promoting successful psychologic and social adjustments. Cleft lip or palate parent support groups are strong advocates.

Additional Considerations

Recurrence Risk

Family members of an individual with a cleft may predictably have questions regarding their chance of conceiving a child with a cleft. To provide families with accurate recurrence risks, the etiologic basis of the cleft must be investigated. Many syndromes associated with clefting are inherited in an autosomal dominant pattern, with variable penetrance. In these cases, each offspring of an affected individual has up to a 50% chance of inheriting the syndrome. In sharp contrast, the recurrence rate of isolated clefts is low. The chance that unaffected parents of a child with a cleft will have another child with a cleft is estimated to be from 2% to 6%: cleft lip with or without cleft palate has a different rate of recurrence than cleft palate alone. The risk increases with the number of affected individuals in the family and decreases with the distance of relatedness.

Prenatal Diagnosis and Prevention

The availability and increased use of fetal ultrasonography have led to a prenatal diagnosis of many birth defects, including oral-facial clefts. Some, but not all, clefts can be diagnosed antenatally by ultrasonography, yet in many instances a cleft, particularly a palatal cleft, is first identified in the delivery room and can be quite unexpected. Some syndromes associated with clefts (eg, trisomy 13) can be diagnosed prenatally, but most syndromes cannot. Level 2 ultrasonography is frequently offered to women who themselves were born with a cleft or who have a first-degree relative with a cleft. Folic acid supplementation (from preconception until the transition to prenatal vitamins) is recommended to all women of reproductive age and for women at increased risk in particular because some data suggest that folic acid deficiency is a contributing factor to clefting.

Summary

- On the basis of strong evidence, orofacial clefts are birth defects identified in approximately 1 in 600 US births, an estimate supported by a recent epidemiologic study of birth defects. (1)
- On the basis of strong evidence, a cleft may be an isolated anomaly or part of an underlying genetic syndrome, usually associated with other abnormalities.

- In a newborn with a cleft whose airway is secure, the first important clinical issue is feeding.
- There are a number of techniques and interventions that clinical experience has found to be useful in establishing early nutrition.
- It is also important to recognize the association with mandibular hypoplasia or micrognathia and upper airway obstruction, such as in Pierre Robin sequence.
- Other problems include speech, hearing, middle ear effusion, and dental issues.
- It is important to recognize more subtle forms of cleft, such as bifid uvula and submucous cleft palate (an apparently intact palate with underlying defects in the bony and/or muscular components of the palate), which can be associated with velopharyngeal insufficiency and middle ear disease.

Resources for Providers and Families:

FACES: The National Craniofacial Association (http://www.faces-cranio.org)

The Cleft Palate Foundation (http://www.cleftline.org/)

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PIR Quiz Requirements

To successfully complete 2014 *Pediatrics in Review* articles for *AMA PRA Category 1 Credit*, learners must demonstrate a minimum performance level of 60% or higher on this assessment, which measures achievement of the educational purpose and/or objectives of this activity. If you score less than 60% on the assessment, you will be given additional opportunities to answer questions until an overall 60% or greater score is achieved.

NOTE: Learners can take *Pediatrics in Review* quizzes and claim credit online only at: http://pedsinreview.org.

1. You are examining an infant in the newborn nursery and note a cleft palate. Of the following genetic syndromes, you should give HIGHEST consideration to:
   A. Neurofibromatosis.
   B. Noonan syndrome.
   C. Russell-Silver syndrome.
   D. Trisomy 21.
   E. Velocardiofacial syndrome (22q11.2 deletion syndrome).

2. You are discussing incidence of cleft lips and palates with parents at a prenatal visit. Among the following, you are MOST likely to say:
   A. Cleft lip with or without cleft palate is more frequent than cleft palate alone.
   B. Cleft lip with or without cleft palate occurs more often in females.
   C. Clefts occur most commonly in African American populations.
   D. Isolated cleft palate is seen more often in males.
   E. Orofacial clefts are relatively uncommon, occurring in approximately 1 in 5000 US live births.

3. A mother brings her 2-week-old son with a cleft palate in for well-child care. Of the following, the statement you are MOST likely to make when counseling the mother is:
   A. Infants with a cleft require less frequent burping.
   B. Children with clefts do not have normal suck or swallow reflexes.
   C. Direct breastfeeding is rarely successful as the sole means of feeding an infant with a cleft palate.
   D. Special nipples are useful to facilitate feeding this child.
   E. Use of a breast pump should be discouraged to maximize the infant's oral training at the breast.

4. You are seeing a 6-month-old girl for well-child care and note an isolated bifid uvula. Among the following, you should evaluate the child for:
   A. Eyelid coloboma.
   B. Otitis externa.
   C. Pierre-Robin sequence.
   D. Submucous cleft palate.
   E. Upper airway obstruction.

5. A 10-month-old infant from your practice is about to undergo repair of her cleft palate. At the time of her surgical repair under anesthesia, you should anticipate that the child will MOST likely also undergo:
   A. Central venous catheter placement for hyperalimentation.
   B. Dental examination.
   C. Percutaneous endoscopic gastrostomy.
   D. Tracheostomy.
   E. Tympanostomy tube placement.

Parent Resources from the AAP at HealthyChildren.org

- http://www.healthychildren.org/English/family-life/health-management/pediatric-specialists/Pages/What-is-a-Pediatric-Plastic-Surgeon.aspx
- Spanish: http://www.healthychildren.org/spanish/family-life/health-management/pediatric-specialists/paginas/what-is-a-pediatric-plastic-surgeon.aspx
- http://www.healthychildren.org/English/health-issues/conditions/developmental-disabilities/Pages/Congenital-Abnormalities.aspx
- Spanish: http://www.healthychildren.org/spanish/health-issues/conditions/developmental-disabilities/paginas/congenital-abnormalities.aspx

Cleft Lip and Palate

Mary-Alice Abbott

Pediatrics in Review 2014;35;177
DOI: 10.1542/pir.35-5-177

Infectious Diseases in Early Education and Child Care Programs

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Pediatrics in Review 2014;35;182
DOI: 10.1542/pir.35-5-182

Infectious Diseases in Early Education and Child Care Programs

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Author Disclosure
Dr Shope has 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.

Practice Gap

Out-of-home care and education are the norms for most young children and lead to increased exposure to infectious diseases. Pediatricians need to be aware of strategies to reduce the risk of infection and guidelines for determining exclusion and return to care for mildly ill children who participate in group care arrangements.

Objectives

After completing this article, readers should be able to:

1. **Recognize the risks of infectious diseases in children who participate in early care and education programs.**
2. **Understand methods for reducing infectious diseases in early care and education settings.**
3. **Identify which infectious diseases require exclusion from early care and education programs.**

Introduction

Two-thirds of children younger than 6 years participate in nonparental out-of-home early education and child care. Demographic trends during the past several decades reflect an increased desire and need to work for men and women who are parents. During the first 2 years of participation, children enrolled in early care and education (ECE) programs experience a higher incidence of respiratory and diarrheal infections, otitis media, and antibiotic-resistant bacteria compared with their peers primarily cared for at home. The types of infection generally reflect common respiratory and gastrointestinal viruses in circulation in the community. However, there are some infectious diseases that can cause outbreaks or clusters of infections in ECE settings. When ill children are excluded from an ECE facility, parents may miss work, lose income, and seek health care services in an effort to return their children to child care. Pediatricians need to be aware of the infectious disease risks of child care attendance and various strategies for reducing them. In addition, pediatricians need to be knowledgeable about rational exclusion and return to care criteria and policies for responsible decision-making. Finally, pediatricians should be aware of the long-term health effects of child care attendance, which will assist parents in making decisions about what is best for their children and families.

There are several different types of out-of-home ECE programs. The terms used to describe various types of programs and what they call themselves can vary. In general, *small* (1-6 children) and *large* (7-12 children) *family child care* is used for groups of children in the residence of the teacher or caregiver. *Child care centers* enroll any number of children in a nonresidential setting or more than 13 children in any setting that is open on a regular basis. Age groups are defined in Table 1, with corresponding expected developmental levels. Age and developmental level are used to determine proper ratios of children to child care staff in various settings. In large centers, an entire room may be composed of children in one age group or developmental stage (ie, there may be a "toddler room"). In family child care homes, children from more than one age group may share the same rooms with

Abbreviations

AAP: American Academy of Pediatrics
CFOC3: *Caring for Our Children*, 3rd ed
ECE: early care and education
RSV: respiratory syncytial virus

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the teacher or caregiver. National guidelines and state licensing regulations define optimal and allowable group sizes and staffing ratios for the different types of programs. (1) Larger size of center, larger group size, and fewer staff members caring for more children have all been linked to increased incidence of infectious diseases.

Epidemiology

Types and Incidence

Infections in children enrolled in early education and child care programs reflect those that occur in the community. It is likely that there is bidirectional transmission: children and child care staff bring infections into the group setting from other family members, and, in turn, newly infected children and staff may transmit their illnesses to previously healthy family members and into the community. A large proportion of these infections are respiratory in nature. Gastrointestinal infections comprise only approximately 10% of these illnesses. (2) Incidence of illness is the highest in infants younger than 1 year compared with older children, regardless of the out-of-home setting. Infants in group care experience approximately 8 respiratory infections per year, 3 to 4 times the rate of kindergarten-age children. However, after the first 2 years of life, children who are continuously enrolled in ECE programs experience approximately the same incidence of illness as children with limited interaction with other children (maternal care or care by a relative, friend, or family member). This finding suggests that children in group out-of-home child care settings are exposed to larger numbers of pathogens and may acquire immunity to pathogens at an earlier time point. This immunity appears to last for years. Children who are cared for in large group child care in their infancy, toddler, and preschool years experience significantly fewer upper respiratory tract infections in their first 5 years after school entry, compared with those primarily cared for at home or in a small child care home setting. (3)

Some controversy surrounds the issue of whether incidence of illness is higher in centers vs family child care homes. The traditional view is that children in centers experience more illness because there are larger numbers of children in the center and group sizes may be larger compared with family child care homes. Studies have found that incidence of respiratory illness increases with increasing exposure to other children in the same group, especially 6 children or more, with the effect beginning to wane when the groups are larger than 8 children. (4) However, some studies report the same or higher incidence of illness in children enrolled in family child care homes compared with child care centers. (2) Some of the differences among studies may be due to different study methods. Different modes of reporting (medical record review or parent or child care professional report) and periods of recall (parents have a poor recall of illness after a week) can also affect results. Children enrolled in centers compared with children at family child care homes are much more likely to have days of absence, presumably due to stricter exclusion criteria. This occurrence may lead to a reporting bias by parents of children in child care centers. Importantly, children in child care centers experience a rapid decrease in illness incidence after the first year of attendance, probably because of earlier acquisition of immunity. (2) Many cross-sectional studies on this subject do not account for the effect of prior accumulated child care exposure. Aside from study method issues, it is possible that earlier development of immunity and stricter infection control and prevention procedures lead to lower incidence of infections in children in centers vs family child care homes.

Because children in out-of-home group settings experience more respiratory infections compared with children cared for only at home, they also experience more acute otitis media and subsequent tympanostomy tube placement. In addition, respiratory infections may last longer in children attending child care centers. These 2 factors lead to more antibiotic prescriptions for otitis media and sinusitis. Antibiotic pressure leads to the development of resistant bacteria. (5)

Table 1. Typical Age and Functional Developmental Groups in Child Care Settings

Group	Age	Functional Definition (by Developmental Level)
Infant	Birth to <12 months	Birth to ambulation
Toddler	12–35 months	Ambulation to accomplishment of self-care routines, such as use of the toilet
Preschooler	36–59 months	From achievement of self-care routines to entry into regular school

Modified from American Academy of Pediatrics. (1)

Exposure to group care early in life also appears to play an important role in the development of atopic disease and asthma. The evolving hygiene theory proposes that decreased stimulation of the immune system from more hygienic environments surrounding children in industrialized countries with smaller family sizes may in part explain the increase in incidence of asthma and allergies seen in the past several decades. Increased microbial exposure among children raised on farms and exposed to certain pets is associated with a lower incidence of asthma and allergic diseases at school age. The same association has generally been demonstrated among children in group care programs, but findings vary among studies, reflecting the complexity of the development of asthma and atopic disease. To confer a protective effect, it appears necessary that the child care exposure occurs in the first year of life. In addition, similar to farm children, genetics seems to play an important role for children who participate in group care programs. Children with the T allele of the *TLR2/-16934* gene are protected, but AA homozygotes tend toward an increased risk of wheezing at school age. (6) In children of mothers with asthma, early participation in group care does not reduce future episodes of wheezing. Respiratory syncytial virus (RSV) infection is more common in children in early group care, and some studies have suggested that early RSV infection may be associated with increased wheezing at a later age. (7) The intestinal flora is also believed to be important in the maturation of the immune system, and antibiotic administration, which is more common in children who participate in group care, has been evaluated and not found to be associated with the development of asthma. (8) Given the high prevalence of asthma, this complex and evolving area of research will be important to follow in the context of children who participate in child care.

How Infectious Diseases Spread

Infectious diseases spread efficiently in ECE settings. Fecal-oral transmission occurs due to fecal contamination of the caregiver's hands during diaper changing or toileting by older children who have not yet mastered proper hand-hygiene techniques. Contaminated hands of staff and children touch surfaces (changing tables, toilet seats, doorknobs, and toys) that are touched by others' hands and then gain entry to the mouth. Respiratory diseases, such as RSV and influenza, are spread by large droplets from sneezing or coughing that travel short distances in the air (<3 ft) and enter the respiratory tract via the conjunctiva, nasal passages, or mouths of others. Less commonly, respiratory diseases, such as varicella and measles, can spread in aerosolized form or by secretions landing on objects (fomites) that are then handled by others. Some infectious diseases, such as influenza, enterovirus, and adenovirus, spread by more than one route. Young children do not reliably cover their mouths and noses when sneezing and coughing, and contagious nasal secretions can also be passed directly to other children or via contact with contaminated surfaces. Finally, some infections or infestations can be caused by direct contact of one child to another, such as scabies, tinea capitis and corporis, and pediculosis. Table 2 provides a detailed breakdown of some of the common pathogens that occur in ECE settings.

Outbreaks

An outbreak is a sudden increase in the incidence of a disease above what is expected as a baseline. Seasonal outbreaks of infectious diseases, such as hand-foot-and-mouth disease (enteroviruses), bronchiolitis (RSV and others), and influenza, are expected to occur in the community each year. These outbreaks can be amplified in group settings. In addition to the predictable seasonal outbreaks, there are some infectious diseases that are more likely to cause outbreaks in ECE settings. Outbreak-causing respiratory pathogens include group A streptococcal pharyngitis, *Neisseria meningitidis,* and some vaccine-preventable diseases, such as pertussis, *Haemophilus influenzae* type b, measles, mumps, rubella, and varicella. As these latter pathogens became vaccine preventable, their incidence in ECE settings significantly decreased. Influenza deserves special mention because clinical disease and serologic conversion in young children in child care during influenza season is high. Influenza morbidity and mortality in young children are also high. Despite routine influenza vaccine recommendation for children 6 months or older since 2010, influenza immunization rates remain low, especially when compared with other vaccine-preventable diseases. Higher influenza immunization rates are hampered by many factors. These factors include the yearly need to vaccinate, lack of parental acceptance, lack of state or child care program requirement for participants and staff members to receive the influenza vaccine, and the need for vigorous health care professional promotion.

