Clinical Practice Guidelines for Management of Children With Down Syndrome: Part I

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KEY WORDS
Down syndrome, practice guideline, trisomy 21

Down syndrome (DS), also known as trisomy 21, is a common genetic disorder that is the result of having an extra copy of chromosome 21. The Centers for Disease Control and Prevention (CDC) estimates that each year about 6000 babies are born with DS (an average of 1 in 691 infants born in the United States), without any predilection of race or socioeconomic class (CDC, 2011). The likelihood of having a baby with DS increases with advanced maternal age. If the odds are 1:1441 when the mother is 20 years old, they increase to 1:338 when the mother reaches 35 years of age and can be as high as 1:84 for a woman 40 years old (Morris, Mutton, & Alberman, 2002).

Approximately 95% of children with DS have this condition because of the presence of one extra chromosome 21. Another 3% to 4% of patients present with an unbalanced translocation; these patients have a karyotype with 46 chromosomes, but one of the chromosomes (usually chromosome 14) carries extra chromosomal material from chromosome 21. Twenty-five percent of children with an unbalanced translocation (0.75% to 1% of those diagnosed with DS) receive the affected chromosome from one of the parents, and thus additional familial studies and genetic counseling are necessary (Bull & the Committee on Genetics, 2011). The remainder of the patients with DS have mosaicism, in which case individuals have both normal cells and cells with an extra chromosome 21.

Apart from characteristic physical features (see the Physical Examination section), most children with DS have a variable degree of cognitive impairment, ranging from mild impairment (intelligence quotient [IQ] of 50 to 70) to severe impairment (IQ of 20 to 35). Children with DS carry a significant degree of morbidity because of associated conditions such as hearing loss (75%), otitis media (50% to 70%), eye disorders (60%), obstructive sleep apnea (50% to 79%), congenital heart defects (50%), gastrointestinal (GI) problems (12%), hip dislocation (6%), thyroid disease (4% to 18%), hematologic disorders (4% to 10%), and neurologic dysfunction (1% to 13%; Bull & the Committee on Genetics, 2011).

The complexity of this condition makes it challenging for primary care physicians, nurse practitioners, and physician assistants alike to render adequate care and follow-up. In 2011 the American Academy of

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Pediatrics (AAP) Committee on Genetics published updated guidelines for the management of children with DS, replacing those published in 2001 (AAP, Committee on Genetics, 2001). The recommendations in the new guidelines span from the prenatal period through adulthood (Bull & the Committee on Genetics, 2011). The purpose of this Practice Guideline, divided into two parts, is to summarize the new guidelines in a more direct manner for the primary care practitioner. Part One will address the health maintenance of patients with DS until their first birthday, whereas Part Two will focus on their care as these children transition to adulthood.

THE PRENATAL VISIT

In 2007, the American College of Obstetricians and Gynecologists (ACOG) recommended that all women be offered aneuploidy screening before 20 weeks of gestation regardless of maternal age. The detection rate of DS through combined prenatal screenings performed during the first and second trimester is 95% (ACOG, 2007). Screening during the first trimester takes into account the maternal age, along with measurement of fetal nuchal translucency through ultrasonography and maternal serum human chorionic gonadotropin and pregnancy-associated plasma protein A. During the second semester, screening again assesses the maternal age risk and also includes measurements of maternal serum human chorionic gonadotropin, unconjugated estriol, alpha fetoprotein, and inhibin levels.

Once the diagnosis is entertained, pediatric health care providers are often involved to counsel the families and should address the following topics:

- Prenatal laboratory and imaging studies that led to the diagnosis
- Available genetic counseling
- Decision to continue or terminate pregnancy (in cases of early prenatal diagnosis)
- Clinical manifestations and prognosis
- Additional fetal studies (e.g., echocardiogram and ultrasound of the GI tract)
- The need for follow-up with various subspecialists (e.g., a cardiologist, gastroenterologist, and ophthalmologist)
- Available treatments and intervention
- Delivery plan and neonatal care
- Local and national support groups

BIRTH TO 1-MONTH VISITS

History

- Review prenatal information (first- and second-trimester screening results and karyotype results).
- Review family history (previous pregnancies that ended in miscarriages, children born with DS, and developmental delay).