Immunizations have succeeded in reducing many pathogens that spread by the respiratory route. In addition, rotavirus outbreaks were common in ECE settings, but the incidence decreased significantly after licensing of the current vaccines in 2006 and their routine recommendation in 2009. As a result, norovirus is increasingly important as a cause of gastroenteritis outbreaks in the United States. Hepatitis A has also historically caused significant outbreaks in group care programs. There has been

Table 2. **Common Pathogens and Modes of Transmission**

Mode of Transmission	Bacteria	Viruses	Parasite, Fungal, or Other
Fecal-oral contact	*Campylobacter* organisms, *Escherichia coli* O157:H7, *Salmonella* organisms, *Shigella* organisms	Astrovirus, norovirus, enteric adenovirus, enteroviruses, hepatitis A, rotaviruses	*Cryptosporidium* sp, *Enterobius vermicularis, Giardia intestinalis*
Respiratory, airborne		Influenza, varicella zoster, measles	
Respiratory, droplet	*Bordetella pertussis*, *Haemophilus influenzae* type B, *Neisseria meningitidis*, *Streptococcus pneumoniae*, diphtheria, group A streptococcus	Adenovirus, influenza virus, human metapneumovirus, measles virus, mumps virus, parvovirus B19, respiratory syncytial virus, rhinovirus, rubella virus	
Respiratory, contact		Mumps virus, rubella virus, rhinovirus, enterovirus, parainfluenza virus, respiratory syncytial virus	
Direct person-to-person or contact with fomite	*Staphylococcus aureus*, group A streptococcus	Herpes simplex, human immunodeficiency virus, hepatitis B, cytomegalovirus, varicella zoster virus	Pediculosis, scabies, tinea capitis, tinea corporis

Modified from the Redbook, 2012, 29th ed., American Academy of Pediatrics. (14)

a marked decrease in hepatitis A incidence in adults and children since the vaccine was licensed in 1995. Recommendations for its use in children broadened in 2005 to include vaccination for all children older than 12 months.

Young children are usually asymptomatic with hepatitis A infection; therefore, the infection is often first recognized when adult teachers or caregivers become symptomatic. Despite these successes, vaccines are not available to prevent diarrheal outbreaks from *Shigella*, Shiga toxin-producing *Escherichia coli*, *Giardia*, and cryptosporidiosis. *Salmonella* diarrheal outbreaks in ECE settings are uncommon but may occur. They are often related to the presence of a reptile or amphibian pet. These animals can be colonized with *Salmonella* in the gastrointestinal tract. They should not be kept in ECE settings.

Strategies to Reduce Disease Transmission

There are 3 main strategies for reducing infectious disease burden in child care settings.

Immunization

Immunization of children is a safe and effective intervention to prevent and reduce transmission of pathogens in child care settings. Program-specific admission rules and state child care licensing regulations define which vaccines and health data are required for attendance. These rules and regulations prompt health care visits, which provide an opportunity for parents and pediatricians to discuss the benefits of vaccines and to ensure the child receives other preventive health care services. Although only a small number of parents refuse vaccinations for religious and philosophical reasons, these unvaccinated children not only are at an increased risk for vaccine-preventable diseases themselves but also may increase the risk for vaccinated children. Parents of infants and toddlers too young to have received all the protective vaccines and parents of any others who are undervaccinated (from alternative immunization schedules or delayed immunizations) should be made aware that their children are at increased risk for contracting vaccine-preventable diseases in a group care setting. If these children are exposed to someone with a vaccine-preventable disease, they may be excluded from care for various periods for their protection. Such exclusion may result in significant loss of parental time from work. Vaccination requirements in state child care licensing regulations may lag behind what is recommended by the American Academy of Pediatrics (AAP) and the Advisory Committee on Immunization Practices. Pediatricians should advocate for the most up-to-date recommendations, regardless of state or program requirements.

Infection Control and Prevention

An effective infection control and prevention program for an ECE program has multiple components. *Caring for Our Children: National Health and Safety Performance Standards, Guidelines for Early Care and Education Programs*, third edition (*CFOC3*), (1) is a large document with a broad scope that contains standards for high-quality child care programs, including guidelines for infection control and prevention. Policies should be written in consultation with a health care professional serving as a child care health consultant. These policies should be the basis for regular training of staff members about infection control and prevention. Policies should cover requirements for documented immunizations for children and staff members; proper procedures for preparing food; diaper changing; cleaning, sanitation, and disinfection; hand hygiene; and other standard precautions. A set of model policies, compatible with *CFOC3*, is available from the AAP (http://www.ecels-healthychildcarepa.org/publications/manuals-pamphlets-policies/item/248-model-child-care-health-policies). Pediatricians should be aware of some of the basic components of infection control and prevention in ECE settings. Pediatricians who are consulted about ECE programs may recommend consultation with a local pediatric infection control and prevention expert. It is helpful to think of infection control and prevention elements in terms of the route of spread of pathogens.

To reduce fecal-oral spread of pathogens, whenever possible staff members involved in diaper changing should not also participate in food preparation. In addition, staff members who are ill should not prepare food. These recommendations are not always possible in family child care homes where only one child care professional is responsible for all of the daily tasks. Food preparation should always be preceded by careful hand hygiene. Diaper changing is also a major cause of fecal-oral transmission. The diaper-changing procedure is a multistep process that involves proper equipment, training, and organization. After diaper changing, hand hygiene is essential for the child and caregiver. In addition, the diaper-changing surface must be disinfected after each use. A free diaper-changing poster that complies with *CFOC3* recommendations and has good graphic illustrations of the steps is available at http://www.ecels-healthychildcarepa.org/tools/posters/item/279-diapering-poster.

To reduce transmission of pathogens from surfaces, cleaning, sanitizing, and disinfecting at various intervals are important. Cleaning is necessary before sanitizing or disinfecting if there is visible soil. The purpose of cleaning is to remove particulate matter and maximize the effectiveness of the sanitizing or disinfecting agents. Sanitizing is less rigorous than disinfecting. The intent of sanitizing is to reduce potential pathogens on food preparation surfaces, utensils, tables, countertops, and plastic toys. The goal of disinfection is to kill most pathogens. Disinfection requires stronger concentrations or different agents than used for sanitizing and may require longer surface contact times. Disinfecting is used for areas with higher likelihood of pathogens: door and cabinet handles, drinking fountains, and all surfaces, including floors in toilet and diaper or soiled underwear–changing areas (for details see *CFOC3*, Appendix K). (1)

The hands of young children carry and transmit pathogens by directly contacting infected secretions or surfaces then touching their own or another child's mucous membranes. Therefore, hand hygiene is second only to immunization as an essential component of infection control and prevention. Proper hand washing consists of wetting the hands, applying soap, and lathering for at least 20 seconds before rinsing off the soap in running water. Hand washing is the preferred method of hand hygiene and is required whenever there is particulate matter, such as stool or nasal secretions, present. However, alcohol-based hand sanitizer can be used as a substitute when soap and water are not available as long as the hands are clean of visible dirt or secretions. Alcohol-based hand sanitizers contain 60% to 95% alcohol and are toxic if ingested and flammable. Their use can cause some contents to aerosolize. Therefore, dispensers should be kept out of reach of children and away from diaper-changing tables or other places where children might inhale the fumes. Alcohol-based hand sanitizers may be used as hand hygiene by children older than 24 months under close adult supervision. Hand hygiene should occur for staff and children on arrival; when moving from one group to another; before and after contact with food or medication administration; and after diaper changing or toileting, contact with nasal or other body secretions, animals, and garbage, and playing outside.

Studies have found that hand hygiene regimens are modestly effective in reducing illness due to infectious diseases, but results vary significantly by study. (9) In general, hand hygiene seems to be more effective for reducing diarrheal compared with respiratory illnesses. This finding may be due to spread of respiratory pathogens primarily by droplet. Covering the mouth or nose during coughing or sneezing is a skill that infants and young toddlers have not mastered. In addition, hand-to-mouth behavior is typical for this age group. So some transmission occurs despite diligent efforts to practice hand hygiene in infant and toddler age groups. Hand hygiene regimens work better the more frequently they are performed.

One study found a reduction in influenza-like illness with hourly hand sanitizer use for teachers or caregivers and children but no benefit when use was every 2 hours. (10)

Finally, other environmental considerations may also be important to reduce infections. Larger group size is associated with an increase in the transmission of respiratory disease. Staffing ratios may be important because more staff may enhance the practice of preventive routines. The amount of space per child, proper layout and equipment, location and number of sinks, and location of food preparation areas and diaper-changing tables can potentially help to limit spread of infection. It is likely that a combination of methods is important for infection control and prevention: training; surface cleaning, sanitizing, or disinfecting; hand hygiene; and procedural and environmental modifications.

Exclusion

Exclusion occurs when an ill child is prevented from entering the program at the drop-off or sent home when the child becomes ill. Decisions about exclusion are often contentious because ECE professionals, parents, and pediatricians do not agree. Evidence-based national guidelines exist, (1) (11) but many decision-makers are not aware of them. State child care licensing bodies have been slow to adopt the national guidelines, further contributing to inappropriate exclusion practices. Finally, each ECE program can develop its own exclusion rules, as long as they meet or exceed state regulations.

Studies demonstrate that ECE professionals unnecessarily exclude many mildly ill children compared with recommendations in the national guidelines. (12) Exclusion practices are influenced by strongly held parent and ECE professional beliefs. Parents whose children are not ill sometimes pressure staff members to apply stricter exclusion criteria to children from other families to reduce exposure of their children. Paradoxically, when their own children are ill, they find the exclusion criteria burdensome. Mistaken beliefs about the benefits of antibiotics may lead ECE professionals or parents to want children

Table 3. General Symptom–Based Exclusion Criteria

Symptom(s)	Management
Illness that prevents participation in activities, as determined by early care and education staff members	Exclusion until illness resolves and able to participate in activities
Illness that requires a need for care that is greater than staff members can provide without compromising health and safety of others	Exclusion or placement in care environment where appropriate care can be provided, without compromising care of others
Severe illness suggested by fever with behavior changes, lethargy, irritability, persistent crying, difficulty breathing, and progressive rash with above symptoms	Medical evaluation and exclusion until symptoms have resolved
Rash with fever or behavioral change	Medical evaluation and exclusion until illness is determined not to be communicable
Persistent abdominal pain (≥2 hours) or intermittent abdominal pain associated with fever, dehydration, or other systemic signs and symptoms	Medical evaluation and exclusion until symptoms have resolved
Vomiting ≥2 times in preceding 24 hours	Exclusion until symptoms have resolved, unless vomiting is determined to be caused by a noncommunicable condition and child is able to remain hydrated and participate in activities
Diarrhea if stool not contained in diaper or if child is toilet trained and having accidents; for all children if stool frequency exceeds ≥2 stools above normal for that child or stools contain blood or mucus	Medical evaluation for stools with blood or mucus; exclusion until stools are contained in the diaper or when toilet-trained children no longer have accidents and when stool frequency becomes <2 stools above that child's normal frequency or a care plan to accommodate the child's special needs can be implemented
Oral lesions	Exclusion if unable to contain drool or if unable to participate because of other symptoms
Skin lesions	Exclusion if lesions are weeping or draining and cannot be covered with a waterproof dressing

*Modified from the Redbook, 2012, 29th ed., American Academy of Pediatrics. (14)

Table 4. Conditions for Which Exclusion Is Required

Condition	Management of Case	Management of Contacts
HAV infection	Serologic testing to confirm HAV infection in suspected cases. Exclusion until 1 week after onset of jaundice.	If ≥1 cases confirmed in child or staff attendees or ≥2 cases in households of staff or attendees, HAV vaccine or immunoglobulin should be administered within 14 days of exposure to unimmunized staff and attendees. In centers without diapered children, HAV vaccine or immunoglobulin should be given to unimmunized classroom contacts of index case. Asymptomatic immunoglobulin recipients may return after receipt of immunoglobulin.
Impetigo	Exclusion until treatment has been initiated. As long as lesions on exposed skin are covered, the child can return.	No intervention unless additional lesions develop.
Measles	Exclusion until 4 days after onset of rash and when the child is able to participate.	Immunize exposed children without evidence of immunity within 72 hours of exposure. Children who do not receive vaccine within 72 hours or who remain unimmunized after exposure should be excluded until at least 2 weeks after onset of rash in the last case of measles.
Mumps	Exclusion until 5 days after onset of parotid gland swelling.	In outbreak setting, people without documentation of immunity should be immunized or excluded. Immediate readmission may occur after immunization. Unimmunized people should be excluded for ≥26 days after onset of parotitis in last case.
Pediculosis capitis (head lice)	Treatment at end of program day and readmission on completion of first treatment (Exclusion only if first treatment not done).	Household and close contacts should be examined and treated if infested.
Pertussis	Exclusion until 5 days of appropriate antimicrobial therapy course completed.	Immunization and chemoprophylaxis should be administered as recommended for household contacts. Symptomatic children and staff should be excluded until completion of 5 days of antimicrobial therapy course. Untreated adults should be excluded until 21 days after onset of cough.
Rubella	Exclusion until 7 days after onset of rash for postnatal infection.	Pregnant contacts should be evaluated.
Salmonella serotype Typhi infection	Exclusion until 3 negative stool culture results, stools contained in the diaper or when toilet trained children no longer have accidents, and frequency <2 stools above normal for the child.	Stool cultures should be performed for attendees and staff.
Nonserotype Typhi *Salmonella* infection or unknown *Salmonella* serotype	Exclusion until stools contained in the diaper or when toilet trained children no longer have accidents and frequency <2 stools above normal for the child. Negative stool culture results not required for nonserotype Typhi *Salmonella* species.	Stool cultures are not required for asymptomatic contacts. Antimicrobial therapy is not recommended for asymptomatic infection or uncomplicated diarrhea or for contacts.

Continued

Table 4. (Continued)

Condition	Management of Case	Management of Contacts
Scabies	Exclusion until after treatment given.	Close contacts with prolonged skin-to-skin contact should have prophylactic therapy. Bedding and clothing in contact with skin of infected people should be laundered.
STEC, including *Escherichia coli* O157:H7, or *Shigella* infection	Exclusion until ≥1 stool culture result is negative, depending on state regulations. Also, exclusion until stools are contained in the diaper or when toilet trained children no longer have accidents and frequency <2 stools above normal for the child.	Meticulous hand hygiene; stool cultures should be performed for any contacts. Center(s) with cases should be closed to new admissions during STEC outbreak.
Staphylococcus aureus skin infections	Exclusion only if skin lesions are draining and cannot be covered with a watertight dressing.	Meticulous hand hygiene; cultures of contacts are not recommended.
Streptococcal pharyngitis	Exclusion until 24 hours after treatment has been initiated and the child is able to participate in activities.	Symptomatic contacts of documented cases of group A streptococcal infection should be tested and treated if test results are positive.
Tuberculosis	For active disease, exclusion until determined to be noninfectious by physician or health department authority. May return to activities after therapy is instituted, symptoms have diminished, and adherence to therapy is documented. No exclusion for latent tuberculosis infection.	Local health department personnel should be informed for contact investigation.
Varicella	Exclusion until all lesions have dried and crusted (usually 6 days after onset of rash in immunocompetent people; may be longer in immunocompromised people). Breakthrough cases are modified and may be maculopapular only and may not crust. In these cases, isolate for 24 hours after appearance of last lesions.	For people without evidence of immunity, varicella vaccine should be administered within 3 days but up to 5 days after exposure, or varicella-zoster immunoglobulin should be administered up to 10 days after exposure when indicated.

HAV=hepatitis A virus; STEC=Shiga toxin–producing *Escherichia coli*.
Modified from the Redbook, 2012, 29th ed., American Academy of Pediatrics (14)

to receive antibiotics to hasten recovery. Despite the fact that health care professionals usually determine when a child has recovered from illness by asking the parent if the child seems well, many ECE professionals request a physician's note for an excluded child to return to care. This practice puts an unnecessary burden on parents and the health care professional. In some cases, parents use the emergency department to fulfill the physician visit requirement because they cannot access their primary care site in a timely fashion, although they recognize the nonurgent nature of their child's condition. There is no evidence that these required health care visits and notes enhance the health of the child or others at the child care setting, yet they are a requirement in many state child care licensing guidelines.

For many parents in the United States, child care is an economic necessity. Exclusion of children from child care accounts for almost half of work absence. A parent of a child younger than 6 years can expect to lose 6 to 29 days of work per year caring for their child when the child becomes ill. (13) Lost time at work can lead to lower wages or job loss, especially for low-income parents,

Table 5. Conditions for Which Exclusion Is Not Required[a]

Condition	Rationale
Common cold, runny nose, cough	No treatment. No effective means to stop transmission.
Bacterial conjunctivitis, pink eye, eye discharge	Treatment for bacterial conjunctivitis is minimally effective. (16) No evidence treatment or exclusion reduces transmission.
Fever without signs of illness in children older than 4 months	Fever, without other signs of illness, does not represent a threat to other children.
Rash without fever or behavior change	We immunize for most harmful viruses that cause rashes. Many harmless viral pathogens cause rash. Nondraining or oozing rash from eczema does not require exclusion.
Lice or nits	Treatment at the end of the day and return the next day.
Ringworm	Treatment at the end of the day and return the next day.
Thrush	*Candida* normally found on skin and in mouth. Not harmful to child or others.
Fifth disease (parvovirus B19)	When rash appears no longer contagious.
MRSA	No exclusion needed as long as draining lesions can be covered.
Cytomegalovirus infection	Long-term shedding occurs in children in child care. Cannot effectively reduce transmission.
Chronic hepatitis B virus infection	Transmission in child care has been reported, but in the United States risk is negligible due to high infant hepatitis B immunization rates. Children with open skin sores or who bite or scratch need to be handled on a case by case basis.
HIV infection	No transmission in child care has occurred.
Diarrhea IF stool contained in diaper for infants or toddlers or no toileting accidents for older children AND frequency of stooling is <2 stools per day above the child's normal baseline	Fecal contamination is lower if there are no stool accidents and facility routinely follows good infection control and prevention procedures. Caveat to allow for exclusion if diapering becomes too labor-intensive (ie, ≥2 stools above normal for child).
Children who are colonized with or shedding a pathogen in their stool (see Table 4 for specifics regarding *Shigella*, *Escherichia coli*, and *Salmonella*)	Many pathogens shed in stool for prolonged periods. General diarrhea exclusion criteria still apply (exclude for stool spills or ≥2 stools above normal for child).

HIV=human immunodeficiency virus; MRSA=methicillin-resistant *Staphylococcus aureus*.
[a]Parents should be notified by child care professionals for all of these conditions. For some of them, a health care visit may be indicated.

who may not have the benefit of paid sick leave and may be struggling to maintain their employment.

To address these conflicting views of exclusion and to provide focused information about management of infectious diseases, the AAP publishes *Managing Infectious Diseases in Child Care and Schools, A Quick Reference Guide*, now in its third edition. (11) This guide contains the *CFOC3* national guidelines in a user-friendly format written as a source of handouts for health care professionals to give to families and for ECE professionals as the gatekeepers of the exclusion process. Each common symptom or disease is presented in a Quick Reference Sheet that can be copied and given to parents at an illness visit or during an outbreak, for example, of hand-foot-and mouth disease. Each handout provides clear guidance regarding exclusion, control of infection within the program, return-to-care criteria, and requirement for health care visits. Recommendations in *Managing Infectious Diseases* parallel those of the AAP's *Redbook* (14) and *CFOC3*. The *CFOC3* guidelines can also be accessed online (http://cfoc.nrckids.org/StandardView/3.6).

According to the *CFOC3* national guidelines, decisions about exclusion should be based on the behavior of the child and the risk of spread of infectious disease to other children and staff. Clearly, children should be excluded for any condition that requires emergency care or urgent care. A mildly ill child should be excluded if the illness (1) is preventing participation in activities, (2) requires care that is greater than staff can provide without compromising the health and safety of others, or (3) poses a risk of spread of harmful disease to others. The first 2 exclusion criteria are decided by the ECE professional. In

the third criterion, the word *harmful* is key. Because vaccines have substantially reduced the incidence of many harmful infectious diseases, exclusion for this reason is not common.

Does exclusion reduce the spread of infectious diseases? Most common infectious diseases have an incubation period followed by several days in which a child may be contagious and can spread disease but may not be symptomatic. After an illness has resolved, pathogens can be shed in body fluids for days to weeks. These children may also be contagious but not ill. In addition, many infections are subclinical; they never produce symptoms, yet the child can spread the pathogen to others. Therefore, excluding only ill children has little effect on the spread of most infectious diseases. After an illness has resolved, it is not practical to keep children out of care for the following days or weeks, when they can still be shedding the pathogen. (15) A small number of conditions are serious enough that exclusion is necessary to reduce the chance of spread. Most exclusions should be determined by the child's symptoms: either not being well enough to participate or requiring too much care for staff members to provide and still attend to the needs of the other children in the group.

Teachers and caregivers recognize illness by observing symptoms but rarely know the diagnosis. When teaching and communicating with ECE staff members about exclusion decisions, pediatricians should discuss symptoms. Symptom-based language, listed in Table 3, helps ECE professionals decide what to do and when referral to a health care professional is appropriate. Although families may seek telephone advice from their child's health care professional, a health care visit is not needed for most children who are excluded from their ECE program. When a child is seen by a clinician, the diagnosis of specific conditions may be made. The diagnoses that require exclusion are listed in Table 4. Note that many vaccine-preventable and outbreak-associated infections require exclusion. Conditions that do not require exclusion are listed in Table 5. Note that bacterial conjunctivitis no longer requires exclusion.

Despite the existence of national exclusion guidelines, unnecessary exclusions still occur frequently. Pediatricians can take a more active role in reducing unnecessary exclusions by offering advice and education to ECE professionals about their patients when these children have been excluded inappropriately. For example, a pediatrician can make a photocopy of the relevant Quick Reference Sheet in *Managing Infectious Diseases* for the ECE staff. Pediatricians can also take a proactive role in educating directors, teachers, and caregivers about exclusion criteria. Two free curricula on the subject are available: Curriculum for Managing Infectious Diseases in Early Education and Child Care Settings (http://www.healthychildcare.org/InstructorsManualID.html) and the online learning module Preventing and Managing Infectious Diseases in Early Education and Child Care (http://www.healthychildcare.org/PDF/MIDAccessFlyer.pdf). Pediatricians should become familiar with their state's exclusion criteria. The current regulations that govern legal operation in each state are on the website of the National Resource Center for Health and Safety in Child Care and Early Education (http://nrckids.org/index.cfm/resources/state-licensing-and-regulation-information/). In some situations where an outbreak is suspected, health department staff can plan and implement an appropriate response. Pediatricians with a high level of interest in working with ECE professionals to improve health and safety in their programs can serve as consultants to local programs or advocate for adoption of the *CFOC3* national guidelines at the local or state level by working with their state AAP chapter.

Summary

- On the basis of strong research evidence, children in group out-of-home child care settings experience more infections, especially in the first year of life, compared with children cared for only at home who have less exposure to other children. (2)(4)(5)
- On the basis of strong research evidence, earlier acquisition of immunity develops among children who participate in early care and education programs after the first year or two. In general, early childhood exposure to group settings leads to fewer infections, asthma, and atopic disease at school age, although some important subgroups exist. (2)(3)(4)(5)(6)(7)(8)
- On the basis of some research and consensus, infection control and prevention measures consisting of immunizations, hand hygiene, and cleaning, sanitizing, or disinfecting are important to reduce the spread of infections in early care and education settings. (9)(10)
- On the basis of some research and consensus, the primary reason for exclusion is the inability of the child to participate in activities, but in some cases exclusion is required to reduce the spread of harmful infectious diseases. (1)(11)(15)
- On the basis of strong research evidence, unnecessary exclusion is common and causes workplace and financial hardships for families. Pediatricians can have a role in reducing unnecessary exclusions. (12)(13)

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PIR Quiz Requirements

To successfully complete 2014 *Pediatrics in Review* articles for *AMA PRA Category 1 Credit*, learners must demonstrate a minimum performance level of 60% or higher on this assessment, which measures achievement of the educational purpose and/or objectives of this activity. If you score less than 60% on the assessment, you will be given additional opportunities to answer questions until an overall 60% or greater score is achieved. NOTE: Learners can take *Pediatrics in Review* quizzes and claim credit online only at: http://pedsinreview.org.

1. A mother comes to see you with her 4-month-old son for a routine health maintenance visit and 4-month vaccinations. She tells you that she is going back to work soon and is looking into various out-of-home child care options. She is worried about her son getting sick. Of the following, which is the most accurate statement regarding out-of-home child care?
   - A. Because her son is up to date with vaccinations, he will be at decreased risk of contracting infectious diseases in a child care setting.
   - B. Infants and young children in group child care settings have an increased rate of respiratory infections compared with those children who are cared for in their home.
   - C. There is an increased risk of developing asthma for those infants and young children cared for in an out-of-home child care setting.
   - D. Gastrointestinal infections comprise the most infectious illnesses in child care settings
   - E. Scabies and lice are the most common infectious diseases to which children in group child care settings are exposed.

2. Reducing the infectious disease burden in child care settings requires a multifaceted approach. Of the following, the strategy found to be most effective in the reduction of infectious diseases in child care programs is:
   - A. Use of alcohol-based hand sanitizers.
   - B. Use of prophylactic antimicrobials in all contacts of children with infectious diseases.
   - C. Immunizations.
   - D. Exclusion of mildly ill children until they are examined by a health care professional.
   - E. Use of sanitization methods over disinfecting methods.

3. The parents of a 6-month-old girl come to see you for follow-up after hospitalization for respiratory syncytial virus bronchiolitis. The parents report that the child has been afebrile for several days, is starting to eat better, and has less nasal congestion, cough, and rhinorrhea. They want to know when it is safe to have the child return to child care. Of the following, which would be the BEST response?
   A. Mildly ill children should be excluded if their illness prevents them from participating in activities or requires more care than staff can provide without compromising well-being of other children.
   B. A mildly ill child should be allowed to return to the program as long as the fever has been gone for at least 24 hours regardless of other symptoms.
   C. A child should be excluded from the program with any rhinorrhea, cough, or congestion until these symptoms completely resolve.
   D. The child should be retested for respiratory syncytial virus and only be allowed to return to the program if the test result is negative.
   E. It is at the discretion of the child care center as to when the child is safe to return.

4. A mother brings her 4-year-old daughter to see you in the morning for acute onset of fever and sore throat. You obtain a pharyngeal swab and perform a rapid diagnostic test. The patient tests positive for group A streptococcus. She is prescribed amoxicillin. Later that day, the child care center director calls you to ask what to do with the other 6 children in her room. Of the following, which would be the BEST response?
   A. Long-term shedding of group A streptococcus occurs in children in child care, and it is difficult to reduce transmission.
   B. Those children who are close contacts of the index case with group A streptococcus should start prophylactic antibiotic therapy.
   C. Your patient with group A streptococcus can return to the center after completing 48 hours of antimicrobial therapy.
   D. All contacts, including staff, should be tested for group A streptococcus.
   E. Symptomatic contacts of documented cases of group A streptococcal infection should be tested and treated if test results are positive.

5. You are the health care consultant for the local community child care program. The director of the program calls you because there is a toddler who was recently hospitalized for a skin abscess that was drained. The child has been taking antibiotics for 3 days. The director was told that the wound culture yielded methicillin-resistant *Staphylococcus aureus* (MRSA). She would like advice on what to do next. Of the following, which is the BEST response?
   A. The child should be excluded until 5 days of appropriate antimicrobial therapy is completed.
   B. The child should be excluded until there are 3 negative skin or wound culture results for MRSA.
   C. All contacts of the child, including staff, should be tested for MRSA.
   D. The child should be excluded until the wound can be covered with a watertight dressing without drainage outside the dressing.
   E. Local health department personnel should be informed for contact investigation.

Parent Resources from the AAP at HealthyChildren.org

- http://www.healthychildren.org/English/health-issues/conditions/prevention/Pages/Prevention-In-Child-Care-or-School.aspx
- Spanish: http://www.healthychildren.org/spanish/health-issues/conditions/prevention/paginas/prevention-in-child-care-or-school.aspx
- http://www.healthychildren.org/English/safety-prevention/immunizations/Pages/Preventing-the-Flu-Resources-for-Parents-Child-Care-Providers.aspx
- Spanish: http://www.healthychildren.org/spanish/safety-prevention/immunizations/paginas/preventing-the-flu-resources-for-parents-child-care-providers.aspx

Infectious Diseases in Early Education and Child Care Programs

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Pediatrics in Review 2014;35;182
DOI: 10.1542/pir.35-5-182

Cystic Fibrosis

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Pediatrics in Review 2014;35;194
DOI: 10.1542/pir.35-5-194

Cystic Fibrosis

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Author Disclosure
Drs Paranjape and Mogayzel 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.

Practice Gap

1. The median survival of individuals affected with cystic fibrosis is currently 41.1 years. Whereas standard treatments in cystic fibrosis optimize lung health and nutritional status, treat chronic respiratory infection, and enhance quality of life, newer therapies that target the basic genetic defect hold significant promise for continued improvement in overall health and survival.
2. Pediatric clinicians should be familiar with the clinical presentation, diagnosis, and current management of cystic fibrosis and some of the common disease-related concerns and complications.

Objectives

After completing this article, readers should be able to:

1. Describe the current recommendations for the clinical, laboratory, and genetic analysis tools needed to confirm a diagnosis of cystic fibrosis.
2. Describe the current recommendations for the long-term medications and therapies for maintenance of optimal lung health and nutritional status in children with cystic fibrosis.
3. Recognize the clinical presentations of common cystic fibrosis–related complications.

Introduction

Cystic fibrosis (CF), among the most common of life-shortening genetic diseases, is characterized by chronic, progressive obstructive lung disease along with other systemic manifestations, such as nutrient malabsorption and malnutrition due to pancreatic insufficiency, liver disease and cirrhosis, and CF-related diabetes mellitus (CFRD). Median survival has improved steadily from less than 2 years (1)(2) at the time of the initial description of the disease in 1938 (3) to 41.1 years currently. (4) This improvement in survival largely results from early diagnosis and implementation of therapies to optimize lung health and nutritional status, treat chronic respiratory infection, and improve quality of life. Although there is currently no cure for CF, newer therapies target the basic genetic defect and hold significant promise for continued improvement in overall health and survival. Because the role of the primary care physician is vital to the well-being of children with CF, this review covers the clinical presentation, diagnosis, and current management of CF and some of the common disease-related concerns and complications.