Physical Examination

Physical examination in the first 24 hours of life is a very important tool for diagnosing DS (Bull & the Committee on Genetics, 2011). Although the clinical presentation of children with DS is variable, the following physical features are quite suggestive:

- Epicanthal folds (i.e., skin fold of the upper eyelid, covering the medial canthus of the eye)
- Flat nasal bridge
- Narrow, upward-slanting palpebral fissures
- Brushfield spots (i.e., white or yellow spots seen on the anterior surface of the iris)
- Small, brachycephalic (flat) head
- Small mouth and small dysplastic ears
- Excessive skin on the nape of the neck
- Single (or bridged) palmar crease
- Short fifth finger with clinodactyly (i.e., a bent or curved finger due to mid phalanx hypoplasia)
- Generalized hypotonia (one of the most striking characteristics; Weijerman & de Winter, 2010)

Other common physical findings or symptoms in newborns with DS are:

- Head, eyes, ears, nose, throat
  - — Abnormally large anterior fontanelle
  - — Fine, soft, and sparse hair
  - — Midfacial hypoplasia
  - — Abnormal/asymmetric red reflex
  - — Large tongue compared to the size of the mouth
- Respiratory
  - — Stridor
  - — Wheezing
  - — Noisy breathing
- Cardiac
  - — Dyspnea
  - — Cyanosis
  - — Murmur(s)
- GI
  - — Easy fatigability with feedings
  - — Poor suck
  - — Emesis
  - — Abdominal distention
  - — Diastasis recti (separation of the rectus abdominis muscles into right and left halves)
  - — Imperforate anus
- Genitourinary
  - — Micropenis (in boys) or lower labial index (labia majora shorter and wider than normal in girls)
  - — Cryptorchidism
  - — Hypospadias
- Extremities
  - — Wide gap between the first and second toe
- Skin
  - — Pale, blotchy skin
  - — Persistent, worsening jaundice

Certain elements of the physical examination will point toward specific medical problems that require immediate attention and intervention:

- Asymmetric red reflex suggests cataract development; referral to a pediatric ophthalmologist is necessary.
- If the baby does not seem to respond to the mother's voice or the sound of a bell, his or her hearing needs to be assessed. Because of the high risk of congenital hearing loss in persons with DS, objective screening at birth with brainstem auditory evoked response (BAER) or otoacoustic emission is important.
- The presence of heart murmurs and cyanosis in the neonatal period necessitates a cardiology consultation. However, an echocardiogram should be performed for *all* babies with DS (preferably before hospital discharge) despite the absence of any cardiac signs and symptoms and *regardless* of whether an echocardiogram was performed in the prenatal period.
- If the ability to suck or latch on is impaired, consider formula supplementation until a successful breastfeeding pattern is established.
- If the newborn has slow feeding, choking, respiratory symptoms with feeding, or poor weight gain, consider obtaining a radiographic study of the swallowing process.
- Significant abdominal distention along with emesis suggests duodenal atresia. Radiographic evaluation shows air in the stomach and first part of duodenum, with no air beyond that (the "double bubble" sign). Surgery consultation is indicated for suspected or confirmed duodenal atresia and/or anal atresia.
- Babies with DS are at risk for atlantoaxial instability (AAI), which is characterized by excessive movement at the junction between the atlas (C1) and axis (C2) vertebrae as a result of a ligamentous abnormality (the transverse ligament, which holds the dens against the posterior border of the anterior arch of C1). AAI can lead to spinal cord impingement.
- Decreased muscle tone may lead to apnea, bradycardia, and oxygen desaturation in a car seat. A car seat challenge needs to be conducted before hospital discharge.
- If constipation is noted (all newborns should pass meconium in the first 24 hours of life), the feeding process and intake need to be evaluated. If normal, further evaluation for hypothyroidism (discussed later) or GI tract malformations (such as Hirschsprung disease and anal stenosis) with radiologic studies is required.
- Gastroesophageal reflux disease (GERD), if present, can be managed initially with specific positioning of the infant after feedings and/or antireflux medication. However, if GERD leads to poor weight progression or is accompanied by significant respiratory symptoms, subspecialty intervention is suggested.
- For babies presenting with stridor, wheezing, or noisy breathing, consider pediatric pulmonology assessment for airways anomalies or pediatric gastroenterology assessment for severe GERD.