Abbreviations

CF: cystic fibrosis
CFLD: cystic fibrosis liver disease
CFRD: cystic fibrosis–related diabetes mellitus
CFTR: cystic fibrosis transmembrane conductance regulator
DIOS: distal intestinal obstruction syndrome
IRT: immunoreactive trypsinogen

Epidemiology

On the basis of 2012 statistics from the Cystic Fibrosis Foundation, there are approximately 30,000 affected individuals in North America, with a predicted median survival of 41.1 years, and 49.1% are adults 18 years or older. (4) Approximately 1000 new cases are diagnosed annually; 70% of affected children are diagnosed by age 2 years, largely as a result of newborn screening, which was implemented in all 50 states by 2010. The incidence varies by race and ethnicity and is estimated to be 1:3200 in whites, (5) 1:15,000

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in people of African descent, 1:35,000 in people of Asian descent, and 1:9200 to 1:13,500 in Hispanics. (6) Early disease diagnosis, treatment of chronic infection and malnutrition, and other interventions, such as lung transplantation for end-stage lung disease, have had a significant effect on survival during the past 40 years.

Pathogenesis

The disease results from genetic mutations located on chromosome 7q31.2, which codes for a protein known as the cystic fibrosis transmembrane conductance regulator (CFTR), which functions as an apical epithelial chloride channel. To date, more than 1900 mutations have been identified and categorized into 6 distinct classes that reflect abnormalities of CFTR synthesis, structure, and function (7)(8) (Figure 1). Class I mutations result in no functional CFTR protein being produced because of absent or defective protein biosynthesis. Class II mutations lead to protein variants that are improperly processed or transported to the apical cell membrane. For example, the most common and best characterized CFTR mutation, F508del, is a class II mutation. One copy of F508del is present in 70% of the affected population, and 2 copies are present in approximately 50%. Class III mutations affect CFTR activation and hinder chloride movement through channels at the cell surface. For example, G551D is a class III gating mutation targeted by the medication ivacaftor, which improves chloride conductance in individuals with CF with at least one copy of this mutation. Class IV mutations result in defects that produce a normal or diminished amount of CFTR with decreased function at the apical epithelial cell membrane. Class V mutations result from decreased amounts of fully active CFTR. A sixth mutation class is characterized by diminished stability of a fully processed and functional CFTR at the cell surface and often results in the truncation of CFTR toward the carboxyl terminus. (9)

The disease results from 2 *CFTR* mutations; however, they need not be from the same class. The amount of functional CFTR present at the cell surface, which is determined by genotype, partially accounts for the wide spectrum of CF phenotypes and, to some extent, correlates with the degree of organ involvement and disease severity. Class I, II, and III mutations are typically

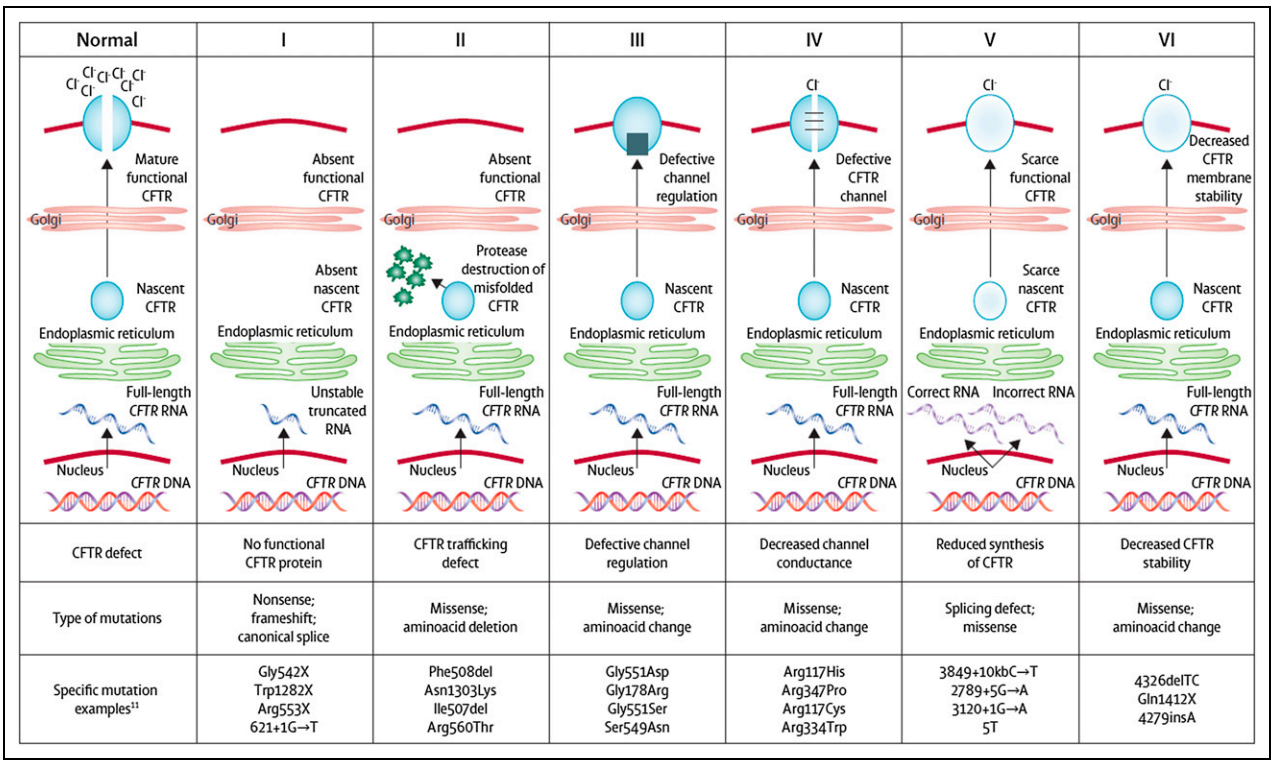

Figure 1. Cystic fibrosis transmembrane conductance regulator (CFTR) mutation classes. CFTR mutations have been grouped into 6 distinct classes based on abnormalities of CFTR synthesis, structure, and function. Reprinted from *The Lancet Respiratory Medicine*, Vol. 1, Issue 2, Boyle MP, DeBoeck K, "A new era in the treatment of cystic fibrosis: correction of the underlying CFTR defect," pages 158–163, (C) April 2013, with permission from Elsevier.

associated with early involvement of respiratory and digestive manifestations (ie, chronic cough, recurrent sinopulmonary infections, and exocrine pancreatic insufficiency). Class IV and V mutations are generally associated with milder or later-onset lung disease and exocrine pancreatic sufficiency.

Diminished or absent chloride channel function results in dehydrated, viscid secretions that contribute to organ dysfunction (Figure 2). In the lungs, mucous plugging leads to inflammation, chronic infection, progressive small airways obstruction, and bronchiectasis. In the exocrine pancreas, intestinal tract, and liver, inspissation of viscid secretions leads to pancreatic insufficiency and results in the malabsorption of fat and protein, intestinal obstruction, and cholestasis. Other clinical manifestations include chronic pansinusitis, nasal polyposis, and reduced fertility. In the sweat gland, abnormal chloride channel function results in excessive salt loss in sweat and forms the basis of the gold standard pilocarpine iontophoresis sweat test for CF diagnosis. (10)

Diagnosis

In 2008, a Cystic Fibrosis Foundation Consensus Panel established diagnostic criteria (11) that include the following: (1) the presence of one or more characteristic phenotypic features of chronic, recurrent sinopulmonary disease, nutritional and gastrointestinal abnormalities, male urogenital abnormalities (eg, absence of vas deferens), and salt depletion syndromes; (2) a family history of CF in a sibling; and (3) a positive newborn screening test result associated with laboratory-demonstrated evidence of CFTR dysfunction, such as elevation of sweat chloride concentration, identification of 2 disease-causing *CFTR* mutations, or demonstration in vivo of characteristic ion transport abnormalities across the nasal epithelium. Approximately 2% of cases are known as nonclassic, (12)(13) in which the genotype-CFTR functionality-phenotype correlations are less clear-cut and result in wide disease variability, which in turn is exaggerated further by the large number of identified mutations. A more appropriate diagnostic term for these individuals is *CFTR-related disorder*. Although the diagnosis of these cases can be challenging, the established diagnostic criteria should be used.

The gold standard for diagnosis of CF remains the pilocarpine iontophoresis sweat test developed by Gibson and Cooke in 1959, (10) which measures the chloride concentration in sweat that is typically elevated in those with CF. To maintain quality control, testing must be performed by experienced personnel using standardized

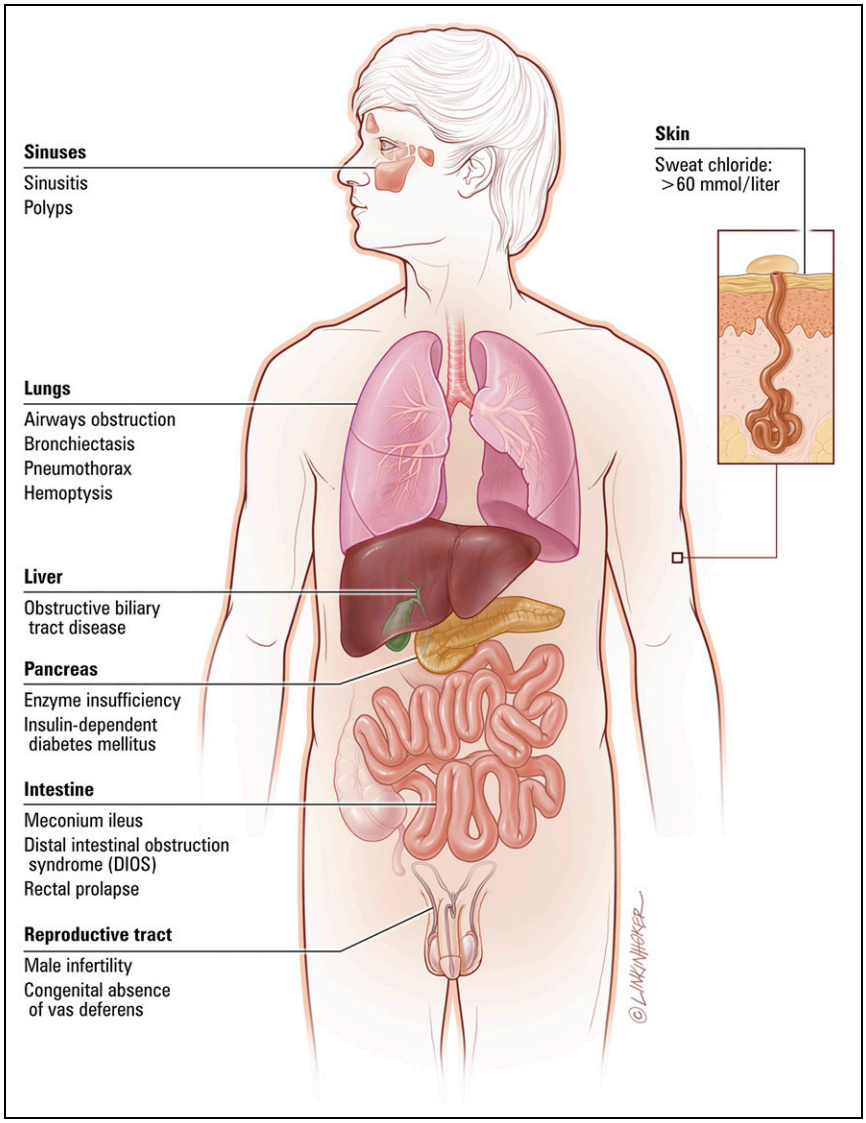

Figure 2. Common clinical manifestations of cystic fibrosis. Reproduced with permission from Link Studio LLC.

Table. **Interpretation of Sweat Chloride Concentration**

Group	Interpretation
Infants age 0–6 months	
Sweat chloride concentration (mEq/L)	
0–29	CF is unlikely[a]
30–59	Intermediate
≥60	Indicative of CF
Infants age >6 months, children, and adults	
Sweat chloride concentration (mEq/L)	
0–39	CF is unlikely[a]
40–59	Intermediate
≥60	Indicative of CF

CF=cystic fibrosis.
SI conversion factor: To convert chloride to mmol/L, multiply by 1.
[a]There are individuals with CF who have sweat chloride concentrations in this range.

methods in accredited laboratories. Normal sweat chloride values are age dependent, but a chloride concentration ≥60 mEq/L (60 mmol/L) is indicative of CF in individuals of all ages (Table). Additional sweat testing or genetic testing should be performed to confirm abnormal sweat chloride test results.

Genetic analysis is often helpful to confirm diagnosis, particularly for cases that present with indeterminate sweat chloride measurements. The genotypic criteria for diagnosis (11) include identification of 2 disease-causing mutations on distinct chromosomes. *CFTR* mutations should meet at least one of the following conditions: (1) alteration of the CFTR sequence with the result of affecting protein structure and/or function; (2) introduction of a premature stop codon, such as with an insertion, deletion, or nonsense mutation; (3) alteration of intron splice sites; and (4) creation of a novel amino acid sequence that does not occur in the normal *CFTR* genes of the affected individual's ethnic group. Commercial laboratories test for the most common *CFTR* mutations (often referred to as CF carrier testing), which will identify most individuals with CF. Complete sequencing of the *CFTR* gene is also available and can be helpful for confirming diagnosis of clinically atypical cases. Information about the clinical features associated with individual *CFTR* mutations can be found in the CFTR2 database sponsored by the Cystic Fibrosis Foundation (www.cftr2.org).

Nasal potential difference measurements can be beneficial in establishing a CF diagnosis, especially in clinically atypical cases. (14)(15)(16) However, this test is not considered to be a standard diagnostic method and is only performed at a limited number of CF centers. Cystic fibrosis is caused by abnormalities in salt transport that result from a defective CFTR protein, which is a chloride channel that regulates the salt content in the fluid that covers the surface of the nasal passages and airways. Transport of ions, such as sodium and chloride, creates an electrical potential difference across the airway lining. This potential difference can be measured by placing an electrode on the lining of the nose. Because individuals with CF do not have normal CFTR function, the epithelial nasal potential difference responds differentially to administration of the various salt solutions to the nasal epithelium.

Newborn screening was pioneered in the United States in the 1980s and by 2010 was implemented in all 50 states. (17) The benefits of newborn screening include early diagnosis, slowing of lung disease progression, prevention of malnutrition, and provision of psychosocial and extended medical support, such as genetic counseling, for individuals with CF and their families. Potential risks of newborn screening include increased medical interventions and increased risk for complications (ie, early treatment of bacterial infection, leading to antimicrobial resistance), earlier exposure to pathogenic bacteria, financial considerations given the high costs of therapies, and psychosocial repercussions stemming from false-positive screening results. (18)

Newborn screening for CF is performed by measuring the amount of immunoreactive trypsinogen (IRT) in the newborn blood spots typically obtained by heelstick. State laboratories either perform 2 IRT measurements (IRT/IRT) or perform *CFTR* mutation testing (IRT/DNA) if the IRT level is elevated. Positive screening results indicate that IRT levels remain persistently elevated by the time the neonate is ages 7 to 14 days or that at least one CFTR mutation has been identified. This result will trigger notification of the primary care physician and the infant's family. At this point, the infant should be referred to an accredited facility for definitive evaluation with a sweat test. A normal sweat chloride result (<30 mEq/L [<30 mmol/L]) means that CF is unlikely. An elevated (≥60 mEq/L [≥60 mmol/L]) sweat chloride measurement confirms the diagnosis, leading to further diagnostic measures (ie, genetic analysis to identify one or both CFTR mutations, depending on the type of newborn screen performed) and clinical assessment at a CF center accredited by the Cystic Fibrosis Foundation. Indeterminate sweat chloride levels (30–59 mEq/L [30–50 mmol/L]) require further genetic analysis and clinical assessment. With the current practices for newborn screening, the possibility exists for identification of a CFTR abnormality at birth that

does not immediately produce clinical manifestations, a syndrome known as CFTR-related metabolic syndrome. (19) (20) It is also important to remember that newborn screening for CF can have false-negative results as well, especially in infants with meconium ileus. Therefore, sweat testing should be performed if there is a clinical suspicion of CF regardless of the individual's age, even if he or she had a normal newborn screen result.

The present diagnostic methods take into account the wide clinical spectrum of disease and permit diagnosis of milder cases earlier in life. Early diagnosis has been found to have a profound effect on preventing lung disease progression and optimizing nutrition, which have had significant effects on survival and quality of life.

Clinical Presentations

The clinical diagnosis of CF in most individuals not detected by newborn screening is based on a triad of (1) recurrent sinopulmonary infections, (2) steatorrhea, and (3) failure to thrive. Exocrine pancreatic insufficiency is present in 85% of affected individuals. In infancy and early childhood, particular manifestations are strongly suggestive of a CF diagnosis. For example, the prenatal ultrasonographic finding of hyperechoic bowel is suggestive of intestinal obstruction; CF is present in approximately 10% of fetuses with this finding. Delayed meconium passage, meconium plug syndrome, or meconium ileus are present in approximately 15% to 20% of neonates with CF and result from abnormal meconium with a high protein concentration. Meconium ileus results from inspissation in the small intestine, leading to bowel obstruction; is associated with the clinical findings of abdominal distension and dilated bowel loops on imaging studies; and is complicated by intestinal perforation and peritonitis in approximately 50% of cases. Treatment generally involves surgical intervention. Rectal prolapse occurs in 20% of untreated children with CF between ages 6 months and 3 years and results primarily from malabsorption, malnutrition, and the elimination of bulky stools. Other less common clinical presentations in infancy include the following: (1) salt depletion syndrome, which results in a hyponatremic, hypokalemic, and hypochloremic metabolic alkalosis; (2) prolonged neonatal jaundice, resulting from intrahepatic biliary stasis or extrahepatic bile duct obstruction; (3) edema, hypoproteinemia, and acrodermatitis enteropathica, resulting from malabsorption; and (4) hemorrhagic disease of the newborn secondary to vitamin K deficiency.

In older children, adolescents, and adults, clinical findings suggestive of a CF diagnosis include both respiratory and gastrointestinal presentations. Chronic and recurrent infections of the sinuses and respiratory tract, poorly controlled or refractory asthma, and the findings of nasal polyposis, bronchiectasis, and digital clubbing are typical of respiratory involvement. Alternatively, individuals in this age group may also present at diagnosis with gastrointestinal features, such as poor weight gain and growth, steatorrhea, rectal prolapse, intestinal obstruction, chronic constipation, or liver disease. Pancreatitis can be seen in individuals with pancreatic sufficient CF. These clinical presentations will become less common because most children diagnosed as having CF are now identified by newborn screening.

Therapies to Maintain Optimal Lung Health and Nutritional Status

Cystic fibrosis results in inspissation of mucous secretions in the airways, leading to chronic obstruction, infection, and inflammation that eventually lead to bronchiectasis and parenchymal destruction (Figure 3). As lung disease progresses, chronic respiratory symptoms such as cough and sputum production develop. The major aims of the treatment of respiratory disease focus on optimizing lung function and preventing disease progression and other disease-associated complications. The overall goals of treatment of CF gastrointestinal disease are to optimize nutritional status and attain age-appropriate growth and weight gain. For both pulmonary and gastrointestinal manifestations, treatment is lifelong and generally begins at the time of diagnosis. In the United States, individuals with CF require routine quarterly visits at a care center accredited by the Cystic Fibrosis Foundation, which provides multidisciplinary, patient- and family-centered care.

The treatment of CF lung disease includes the control of chronic airways infection, particularly with bacterial agents against organisms such as *Pseudomonas aeruginosa*, airway clearance of secretions, and the use of anti-inflammatory therapies. In 2007, the Cystic Fibrosis Foundation's Pulmonary Clinical Practice Guidelines Committee developed recommendations that were based on a systematic review of the literature and assessment of the available evidence based on an established grading scale. (21) These guidelines were updated in 2013 (22) to review the latest evidence on long-term therapies to maintain optimal lung health and included newer therapies.

Chronic Airways Infection

Management of chronic airways infection includes routine surveillance cultures of respiratory secretions for bacterial pathogens, including *Staphylococcus aureus* and *Pseudomonas aeruginosa* (Figure 4). Other organisms, including atypical mycobacteria and fungal pathogens, can have a significant effect on CF lung disease. Treatment of

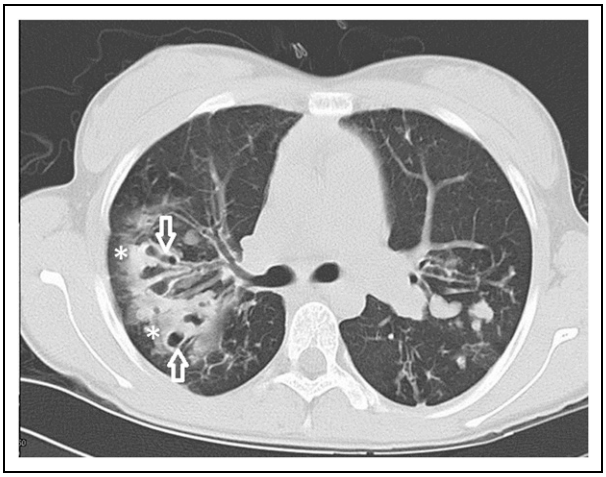

Figure 3. Chest computed tomographic (CT) findings. A CT image of an adolescent girl with cystic fibrosis demonstrates significant bronchiectasis (white open arrows) and mucous plugging (white asterisks).

newly acquired *P aeruginosa* typically uses inhaled tobramycin with the goal of eradication of initial infection. Individuals with chronic infection with *P aeruginosa* and other gram-negative species can benefit from regular use of inhaled antibiotics, such as tobramycin or aztreonam, typically used every other month.

Clearance of Airway Secretions

In the management of CF lung disease, airway clearance therapy serves to remove airway secretions and lessen the burden of infection through the removal of bacteria and other irritants and thus improve gas exchange, reduce airway resistance, correct ventilation-perfusion mismatch, and decrease proteolytic activity. Commonly used airway clearance techniques include postural drainage and percussion, active cycle of breathing, autogenic drainage, positive expiratory pressure (high pressure or oscillating), high-frequency chest wall oscillation, and exercise. Airway clearance maneuvers are typically used in conjunction with inhaled mucous-altering therapies designed to thin viscous mucus and facilitate their removal from the airways. Inhaled mucous-altering agents include recombinant human DNase (dornase alfa) and hypertonic saline. Airway clearance therapies are typically performed twice daily as maintenance therapy and increased in frequency as treatment of acute lung disease exacerbations. (23)

Disease-Modifying Therapies

Ivacaftor is an oral pharmacologic potentiator that activates defective CFTR at the cell surface caused by the class III mutation G551D. Randomized, placebo-controlled trials demonstrated improvements in lung function, weight, quality of life, and sweat chloride levels and reduction in exacerbation frequency. Ivacaftor is currently approved by the US Food and Drug Administration for individuals with CF due to at least one class III *CFTR* mutation such as G551D. Clinical trials on the effects of ivacaftor in combination with other *CFTR* mutation–specific therapies for individuals the most common mutation, F508del, are in progress. (24)(25)

Chronic Airways Inflammation

Cystic fibrosis lung disease is caused in part by chronic airways inflammation. Currently used anti-inflammatory therapies include high-dose ibuprofen and oral azithromycin. (21)(22) The routine use of oral or inhaled corticosteroids as long-term maintenance therapy is not recommended for individuals with CF unless the treatment is for other coexisting inflammatory conditions, such as asthma or allergic bronchopulmonary aspergillosis. High-dose ibuprofen has been reported to decrease neutrophil migration in CF individuals between ages 6 and 17 years when serum ibuprofen levels are between 50 and 100 μg/mL (242–485 μmol/L). Although clear benefit of this anti-inflammatory therapy has been demonstrated in clinical trials, treatment in clinical practice with high-dose ibuprofen is not widely used in clinical practice because of the small increased risk of gastrointestinal bleeding and need for drug level monitoring. (26)

Oral azithromycin, typically dosed 3 times a week, has been found to improve lung function and reduce the frequency of pulmonary exacerbations in individuals with and without evidence of chronic *P aeruginosa* infection. There is concern that long-term azithromycin use in individuals who have occult atypical mycobacterial infection will lead to mycobacterial resistance and further complicate treatment. Individuals with CF should be screened for atypical mycobacterial infection before starting oral azithromycin therapy. However, recent data suggest that long-term azithromycin therapy may in fact decrease the risk of acquiring an atypical mycobacterial infection. (27)

Pancreatic Enzyme Replacement Therapy

Pancreatic insufficiency is seen in 85% of the CF population and results in the malabsorption of fat and protein. The clinical consequences of malabsorption include bulky, malodorous stools, poor weight gain, and failure to thrive. Pancreatic insufficient individuals require lifelong replacement of pancreatic enzymes with capsules that must be taken with every meal and snack. The usual dosage ranges from 2000 to 2500 U/kg of lipase per meal

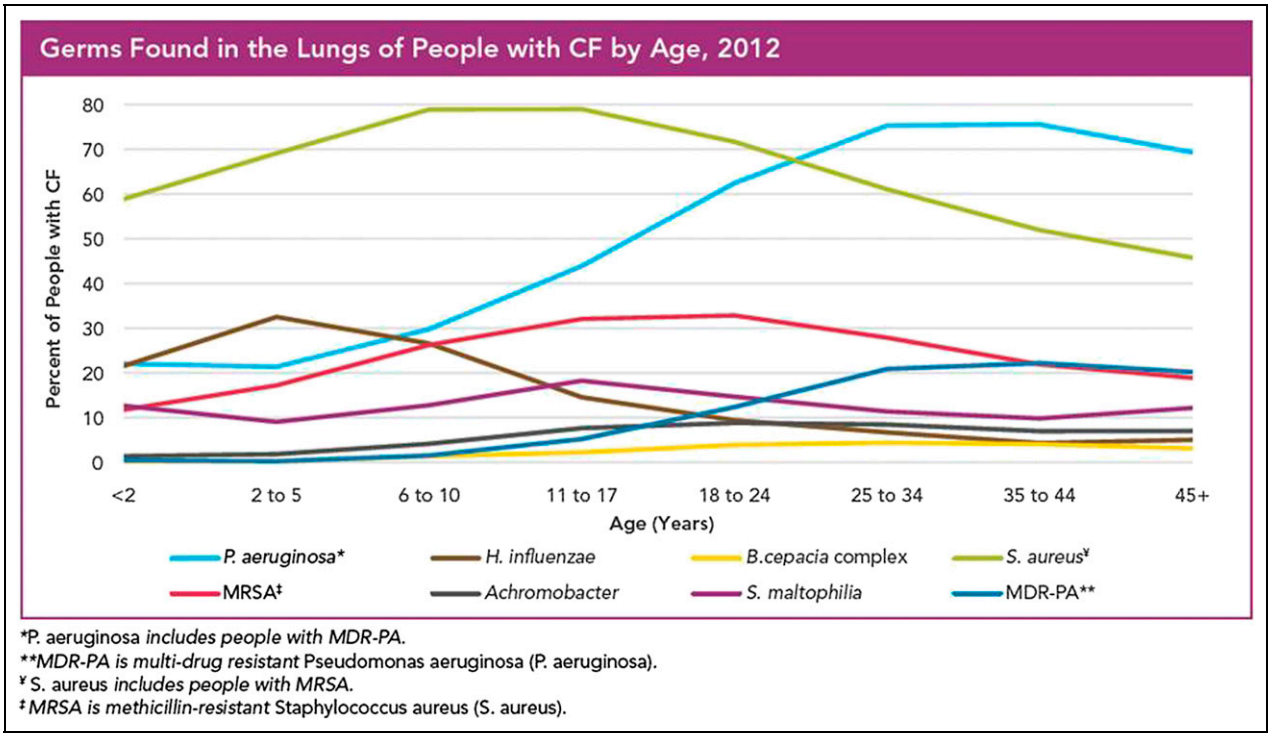

Figure 4. Prevalence of bacterial pathogens in cystic fibrosis. Cystic Fibrosis Foundation Patient Registry (C) 2013 Cystic Fibrosis Foundation. (4)

or feeding to a maximum of 10,000 U/kg of lipase per day. (28)(29) Higher pancreatic enzyme dosages are generally not needed to achieve adequate nutrient absorption. In fact, exceedingly high pancreatic enzyme dosages (>6000 U/kg of lipase per meal) are associated with fibrosing colonopathy, a rare but serious complication, in a small proportion of individuals. Optimal pancreatic enzyme replacement therapy can significantly decrease fecal fat excretion and steatorrhea, allowing individuals with CF to achieve age-appropriate growth and weight gain. (30)

Fat-Soluble Vitamin Replacement Therapy

Another consequence of fat malabsorption in pancreatic insufficient individuals is deficiency of the fat-soluble vitamins A, D, E, and K. Vitamin A deficiency results primarily in ocular consequences, such as night blindness and conjunctival and corneal xerosis. Skin involvement, such as follicular hyperkeratosis, is also associated with vitamin A deficiency. Vitamin D is integral in calcium homeostasis and bone mineralization, as well as immunomodulatory processes. Vitamin D deficiency results in nutritional rickets, osteopenia, and osteoporosis and can predispose severely malnourished individuals with CF to pathologic fractures. Vitamin E deficiency results in peripheral neuropathy, myopathy, and hemolysis. Vitamin K deficiency results in coagulopathy and can contribute to bone disease in CF. Replacement of these vitamins begins at diagnosis, and monitoring of serum levels is performed annually. The usual doses are typically higher than those required for an individual without CF; commercially available vitamin combination products supply doses within the target range.

Diagnosis and Management of Common Pulmonary and Extrapulmonary Complications in CF

Pulmonary Exacerbation

Cystic fibrosis lung disease results from inspissation of mucus and chronic bacterial infection, leading to progressive airways obstruction and chronic daily respiratory symptoms. Intermittent worsening of these ongoing daily symptoms is generally termed a *pulmonary exacerbation*, which is characterized by increased respiratory symptoms, such as increased cough and sputum production, and interval worsening of objective measures, such as pulmonary function, and nonspecific constitutional

symptoms, including increased fatigue, decreased appetite, and interval weight loss. (31) Fever is not a typical symptom of pulmonary exacerbations. Treatment includes oral, inhaled, or intravenous antibiotics, depending on the severity of the exacerbation. The choice of antibiotics is guided by previous airway culture results and the prevalence of various pathogens in the airway (Figure 4). In addition, escalation of the long-term regimen of maintenance therapies, such as airway clearance, is important to clear secretions from the airways.