If the newborn has slow feeding, choking, respiratory symptoms with feeding, or poor weight gain, consider obtaining a radiographic study of the swallowing process.

Diagnostic Studies

- To confirm the diagnosis, obtain a fluorescent in situ hybridization (FISH) study (where available); results are accessible in 24 to 48 hours but can only identify an extra copy of chromosome 21 (not translocations).
- Obtain a karyotype, which is important in detection of translocation (note: obtaining a karyotype takes longer than obtaining results of a FISH study).
- Obtain a complete blood cell count to assess for the presence of leukemoid reaction or polycythemia. Transient myeloproliferative disorder associated with pancytopenia, hepatosplenomegaly, and circulating immature white blood cells is found almost exclusively in infants with DS with an incidence of approximately 10% (Dixon, Kishnani, & Zimmerman, 2006). Consult a pediatric hematologist if necessary.
- Congenital hypothyroidism: If newborn screening doesn't include thyroid-stimulating hormone, it should be obtained. Consider a pediatric endocrinology consultation if necessary.

Anticipatory Guidance

- Discuss physical findings and the laboratory/radiological evaluation with parents and provide information about DS in a supportive manner.
- Discuss increased susceptibility to respiratory infections and the need for assessment and treatment by a medical provider.
- Discuss the need for respiratory syncytial virus prophylaxis for infants with complex cardiac malformations.

- Review the importance of cervical spine positioning, avoiding excessive extension or flexion during any types of therapy or procedures.
- Counsel the parents about the increased risk of leukemia (acute megakaryoblastic leukemia is 500 times more likely to develop in children with DS, and acute lymphoblastic leukemia is 20 times more likely to develop in children with DS; Seewald, Taub, Maloney, & McCabe, 2012) and ask the parents to monitor the child for suggestive signs (e.g., bruising, petechiae, and change in feeding pattern).
- Discuss the importance of Early Intervention services, and arrange a referral prior to hospital discharge.
- Discuss the importance of the support of family, clergy, and friends and local/national DS support groups.
- Discuss the availability of genetic counseling and recurrent risk in subsequent pregnancies.

Controversial Issues

- Discuss complementary/alternative treatments and their efficacy (Roizen, 2005).
- Discuss the need for urinary tract imaging; although urinary tract anomalies have been reported with increased frequency among patients with DS (Kupferman, Druschel, & Kupchik, 2009), no studies have shown that routine screening improves the outcome in these patients, and thus currently renal or urologic screening is not recommended (Bull & the Committee on Genetics, 2011).

1-MONTH TO 1-YEAR VISITS

History

- Review prenatal/postnatal laboratory tests, which include prenatal screening results, postnatal FISH and karyotype results, newborn screening results, and thyroid function tests.
- Review radiologic results, along with any available information that led to the diagnosis (if not done previously).
- Assess feeding process and any associated difficulties (e.g., reflux, respiratory symptoms, sweating, fatigue, and cyanosis).
- Monitor for signs and symptoms of congestive heart failure in children with cardiac defects (e.g., tachypnea, feeding difficulties, and poor weight gain).
- Assess for any difficulties associated with stooling and bowel movements pattern. If constipation is present, assess for hypotonia and adequacy of fluid intake and review previous laboratory work pointing toward hypothyroidism, GI malformations, or Hirschsprung disease.
- Evaluate the sleep routine and discuss with parents symptoms of obstructive sleep apnea (e.g., heavy breathing, snoring, unusual sleep positions, frequent awakening during sleep, increased sleepiness during the day, and worsening behavior problems).
- Review with parents signs and symptoms of myelopathy—strength, changes in bowel/bladder function, neck pain, stiff neck, and weakness.
- Because children with DS have an increased risk of seizures (e.g., infantile spasms), ask parents about recurrent episodes of unresponsiveness or repetitive movements of their extremities.
- Ask parents about age-specific milestones and about the enrollment status with Early Childhood Intervention.
- Inquire about parental and family well-being and the need for supportive services.