Hemoptysis

Hemoptysis occurs in approximately 9% of individuals with CF annually. Typically associated with advanced lung disease, it can also be a symptom of worsened airways infection. (32) CF-associated conditions, such as vitamin K deficiency, either from malabsorption of fat-soluble vitamins or from liver disease and hypersplenism, can worsen hemoptysis. The pathogenesis of hemoptysis is multifactorial and likely results from proliferation and hypertrophy of the bronchial arteries, which can then rupture into the airway as a consequence of chronic infection and inflammation. (33) Hemoptysis is characterized by the amount of blood expectorated: scant (<5 mL), moderate (5–240 mL), or massive (>240 mL). (32) The management of scant to moderate hemoptysis drugs includes medical evaluation, initiation of antibiotic therapy for treatment of pulmonary exacerbation, cessation of anti-inflammatory agents (such as nonsteroidal anti-inflammatory drugs), and consideration for limiting certain therapies, such as mucous altering agents and airway clearance, as clinically appropriate. The management of massive hemoptysis is considered a life-threatening emergency. Medical management includes clinically appropriate stabilization of cardiorespiratory status and supportive care; nonsteroidal anti-inflammatory and airway clearance measures should be limited. Bronchial artery embolization is considered for the treatment of massive hemoptysis or significant recurrent hemoptysis once the site of bleeding has been localized. (33)

Pneumothorax

Another common pulmonary complication in CF is pneumothorax, which will develop in approximately 3.4% of all individuals. Pneumothorax is more common in adults (median age, 21 years) and individuals with advanced lung disease. (32)(34) The pathogenesis of pneumothorax involves air trapping. When alveolar pressure exceeds interstitial pressure, air escapes the alveoli into the interstitium and tracks along the airways toward the hilum with eventual rupture into the mediastinal parietal pleura. The typical presentation is the acute onset of chest pain and dyspnea. Diagnosis is generally confirmed by chest radiography, although in some cases, computed tomography may better demonstrate the pneumothorax in the setting of advanced lung disease with pleural adhesions. Pneumothoraces are characterized by size: small (<5 cm) or large (≥5 cm). (32) Management is largely guided by the degree of clinical compromise. Small pneumothoraces can be managed with observation or aspiration using a small catheter, depending on clinical stability. Other measures to facilitate airway clearance can be continued, with the exception of devices that use positive pressure because these can hinder resolution of the pneumothorax. Large pneumothoraces should be managed in the hospital with placement of a chest tube. Chemical or surgical pleurodesis is reserved for recurrent large pneumothoraces. (34)

Chronic Rhinosinusitis and Nasal Polyposis

The upper airway manifestations of CF include chronic rhinosinusitis and nasal polyposis. Nearly all individuals with CF will have radiographic demonstration of chronic pansinusitis. The prevalence of nasal polyposis is variable but ranges from roughly 18% in children younger than 6 years in one report to approximately 45% in adolescents. (35)(36) The pathophysiology of chronic rhinosinusitis and nasal polyposis results from mechanical obstruction of the sinus ostia by mucous stasis, which ultimately leads to local infection and inflammation. The clinical manifestations of chronic rhinosinusitis and nasal polyposis include headache, facial pressure, and nasal obstruction that can lead to broadening of the nasal bridge and septal deformation. Medical treatment includes saline nasal irrigation and topical anti-inflammatory therapies, such as nasal steroids. Surgical treatment is necessary for severe and recurrent disease. Functional endoscopic sinus surgery is the gold standard procedure to improve sinus drainage and remove inflamed and diseased mucosa. Although safe and beneficial in terms of reducing symptoms and decreasing the burden of infection, surgery generally does not result in improvement in lung function. Further prospective studies are needed to determine the effects of functional endoscopic sinus surgery on management and recurrence of rhinosinusitis in individuals with CF.

Distal Intestinal Obstruction Syndrome

Distal intestinal obstruction syndrome (DIOS) is a common complication in both pancreatic-insufficient and pancreatic-sufficient individuals with CF characterized by accumulation of viscous fecal matter in the distal small intestine, which leads to partial or complete small bowel

obstruction that presents clinically with abdominal pain, abdominal distension, and vomiting. Because the intestinal epithelium shares similar secretory processes seen in the airways, CFTR dysfunction leads to dehydration of mucous and intestinal obstruction. Bile acid stimulation of secretion and active reuptake by the terminal ileum are dependent on both CFTR-dependent and sodium gradient–driven cotransporter mechanisms and offer a plausible pathophysiologic mechanism for the involvement of the distal ileum.

Several risk factors predispose patients to the development of DIOS, including pancreatic insufficiency, suboptimal fat absorption (ie, inadequate pancreatic enzyme replacement therapy), a history of meconium ileus, and dehydration. (37) The differential diagnosis of DIOS includes constipation, adhesions after surgery, intussusception, volvulus, appendicitis, and inflammatory bowel disease, such as Crohn disease. Management is geared toward rehydration and treatment with osmotic laxatives, such as polyethylene glycol, to achieve a clear fecal effluent and typically lead to resolution of abdominal pain and other symptoms, such as vomiting. The use of procedures such as sodium meglumine diatrizoate (Gastrografin) enemas are recommended for near-complete obstruction. Retrograde lavage with visualization of the terminal ileum should be performed by an experienced radiologist. Surgical interventions are generally not required for DIOS with early diagnosis and implementation of appropriate medical management.

Cystic Fibrosis Liver Disease

In the liver, CFTR is expressed on the apical membrane of biliary epithelium. The putative role of CFTR is to facilitate water and solute movement via chloride secretion, thus promoting bile flow. The mechanism by which abnormal CFTR leads to liver disease in CF is uncertain. The end result of liver disease in CF is the development of biliary fibrosis, leading to biliary cirrhosis that may progress to multilobular cirrhosis. Some affected individuals develop portal hypertension and its associated complications. The sequelae of portal hypertension cause enhanced morbidity and mortality of CF patients such that liver disease is the third leading cause of death in CF, accounting for 2.5% of overall CF mortality. Most of the studies of the natural history of CF liver disease (CFLD) suggest a prevalence of cirrhosis between 5% and 15%, although it is difficult to accurately assess the full extent of liver disease in the CF population.

The most common clinical presentation of CFLD is the physical examination finding of hepatomegaly. Many affected individuals are asymptomatic with respect to signs and symptoms of liver disease even after the development of multilobular cirrhosis. Because sensitive and specific tests are not available to screen for biliary and hepatic cellular dysfunction, the early diagnosis of CFLD rests on clinical examination and the use of biochemical tests and imaging techniques to evaluate for the development of cirrhosis. The gold standard of diagnosis remains tissue biopsy.

The presence of CFLD should be considered with at least 2 of the following: (1) abnormal physical examination findings (hepatomegaly and/or splenomegaly); (2) abnormalities of liver function test results above the reference range of normal on at least 3 consecutive determinations during a 12-month period; (3) ultrasonographic evidence of abnormal liver echotexture or portal hypertension; and (4) confirmation of cirrhosis by tissue biopsy. Treatment with ursodeoxycholic acid is recommended when the diagnosis of CFLD is made. Annual screening of individuals with liver disease is recommended and should include assessment of biochemical liver function, ultrasound evaluation as clinically indicated, and evaluation by a gastroenterologist for other causes and morbidities associated with liver disease (such as variceal development) and for consideration for other treatments such as liver transplantation. (38)

Cystic Fibrosis–Related Diabetes Mellitus

Abnormal chloride channel function leads to thick viscous secretions that cause obstructive damage to the exocrine pancreas and results in fatty infiltration and destruction of islet cell architecture, which in turn produces an insulin-insufficient state. Typically, CFRD is more common in individuals with pancreatic insufficiency and has been associated with a higher mortality rate. More recent studies suggest early diagnosis and aggressive glucose control may prevent this increase in mortality. CFRD has been associated with decreased body mass index and lung function. Unexplained decrease in these clinical parameters may be due to occult CFRD. Microvascular complications, such as retinopathy, microalbuminuria, and autonomic neuropathy, occur in CFRD, as in other forms of diabetes, and are associated with the presence of fasting hyperglycemia. Ketoacidosis is uncommon with CFRD. Typically presenting after the first decade of life, the annual incidence of CFRD increases approximately 5% per year in individuals older than 10 years and approximately 10% per year in individuals older than 20 years. (39)

According to the 2010 recommendations, annual screening using the oral glucose tolerance test is recommended for those with CF who are older than 9 years. (40) Measurement of hemoglobin A_{1C} is not an effective screening tool because it underestimates overall glycemic

control. Insulin is the treatment of choice for CFRD; oral hypoglycemic agents are not recommended. Nutritional treatment remains focused on increasing and not restricting caloric intake in this patient population. The intake of carbohydrates is not discouraged; however, avoidance of foods that are high in simple sugar content and low in nutritional value is recommended to limit glucose excursion.

Prognosis

Overall, survival is improving for individuals affected with CF. Treatment goals include early diagnosis, screening, and treatment of the disease and its associated manifestations toward optimizing pulmonary function and nutritional status. Pharmacologic interventions, including the newer, mutation-specific therapies, have had a profound effect on the overall health and well-being for individuals with CF. Effective communication among primary care physicians, subspecialists, and the patient and family are paramount to maintaining optimal health and quality of life.

Summary

- On the basis of consensus, (11) the diagnosis of cystic fibrosis (CF) is based on (1) the presence of one or more characteristic phenotypic features of chronic, recurrent sinopulmonary disease, nutritional and gastrointestinal abnormalities, male urogenital abnormalities, and salt depletion syndromes; (2) a family history of CF in a sibling; and (3) a positive newborn screening test result associated with laboratory-demonstrated evidence of cystic fibrosis transmembrane conductance regulator (CFTR) dysfunction, such as abnormal sweat chloride concentration, identification of 2 disease-causing CFTR mutations, or demonstration in vivo of characteristic ion transport abnormalities.
- On the basis of consensus, (40) annual oral glucose tolerance tests are recommended for people with CF older than 9 years to screen for CF-related diabetes mellitus.
- On the basis of research evidence, (21)(22) the long-term therapies to maintain optimal lung health for children and adults with CF include control of chronic airways infection and inflammation, clearance of mucous secretions, and, where clinically applicable, treatments aimed at the basic CF genetic defect.
- On the basis of strong research evidence, (24)(25) treatment with ivacaftor, the first US Food and Drug Administration–approved drug that targets the basic CF genetic defect, resulted in improvements in lung function, weight, quality of life, and sweat chloride levels and reduction in exacerbation frequency in people with CF carrying at least one G551D mutation.

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PIR Quiz Requirements

To successfully complete 2014 *Pediatrics in Review* articles for *AMA PRA Category 1 Credit*, learners must demonstrate a minimum performance level of 60% or higher on this assessment, which measures achievement of the educational purpose and/or objectives of this activity. If you score less than 60% on the assessment, you will be given additional opportunities to answer questions until an overall 60% or greater score is achieved.

NOTE: Learners can take *Pediatrics in Review* quizzes and claim credit online only at: http://pedsinreview.org.

1. You have been notified by the state laboratory that a 10-day-old boy has a positive cystic fibrosis neonatal screen (immunoreactive trypsinogen test) result. You contact the family and have them return for an evaluation. They report that the infant has been nursing well and passing 5 soft bowel movements daily. They also report an occasional cough. On examination, the infant has gained 200 g and appears well hydrated. His lungs are clear, and his abdomen is soft without distension or hepatomegaly. The most appropriate next step is to:

   A. Hospitalize for intravenous antibiotics.
   B. Perform chest radiography.
   C. Refer for sweat chloride testing.
   D. Refer to a pediatric pulmonologist.
   E. Repeat immunoreactive trypsinogen assay.

2. You are asked to evaluate a newborn infant in the nursery for abdominal distension and vomiting. Prenatal ultrasonography had suggested a hyperechoic bowel. Examination confirms the abdominal distension, and the abdominal plain radiograph demonstrates dilated small bowel loops and air fluid levels suggestive of meconium ileus. A pediatric surgeon is consulted. Newborn screening for cystic fibrosis performed that day revealed a normal immunoreactive trypsinogen (IRT) level. The most likely explanation for the normal sweat chloride finding is that:

   A. The infant does not have cystic fibrosis.
   B. The infant has a single *CFTR* gene mutation.
   C. The infant has meconium peritonitis.
   D. The infant has a pancreatic sufficient form of cystic fibrosis.
   E. The infant's cystic fibrosis newborn screening result is false negative.

3. You are seeing a teenager with cystic fibrosis with pancreatic insufficiency, who is receiving 2500 U/kg of lipase per meal, for a total of 10,000 U/kg of lipase per day. He is bothered by abdominal pain and excessive flatus and asks you if he can just triple his dosage of pancreatic enzymes. Which of the following is a known complication of high-dose pancreatic enzyme intake?

   A. Colonic polyps.
   B. Diarrhea.
   C. Fibrosing colonopathy.
   D. Rectal bleeding.
   E. Vomiting.

4. A 13-year-old girl with cystic fibrosis followed up at your practice has had symptoms of recurrent sinusitis, including headache, facial pain, and chronic nasal drainage. Nasal irrigation, intranasal steroids, and several courses of antibiotics have failed to clear the infection. An appropriate next step would be:

   A. Endoscopic sinus surgery.
   B. Intranasal tobramycin.
   C. Ivacaftor.
   D. Nasal polypectomy.
   E. Nebulized albuterol.

5. A 5-year-old girl with cystic fibrosis is a new patient to your practice. The family has read about the possibility of diabetes in patients with CF and asks whether she should be screened for diabetes. Which of the following is currently recommended as a screening protocol for cystic fibrosis–related diabetes?

   A. Annual fasting blood glucose measurement beginning at age 5 years.
   B. Annual fasting blood glucose measurement beginning at age 9 years.
   C. Annual glucose tolerance test beginning at age 5 years.
   D. Annual glucose tolerance test beginning at age 10 years.
   E. Annual hemoglobin A_{1C} measurement beginning at age 5 years.

Parent Resources from the AAP at HealthyChildren.org

- http://www.healthychildren.org/English/health-issues/conditions/chronic/Pages/Cystic-Fibrosis.aspx
- Spanish: http://www.healthychildren.org/spanish/health-issues/conditions/chronic/paginas/cystic-fibrosis.aspx

Cystic Fibrosis

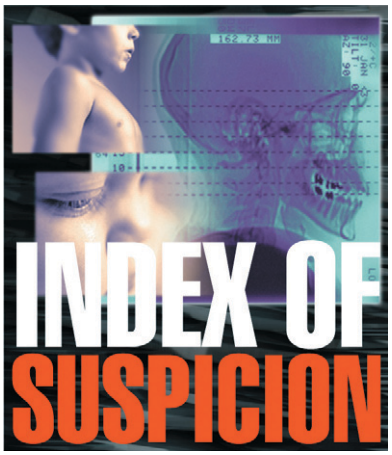
Shruti M. Paranjape and Peter J. Mogayzel Jr

Pediatrics in Review 2014;35;194
DOI: 10.1542/pir.35-5-194

Index of Suspicion

Shagun Sachdeva, Corrie Fletcher, Heather Miller, Priti Bhansali, April Jones and Vineeta Mittal

Pediatrics in Review 2014;35;206
DOI: 10.1542/pir.35-5-206



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 use the Submit and Track My Manuscript link on the Pediatrics in Review homepage: http://pedsinreview.aappublications.org.

Author Disclosure

Drs Sachdeva, Bhansali, Fletcher, Jones, Miller, and Mittal 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.

Case 1: Recurrent Syncope in an 18-Year-Old Boy
Case 2: Altered Mental Status in 4-Month-Old Boy
Case 3: Fever, Cough, and Dysentery in a 17-Year-Old Hispanic Girl

Case 1 Presentation

An 18-year-old boy presents to the emergency department (ED) for evaluation of syncope after 20 minutes of exercise. He felt lightheaded, had palpitations and blurry vision, and then lost consciousness for 10 minutes. He recovered slowly. He had a similar episode 8 months ago. Since then he reports that he gets lightheaded with palpitations every time he exercises for 5 to 10 minutes. He reports that he drinks 60 to 80 oz of noncaffeinated beverages daily and generally has clear urine. Before exercising heavily, he generally drinks approximately 500 mL of water or Gatorade. He is asymptomatic at rest. Other than attention-deficit/hyperactivity disorder, he is in good health and is not taking any medications.

On physical examination, he is alert, oriented, and in no acute distress. His height and weight are between the 50th and 75th percentiles. His heart rate is 45 beats/min, his blood pressure is 98/78 mm Hg, and he is not orthostatic. Femoral pulses are equal and regular. During auscultation, a grade 2/4 systolic ejection murmur is heard at the left upper sternal border without any radiation. His pupils are equal and reactive, and cranial nerves are grossly intact; he has normal speech. His tone, strength, and sensations are normal in all 4 extremities. The deep tendon reflexes are 2+ with normal gait and coordination. Lungs are clear to auscultation. The rest of the examination findings are unremarkable.

Initial laboratory evaluations include normal complete blood cell count, basic metabolic panel, and chest radiographic findings. Electrocardiography reveals sinus bradycardia, left ventricular hypertrophy, and ST elevation with T-wave inversions in the left and inferior leads (Figure 1). The results of head computed tomography and electroencephalography are normal. Subsequent test results include the following: creatine kinase, 748 U/L (reference range, 34–147 U/L), creatine kinase–MB fraction, 2.4 ng/mL (2.4 μg/L) (reference range, <1.7 ng/mL [<1.7 μg/L]); and normal troponin level.

Case 2 Presentation

A 4-month-old boy born 24 weeks prematurely with a history of stable hydrocephalus secondary to grade 3 intraventricular hemorrhage presents to the ED with altered consciousness, hypotension, and hypothermia. The patient had undergone elective magnetic resonance imaging (MRI) with sedation 2 days before admission to evaluate the hydrocephalus. The MRI revealed mild ventricular dilation, and the patient was at baseline, according to the mother, before leaving the hospital. The mother states that the infant initially fed well but then became progressively sleepy and did not wake to feed. She denied any associated fevers, vomiting, diarrhea, new rashes, or seizure like activity.

On examination, his vital signs are as follows: temperature, 96.6°F (35.9°C); blood pressure, 62/40 mm Hg; heart rate, 173 beats/min; and respiratory rate, 16 breaths/min. Growth parameters are 25th percentile for height and 15th percentile for weight and head circumference, corrected for gestational age. The patient is somnolent,

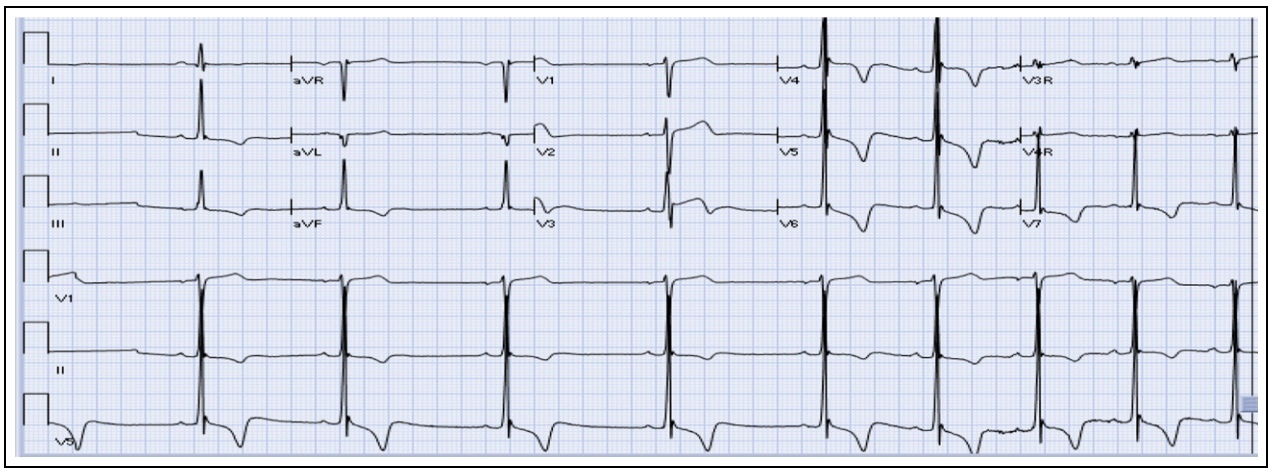


Figure 1. Electrocardiogram showing sinus bradycardia, left ventricular hypertrophy, and ST elevation with T-wave inversions in the left and inferior leads.

minimally arousable, and awakening to pain but without crying. His tone is flaccid, his anterior fontanelle is open and flat without bulging, and his pupils are sluggish in response to light. He is noted to have nonlabored, shallow breathing, and lungs are clear to auscultation. There are no murmurs, rashes, clubbing, or cyanosis noted on examination.

The infant receives multiple normal saline boluses with minimal improvement of tachycardia but without improvement of blood pressure and subsequently is admitted to the pediatric intensive care unit. The patient requires intubation for worsening respiratory depression, persistent hypotension, and lethargy. A full septic evaluation is performed. An additional laboratory test reveals the cause of the patient's condition.

Case 3 Presentation

A 17-year-old Hispanic girl is admitted with 10 days of high temperatures, dry cough, and 10 to 15 bloody stools per day with urgency and tenesmus. She reports poor appetite and has had a 9.1-kg weight loss since her grandfather's death 6 months ago. She has been depressed since and is currently taking an oral iron supplementation for anemia (hemoglobin, 8.7 g/dL [87 g/L]) and fatigue. She is sexually active with multiple sexual partners and denies drug abuse, dysuria, or abnormal vaginal discharge. Approximately a month ago, she visited a boyfriend in jail and her grandmother in Mexico. She was born in the United States, where she has lived all her life.

Physical examination is significant for a cachectic-looking girl with significant pallor and jaundice. Her weight is 48 kg (9.1 kg less than last ED weight measurement 6 months ago), height is 150 cm, temperature is 36.2°C (97.2°F), pulse is 122 beats/min, respiratory rate is 24 breaths/min, and blood pressure is 115/75 mm Hg. She has right posterior lung crackles, abdominal distension with generalized tenderness and a positive fluid wave, hepatomegaly, and an anal fissure.

Laboratory evaluation reveals the following: white blood cell count, 6,500/μL (6.5 $\times$ 10^3/μL) with lymphopenia (lymphocytes, 3.3%); hemoglobin, 7.5 g/dL (75 g/L); platelet count, of 35 $\times$ 10^3/μL (35 $\times$ 10^9/L); erythrocyte sedimentation rate, 110 mm/h; aspartate aminotransferase, 14 U/L; alanine aminotransferase, 27 U/L; total bilirubin, 2.68 mg/dL (45.8 μmol/L); direct bilirubin, 2.33 mg/dL (39.8 μmol/L); γ-glutamyltransferase, 230 U/L; alkaline phosphate, 116 U/L; and an elevated lipase level. Abdominal ultrasonography confirms ascites. Additional laboratory evaluation leads to the diagnosis.

Case 1 Discussion

After further questioning, it was found that his maternal cousin had a "heart attack" when he was age 18 years. A cardiologist is consulted for further evaluation. Echocardiography revealed an intramural left main coronary artery arising from the right sinus of Valsalva (Figure 2). Right coronary, left ventricular systolic, and left ventricular diastolic function were normal, with minor apical concentric hypertrophy confirmed by cardiac MRI, which also revealed evidence of previous infarction. He was then taken to the operating room on hospitalization day 2 for repair of an anomalous left coronary artery, where unroofing of its intramural portion and resuspension of the aortic valve commissure along with creation of

a neo-ostium for the left coronary artery was performed. He tolerated the procedure well, recovered well, and was discharged on hospitalization day 6 without any postoperative arrhythmias. He has remained free of symptoms for 6 months.

Differential Diagnosis

Various medical conditions can present with syncope, the most common one being dehydration or vasovagal syncope. However, it is important to do a complete evaluation to rule out underlying neurologic or cardiac causes to decrease morbidity and mortality given the risk of sudden death associated with some of these conditions.

One must distinguish syncope from seizure. This distinction can often be made by taking a careful history. Abnormal movements with abnormal gaze, loss of bladder or bowel function, tongue biting, injury during the episode, and being dazed for a period after the episode all point to the possibility of a seizure as opposed to syncope. Several life-threatening cardiac conditions can also present with syncope, especially with exertion. Hypertrophic cardiomyopathy and coronary artery abnormalities are 2 of the most common structural heart diseases that pose a threat of sudden death. Long QT syndrome has the potential to cause fatal ventricular arrhythmias and should also be in the differential diagnosis.

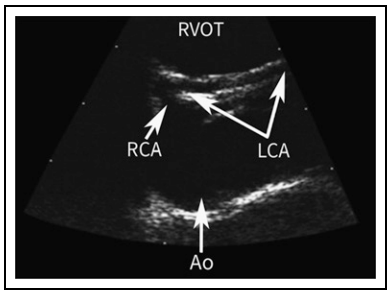


Figure 2. Echocardiogram showing an intramural left main coronary artery arising from the right sinus of Valsalva.

Dilated cardiomyopathy, coarctation of aorta, and aortic stenosis are other conditions that decrease systemic blood flow during exertion, thereby leading to syncope. Patients with aortic valve stenosis will have a characteristic suprasternal notch thrill, ejection click, and harsh systolic ejection murmur at the right upper sternal border radiating to the neck, whereas patients with coarctation, especially adolescents, may have elevated blood pressure, decreased femoral pulses, and higher arm than leg blood pressures.

The Condition

Anomalous origins of the left main coronary artery from the right sinus of Valsalva or anomalous origins of the right coronary arteries from the left sinus of Valsalva are rare congenital anomalies. They have a combined incidence ranging from 0.17% to 1.2%. The most important associated risk is sudden death, most notably in young athletes. These anomalies, along with hypertrophic cardiomyopathy, are the most common causes of sudden cardiac death in the pediatric population.

The pathophysiology involves obstruction resulting from either hypoplasia of the ostium or angulation at the ectopic origin of the coronary artery. The coronary artery may be tunneled between the aorta and right ventricular outflow tract, leading to compression of the coronary artery between the structures, especially during exercise. This compression can produce focal myocardial ischemia, infarction, and myocardial fibrosis, leading to ventricular tachydysrhythmias. All these changes can compromise cardiac output, thereby leading to syncope.

Cardiovascular symptoms, such as chest pain, exertional dyspnea, syncope, or dizziness, occur in only 18% to 30% of patients. Most are asymptomatic. The diagnosis is often made post mortem. Although typical vasodepressor syncope evaluation should include only electrocardiography, in patients with this type of presentation, evaluation should include electrocardiography (usually normal or ST changes or Q waves showing infarction), stress testing, 2-dimensional echocardiography, cardiac computed tomography or MRI, and sometimes cardiac catheterization with selective coronary angiography.

Treatment is indicated for obstructed vessels in symptomatic patients. It consists of aortoplasty with reanastomosis of the aberrant vessel after unroofing its intramural course and creation of a neo-ostium or, occasionally, coronary artery bypass grafting.

Lessons for the Clinician

- The differential diagnosis of syncope is broad. Cardiac and neurologic conditions must be considered.
- Anomalous origins of the left main coronary artery and anomalous origins of the right coronary arteries can cause sudden death, especially in young athletes, and are rarely diagnosed in children.
- The diagnosis is often made post mortem because most patients are asymptomatic. Cardiovascular symptoms occur in only 18% to 30% of patients.
- Because of the high risk of sudden cardiac death, aggressive surgical management and follow-up are necessary.

(*Shagun Sachdeva, MD, Pediatric Residency Program, Children's National Medical Center, Washington, DC; Priti Bhansali, MD, Division of Hospitalist Medicine, Children's National Medical Center, Washington, DC*)

Case 2 Discussion

The patient continued to have progressive deterioration of his mental

status after the hospitalization. His urinary toxicology screen result was positive for barbiturates, despite none being administered.

Because of the unexplained barbiturates revealed in the urinary toxicology screen, a phenobarbital level was checked and found to be 138 μg/mL (595 μmol/L), and this level continued to increase for 2 days while the patient was in the hospital. The patient was not prescribed any medications, and the mother denied anyone at home taking phenobarbital. Through investigation it was discovered that the mother had filled a prescription for phenobarbital 2 days before the patient's presentation to the ED. The police were contacted, and the mother admitted giving the patient phenobarbital for his fussiness at home and continuing to administer it during the patient's initial hospital presentation. The patient was ultimately diagnosed as having phenobarbital intoxication secondary to Munchausen syndrome by proxy.

Differential Diagnosis

The presentation of altered levels of consciousness or lethargy in infants and children has many causes. In an infant, the diagnosis of sepsis is high on the differential diagnosis list and should prompt an early evaluation and appropriate administration of antibiotics. The differential diagnosis beyond sepsis is extensive and includes metabolic and inborn errors of metabolism, cerebrovascular accident, trauma, and toxins.

The Condition

Our patient presented with symptoms of barbiturate overdose. These symptoms can include altered level of consciousness, decreased pupillary light reflex, vertigo, ataxia, and incoordination. In addition, these patients can develop shallow breathing, slowness or slurred speech, and delirium. On physical examination, hypothermia, hypotension, respiratory depression, and tachycardia or bradycardia are commonly observed. Drug screens, both urine and serum, can detect barbiturates for up to 5 days after ingestion. Unfortunately, there is not a direct antidote to barbiturate intoxication. In cases of overdose that cause respiratory failure, the patient will require assisted ventilation until the drug is cleared.

The patient's unexplained positive toxicology screen result for barbiturates with continued, progressive worsening of his mental status prompted investigation into intentional abuse. Munchausen syndrome by proxy consists of fabricating or inducing an illness in a child by a caregiver to get attention. It is defined by the American Psychiatric Association as an intentional production or feigning of physical or psychological signs or symptoms in another person who is under the individual's care. The motivation for the perpetrator's behavior is to assume the sick role by proxy. In addition, it is the perpetrator who is diagnosed as having Munchausen syndrome by proxy, whereas the child has the illness as a result of the perpetrator's action

Munchausen syndrome by proxy is a relatively rare form of child abuse that poses significant danger of morbidity and mortality to the affected child. Hospitalization of children affected by Munchausen syndrome by proxy is required in almost all cases. The perpetrator, who is the mother in most cases, often has a personal history of strange or unexplainable illnesses or behaviors, including factitious or somatoform disorders. Munchausen syndrome by proxy may present as either a simulation of events (eg, warming a thermometer to simulate a fever) or an actual induction of symptoms in the child (eg, administration of ipecac to induce emesis in the child).