Physical Examination

- Monitor growth parameters using the growth charts of the National Center for Health Statistics or the World Health Organization. The previously used DS growth charts no longer reflect the current population growth trend and body proportions (Bull & the Committee on Genetics, 2011).
- Detect specific physical features (as mentioned in the previous section).
- Assess ears for serous otitis media development either by direct otoscopic examination or with tympanometry (in case of poor visualization of the tympanic membrane and tympanic membrane mobility) and treat promptly if indicated.
- Assess the infant's vision by using developmentally appropriate criteria.
- Assess for the presence of cataracts by performing a red reflex examination.
- Assess dental development.
- An enlarged, protruding, fissured, and geographic tongue is common in children with DS.
- Oral, loud breathing should point toward the possibility of a narrow nasopharynx and enlargement of adenoids or tonsils.
- The presence of torticollis or neck stiffness should alert one about the possibility of AAI and subsequent spinal cord compression.

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- Wheezing and stridor are suggestive of upper and/or lower airways abnormalities such as laryngomalacia, tracheomalacia, airway compression from

large vessels, tracheal bronchus, bronchomalacia, tracheoesophageal fistula, or severe GERD.
- Cyanosis, heart murmurs, and tachycardia are supportive findings for complex cardiac malformations (e.g., atrioventricular canal, ventricular septal defects, atrial septal defects, patent ductus arteriosus, tetralogy of Fallot, hypoplastic left heart syndrome, and pulmonary hypertension).
- Assess genitalia for micropenis, cryptorchidism, and hypospadias (in boys) or lower labial index (a labia majora that is shorter and wider than normal in girls).
- Perform a careful neurologic examination, paying attention to the tone of lower/upper extremities; hypertonia and/or weakness suggest AAI and subsequent spinal cord compression.

Diagnostic Studies

- Hearing should be tested (if not done at birth). If results are normal, repeat at 6 months (BAER) and 12 months (behavioral audiogram or BAER).
- Review newborn screening results. If results of thyroid screening are normal, repeat TSH at 6 and 12 months.
- Hemoglobin concentration should be obtained at age 1 year and yearly thereafter.
- Mean corpuscular volume is *not* useful for assessment of iron deficiency anemia, lead toxicity, or thalassemia because of the fact that approximately 45% of children with DS have increased mean corpuscular volume even in the absence of heart disease.
- For patients at risk for iron deficiency, obtain a serum ferritin level (along with a C-reactive protein level, because ferritin is also an inflammatory marker) or reticulocyte hemoglobin concentration annually (Mast, Blinder, & Dietzen, 2008).
- Radiographic assessment of swallowing should be performed if the child has symptoms (e.g., hypotonia, slow feeding, choking, recurrent respiratory symptoms, and failure to thrive)
- Obtain contrast radiologic studies to assess for GI malformations or Hirschsprung disease if the child has severe constipation.

Referrals

- Ophthalmology (preferably in the first 6 months) for assessment of strabismus, cataracts, and nystagmus
- Ear, Nose, and Throat if the hearing screening revealed problems or upon difficulties with examination of ear canals (stenotic canals)
- Ear, Nose, and Throat/Pulmonology if history/examination is suggestive of obstructive sleep apnea
- Endocrinology if findings of thyroid function tests are abnormal
- Cardiology if signs/symptoms of congestive heart failure are present
- Neurosurgery/Orthopedic Surgery if signs of compression myelopathy are present (obtain cervical spine radiographs, as discussed later)

ANTICIPATORY GUIDANCE

- Ensure that the child's immunization status is adequate, including influenza vaccine.
- Provide respiratory syncytial virus prophylaxis if necessary (see previous section).
- Review the importance of cervical spine positioning during any types of therapy or procedures.
- Review the need to monitor for bruising, petechiae, or change in feeding pattern (i.e., signs/symptoms of leukemia).
- Reassure parents of delayed/irregular dental eruption (hypodontia is common).
- Review availability of and need for Early Intervention services.
- Review/assess the emotional status of the family at each visit.
- Review the availability of DS support groups.
- Review information about DS and availability of genetic counseling (if not already provided).
- Review and discuss the efficacy of complementary/alternative treatments.

SUMMARY

Working with DS patients in primary, specialty, and acute care health settings has always been a demanding task for the busy practitioner. The associated medical conditions, developmental demands, and educational demands makes it challenging for pediatric care providers to address all the specific details for each age group. The purpose of this two-part Practice Guideline is to streamline this process. Part One has summarized the care of the patient with DS until the age of 1 year. Part Two will focus on care from the child's first birthday until he or she transitions to adulthood.

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