Diagnosis

Identifying Munchausen syndrome by proxy requires a high level of suspicion on behalf of the health care team. Key red flags that should prompt considering this diagnosis include the reported history varying from what is observed; the illness being unexplained, unusual, or prolonged and not responding to treatment as expected; the occurrence of the problem only in the presence of the suspected perpetrator; or the alleged perpetrator not appearing as worried by the child's illness as the health care team. Often the caregivers in these cases seem to be attentive and at the child's bedside almost constantly. They are characteristically compliant, overtly concerned with caring for the child, and often familiar with medical terms. In addition, they often form close bonds with the medical staff and may be anxious to impress them with their aptitude for caring for the child and degree of medical knowledge.

When evaluating a child for abuse secondary to Munchausen syndrome by proxy, laboratory evaluation should be performed to confirm the diagnosis or exclude other causes. Child and family medical histories should be reviewed, including history obtained from neutral sources, with attention to unusual illnesses or deaths and the condition of the child when outside the care of the suspected perpetrator. Video surveillance, although controversial and considered by some to be unethical and an invasion of privacy, may reveal deliberate harmful actions by the caregiver.

Management

Once it was determined that the patient's symptoms were attributable to intentional phenobarbital overdose, the police were contacted, and

the mother was removed from the patient's bedside and arrested. The infant underwent a thorough child abuse workup, including ophthalmology evaluation and the skeletal survey; the evaluation result was negative. The patient improved clinically and was successfully extubated by day 8 of admission and discharged home with the maternal grandmother on day 11 at his baseline neurologic status. The mother currently is incarcerated and admitted to giving the patient phenobarbital to seek attention from the patient's father, who is married and has other children.

Management of cases of Munchausen syndrome by proxy requires involvement of law enforcement, child protective services, and social services. Disclosure of the diagnosis to the family should be done in a straightforward and supportive manner, with the emphasis on helping the child rather than eliciting a confession. Measures should be in place to prevent the caregiver from fleeing, and psychiatric evaluation should be readily available for both the child and parent. In addition, there is an increased risk of maternal suicide after the disclosure of suspicion, and the child and siblings should almost always be removed from the house to ensure their safety.

Lessons for the Clinician

- Differential diagnosis for altered levels of consciousness is broad: remember to consider intentional or unintentional intoxication.
- If a child's illness is unexplained, unusual, or prolonged and does not respond to treatment as expected, consider additional diagnoses.
- Diagnosis of Munchausen syndrome by proxy requires a high index of suspicion.
- Munchausen syndrome by proxy requires treatment of the family with the help of social workers and psychiatrists.

(*Corrie Fletcher, DO, April Jones, DO, Advocate Children's Hospital, Oak Lawn, IL*)

Case 3 Discussion

Our working diagnoses included human immunodeficiency virus (HIV) infection, pelvic inflammatory disease with abscess, and inflammatory bowel disease. Our patient had a positive tuberculin test result with induration of 12 × 15 mm. Her sputum and exudative peritoneal lavage samples tested positive for acid-fast bacilli. Her cultures tested positive for *Mycobacterium tuberculosis*, which was sensitive to first-line antituberculosis drugs. MRI of the abdomen confirmed hepatomegaly, ascites, pancreatitis, and ileocecal thickening without any strictures or septations and a recto-vaginal fistula. Chest radiography revealed right-sided pleural effusion with reticulonodular changes in the lung parenchyma. Thus, a diagnosis of abdominal tuberculosis with primary pulmonary involvement was established.

The Condition

Abdominal tuberculosis is rare but well described in pediatrics. A high index of suspicion is required to diagnose it, especially in children with insidious onset of abdominal pain, fever, and abdominal distention. Abdominal tuberculosis can manifest in multiple ways, including peritonitis, ascites, enlarged lymph nodes (mesenteric and para-aortic), ileocecal thickening or mass, strictures, perforation, intestinal obstruction, fissures and chronic fistulas, hepatitis, cholangitis, pancreatitis, Addison disease, renal involvement, pelvic inflammatory disease, and colitis. In young women, infertility may be a presenting feature of abdominal tuberculosis. The most common site for abdominal tuberculosis is the ileocecal area, although any part of the intestine can be affected, including peritoneal involvement and development of ascites. Our patient had ileocecal involvement with thickening of bowel wall, ascites, peritonitis, hepatitis, pancreatitis, and a rectovaginal fistula.

We believe that our patient had her primary focus in the lungs because chest radiography performed 6 months earlier for pneumonia revealed reticulonodular changes in the lung parenchyma. However, at that time these lesions were mistaken for pneumonia. Serosal involvement, such as peritonitis, makes the patient prone to fibrosis and stricture formation. In patients with abdominal tuberculosis, it is important to identify the extent of dissemination to other abdominal organs because that helps to decide both duration of therapy and prognosis. The other sites of disseminated tuberculosis include pericardium, central nervous system, bone and joints, and episcleritis. Although our patient had extensive abdominal tuberculosis, she did not have dissemination to any of these sites.

Differential Diagnosis

Inflammatory bowel disease presenting with weight loss, colitis, and anal fissure was in the differential diagnosis; however, the presence of ascites, pancreatitis, and hepatitis along with pulmonary changes were suggestive of another disease process. The history of high-risk sexual behavior was concerning for pelvic inflammatory diseases with an abscess; however, the chest radiograph findings of ascites, pancreatitis, and hepatitis again were suggestive of a systemic condition. The patient's blood culture results were negative. HIV was also considered in the differential diagnosis; however, our patient's HIV

serologic and polymerase chain reaction test results were negative. We also considered immunodeficiency because of significant lymphopenia. However, the results of evaluation for immunodeficiencies were negative.

Treatment and Prognosis

Abdominal tuberculosis requires prolong duration of therapy (9–12 months). Delay in treatment can worsen the clinical outcome; hence, it is important to start the treatment when there is high index of suspicion and while one is awaiting results. Recommendation for the initial treatment includes 4 drug therapy (isoniazid, rifampicin, ethambutol, and pyrazinamide) for 2 months, which our patient was prescribed, followed by 2- or 3-drug therapy to complete 9 to 12 months of treatment. Considering hepatotoxicity associated with the anti tuberculosis drugs, baseline liver enzyme levels should be checked before prescribing medications. Serosal involvement, such as peritonitis, increases the risk of fibrosis and stricture formation, and a short course of steroids was given to our patient after ruling out a secondary bacterial infection. Use of steroids in serosal tuberculosis is controversial. Duration of therapy and prognosis are dependent on extent of dissemination. With prompt treatment, the prognosis is good.

Our patient improved gradually with 4-drug therapy, with good weight gain, resolution of ascites, improvement in chest radiographic findings, laboratory findings, and improved appetite. Her blood cell count and lymphopenia resolved before discharge. She was discharged home with close follow-up and recovered well within 1 year. She received 4-drug therapy for 2 months and then was transitioned to 3-drug therapy for 10 months. She received daily-observed therapy. Close screening of contacts revealed that her mother also had pulmonary tuberculosis, with cultures that yielded *M tuberculosis*.

Lessons for the Clinician

- Manifestation of abdominal tuberculosis include abdominal pain, abdominal distension, ascites, peritonitis, strictures and fissures, ileocecal involvement, hepatitis, pancreatitis, splenic involvement, cholangitis, nephritis, pelvic inflammatory diseases, lymphadenopathy (mesenteric and para-aortic), and colitis.
- Before treating a child with abdominal tuberculosis, it is important to rule out dissemination to other sites, such as central nervous system, bone and joints, heart and pericardium, and eyes, because this may affect the duration of therapy and prognosis.
- If diagnosed early and treated promptly, the prognosis is good.

(*Heather Miller, MD, Vineeta Mittal, MD, Department of Pediatrics, UT Southwestern Medical Center and Children's Medical Center, Dallas, TX*)

To view Suggested Reading lists for these cases, visit http://pedsinreview.aappublications.org and click on the "Index of Suspicion" link.

Correction

In the March 2014 issue, the article "Gynecologic Examination of the Prepubertal Girl" (Jacobs AM and Alderman EM. *Pediatrics in Review.* 2014:35(3):97–105, doi: 10.1542/pir.35-3–97) mentions mebendazole as a treatment for pinworms. Mebendazole no longer is available in the United States; the AAP *Red Book* recommends pyrantel pamoate or albendazole. Albendazole is not approved for use by the U.S. Food and Drug Administration. The journal regrets the error.

Index of Suspicion

Shagun Sachdeva, Corrie Fletcher, Heather Miller, Priti Bhansali, April Jones and Vineeta Mittal

Pediatrics in Review 2014;35;206
DOI: 10.1542/pir.35-5-206

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Correction

Pediatrics in Review 2014;35;211
DOI: 10.1542/pir.35-5-211

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Pediatrics in Review 2014;35;211
DOI: 10.1542/pir.35-5-211

Syphilis

Rebecca Butterfield

Pediatrics in Review 2014;35;212
DOI: 10.1542/pir.35-5-212

In Brief

Syphilis

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Albany Medical Center, Albany, NY

Author Disclosure
Dr Butterfield has 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.

Syphilis. American Academy of Pediatrics; Pickering LK, ed. *Red Book: 2012 Report of the Committee on Infectious Diseases*. 29th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2012.

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Screening for Syphilis Infection in Pregnancy: US Preventative Services Task Force Reaffirmation Recommendation Statement. *Ann Intern Med*. 2009;150(10):705.

Treponema pallidum is a motile spirochete and the causative microorganism of syphilis. *T pallidum* is transmitted through direct sexual contact with infectious lesions, transplacentally from infected mother to fetus, or via blood transfusion. The most common mode of transmission is sexual. Transmission occurs when the host's highly infectious skin lesions make direct contact with the partner, and the spirochete is able to enter the body through mucous membranes. Transmission via oral sex is possible if the infected individual has active lesions on the oral mucosa. *T pallidum* crosses the placenta and can infect a fetus at any gestational age. There is an inverse relationship between the severity of infection and gestational age at time of infection. Placental transmission can also occur at any clinical stage of syphilis, although mothers are more likely to transmit the infection while in the early stages of the disease. Blood transfusion transmission, although possible, is unlikely today given the universal screening of donors.

The clinical manifestations of syphilis are variable, depending on the stage of the illness. Primary syphilis is characterized by the development of a painless papule at the site of inoculation. This papule ulcerates to produce the classic chancre of primary syphilis, a 1- to 2-cm ulcer with a nonexudative base and raised borders. Chancres spontaneously heal after 3 to 6 weeks even in the absence of treatment, and because of their painless nature, many patients are unaware of their presence. Secondary syphilis symptoms occur weeks to months later and have characteristic systemic signs, including a polymorphic rash, classically described as a maculopapular rash that involves the trunk, extremities, palms, and soles; condyloma lata, which are large gray or white lesions distributed around mucous membranes; and constitutional symptoms, such as lymphadenopathy, malaise, and myalgias. Latent syphilis is defined as the lengthy period (sometimes decades) of asymptomatic indolence before the eruption of tertiary syphilis. Clinical manifestations of tertiary syphilis include dementia, aortic aneurysms and regurgitation, and granulomas, known as gummas, which can occur on the skin, bones, or internal organs.

The symptoms of congenital syphilis are divided into those that are apparent before age 2 years, termed early congenital syphilis, and those manifest after age 2 years and older, termed late congenital syphilis. Most infected infants are asymptomatic at birth. Symptoms of early congenital syphilis include diffuse rash, especially of the palms and often associated with exfoliation; rhinitis, known as snuffles; thrombocytopenia; and hepatomegaly and chorioretinitis. Late congenital syphilis primarily manifests with intellectual disability and cranial nerve palsies, as well as bone and teeth abnormalities, including granulomatous destruction of the nasal septum known as saddle nose, widely spaced and centrally notched incisors known as Hutchinson teeth, interstitial keratitis, sensorineural hearing loss, and arthritis. The possibility of acquired syphilis through sexual abuse must be considered in any child who presents with the disease.

Diagnosis of syphilis is complicated by the inability to culture *T pallidum* in vitro. Nontreponemal serologic tests are used as first-line screens. Nontreponemal tests include the VDRL test, the rapid plasma reagin test, and the automated reagin test. These tests are sensitive but nonspecific and are useful as primary screens given their ease and low cost. There is the potential for false-positive results, however, because of conditions, including pregnancy, autoimmune disease, rickettsial infection, and nonsyphilis treponemal infection.

Therefore, a reactive nontreponemal test result must be confirmed with a specific treponemal test, including the fluorescent treponemal antibody absorption and the *T pallidus* particle agglutination test. Congenital syphilis should be suspected in all newborns whose mothers have reactive nontreponemal and treponemal serologic test results, as well as any child with pertinent signs and symptoms. These children should undergo nontreponemal serologic tests, and children with probable or highly probable disease should undergo lumbar puncture to examine the cerebrospinal fluid cell counts, which would be elevated, and the VDRL test, which would have a positive result. Approximately 40% of newborns with syphilis have asymptomatic seeding of the cerebrospinal fluid.

Treatment of primary, secondary, and early latent syphilis remains a single dose of benzathine penicillin G, and no resistance has been reported. Three doses of benzathine penicillin G are recommended for late latent or tertiary syphilis. All patients who have a positive treponemal test result should be offered human immunodeficiency testing. Congenital syphilis should be treated with 10 to 14 days of aqueous penicillin G or procaine penicillin, in consultation with a pediatric infectious disease specialist. The US Preventive Services Task Force and the Centers for Disease Control and Prevention recommend universal syphilis screening for all pregnant women in the first trimester, again during the third trimester, and at delivery for women at high risk for syphilis.

Comments: While I usually have to check the *Red Book* to review screening and testing for syphilis because of its complexity, I found Dr Butterfield's presentation clear and understandable. Primary syphilis can often be missed because the lesions are painless and may be overlooked. Congenital syphilis transmission can occur at any stage of pregnancy or at birth. Nontreponemal tests that provide quantitative results and level of disease are needed to help define activity and monitor therapy. However, there may be false-positive results with other illnesses, such as Epstein-Barr virus, hepatitis, varicella, measles, lymphoma, tuberculosis, malaria, and connective tissue diseases, along with substance abuse of injection drugs. The nontreponemal test needs to be paired with a treponemal test, which is more specific for syphilis and reactive for life. The combination of these tests reinforces that the patient is truly infected, and the nontreponemal quantitative results allow monitoring of therapy. Specific follow-up is required for infants with congenital syphilis, and nontreponemal tests should be performed again at 2 to 4 months, 6 months, and 12 months until the results become nonreactive or the titer has decreased by 4-fold. Clinicians should always consider consulting with an infectious disease specialist if in doubt, and the *Red Book* is incredibly helpful in determining testing and treatment.

Janet Serwint, MD
Consulting Editor, In Brief

Parent Resources from the AAP at HealthyChildren.org

- http://www.healthychildren.org/English/health-issues/conditions/sexually-transmitted/Pages/Syphilis.aspx
- Spanish: http://www.healthychildren.org/spanish/health-issues/conditions/sexually-transmitted/paginas/syphilis.aspx

Answer Key for May 2014 Issue:
Cleft Lip and Palate: 1. E; 2. A; 3. D; 4. D; 5. E.
Infectious Diseases in Early Education and Child Care Programs: 1. B; 2. C; 3. A; 4. E; 5. D.
Cystic Fibrosis: 1. C; 2. E; 3. C; 4. A; 5. D.

Syphilis

Rebecca Butterfield

Pediatrics in Review 2014;35;212
DOI: 10.1542/pir.35-5-212