

CEREBRAL PALSY



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Learning Objectives

1. Detect risk factors and potential etiologies that contribute to the development of cerebral palsy.
2. Distinguish the type of cerebral palsy present in a patient, based on severity and location of spasticity, abnormal movements, and tonicities.
3. Evaluate nonpharmacological methods for the treatment of spasticity and spasticity-related effects associated with cerebral palsy.
4. Given a clinical scenario, develop or modify an oral drug-therapy plan for the treatment of spasticity or other manifestations of cerebral palsy.
5. Justify the use of newer therapies for the treatment of spasticity, such as intrathecal baclofen and botulinum toxin, and detect potential complications of their use.
6. Assess the quality of life of patients with cerebral palsy and the impact of care for these patients on the family.

Introduction

The first clinical description of the symptom complex of cerebral palsy (CP) was provided in 1862 by William John Little, who noticed “spastic rigidity” in patients that was related to prematurity and birth complications. Little’s disease was later termed cerebral palsy by William Osler in 1888. Currently, the prevalence of CP is about 1–2.5/1000 live births, and despite advances in perinatal care over the past 4 decades, those numbers have not decreased. Cerebral palsy has tremendous impact on the quality of life of patients and their caregivers, and it exerts a heavy burden

financially, with recent estimates showing a cost of \$8.2 billion annually in the United States for patient care.

Definition

Cerebral palsy is not a disease entity; it is a constellation of symptoms referring to nonprogressive, yet sometimes changing, syndromes of motor impairment due to lesions in the brain that occur early in development. Nonprogressive, or static, refers to the fact that the brain lesion does not continue to progress, but does not resolve either. As a result, all neurodegenerative, neoplastic, and metabolic disorders that may appear clinically similar to CP are excluded. Although the brain lesion is unchanged, it can cause symptoms that change and can also prevent proper development in brain function, and deficits result from both. Cerebral palsy is an “umbrella term” that encompasses many etiologies, pathologies, and clinical manifestations. Many abnormal neurological findings in early infancy will resolve with time and will not ultimately result in a diagnosis of CP. Most centers use the lower limit of 2 years of age for initial diagnosis, and the diagnosis is confirmed and validated at 5 years.

There is no solid consensus on the upper age limit for the development of the CP complex. Recent evidence suggests that the central nervous system is not fully developed until much later. Most cases of CP are the result of some prenatal insult, although smaller numbers of cases are caused by postnatal insults, including vascular accidents, infection, or trauma.

Epidemiology

Overall, the prevalence of CP is 1–2.5/1000 live births. Gestational age has the most profound effect on the development of CP. Although prevalence rates of CP in term

Shevell MI, Bodensteiner JB. Cerebral palsy: defining the problem. *Semin Pediatr Neurol* 2004;11:2–4.

Shevell MI. The “Bermuda Triangle” of neonatal neurology: cerebral palsy, neonatal encephalopathy, and intrapartum asphyxia. *Semin Pediatr Neurol* 2004;11:24–30.

Abbreviations in this Chapter

BTX	Botulinum toxin
CP	Cerebral palsy
GABA	Gamma aminobutyric acid
HBO	Hyperbaric oxygen
ITB	Intrathecal baclofen

infants or those greater than 2500 g are about 1/1000, rates in low (less than 2500 g) birth weight and very low (less than 1500 g) birth weight infants can be higher by 40–100 times. International data from the 1960s to the late 1980s have shown an increase in the prevalence of CP that coincided with the increase in survival of low and very low birth weight infants. During this time, rates remained stable in infants with birth weight greater than 2500 g, but rates increased 3-fold from the late 1960s to the late 1970s in infants with birth weights of 1500–2499 g. The prevalence of CP in children less than 1500 g at birth started increasing from 30/1000 to 90/1000 survivors in the late 1970s, with a vast majority of the increase accounted for by those infants less than 1000 g. In the late 1960s to the late 1980s, an increase from one-third to almost one-half of cases of CP occurred in children weighing less than 2500 g at birth. In addition to the increased incidence of CP in low birth weight infants, there has been an increase in the severity of functional disabilities.

Other international data from the 1970s and 1980s reported similar trends of increasing rates of CP accompanying decreasing neonatal mortality rates. Even if the risk for CP remained the same among survivors, a decreasing neonatal mortality rate resulted in an increased prevalence of CP.

Data from the United States in the early 1980s to the mid-1990s, after surfactant use became routine and resulted in dramatic decreases in infant mortality, showed different results. In infants with birth weights of 500–1500 g, mortality was consistent throughout the 1980s, but decreased significantly from 1990 to 1994. Unlike previous data, these data showed that this decrease in mortality in low birth weight infants was accompanied by an overall decrease in the risk of CP. Surfactant use after 1990 contributed to the lower mortality, but had little if any effect on the rate of CP. Other interventions may have contributed to downward trends in rates of CP, such as control of intrauterine infection and inflammation, and magnesium sulfate treatment of mothers at risk of delivering preterm.

Although epidemiological studies have shown differences in the prevalence of CP in an era of increasing survival of low birth weight infants, on analysis some trends

have remained consistent. Over the past 3–4 decades, the overall prevalence of CP has not changed, despite advances in obstetric care such as electronic fetal heart monitoring. The only long-term outcome data showed that there was an increase in the incidence of CP in those infants who were monitored electronically compared with those who were not.

It has been inferred from some epidemiological data that the constant prevalence rates of CP throughout this time period can be explained by a decrease in the incidence of CP in term infants that is masked by the increase in rates in preterm infants who would not have survived 30 years ago. However, the assertion that one group cancels out the other has not been supported by hard data. In addition, although some studies show an increase in CP in patients with birth weight less than 2500 g, none show any change in patients with birth weight greater than 2500 g. Furthermore, underdeveloped nations have the same rates of CP as developed nations, which could be ascribed to poor reporting or diagnosis in the underdeveloped nations. However, there are such clear differences in other preventable disease states that reporting or diagnosis deficiencies are unlikely.

As noted above, earlier studies have shown an increase in CP prevalence as survival of low birth weight infants has increased. But studies done in the 1980s and 1990s show that rates among premature infants have stabilized or actually decreased, with no change in term infants. Cesarean delivery has also failed to have any impact on the prevalence of CP.

Classification of Cerebral Palsy Subtypes

The subtype of CP in a patient is determined by limb involvement and the type and quality of movement disorder. Table 1-1 lists the common classifications of CP. About 75% of children with CP will have a spastic subtype. Recently, a Task Force on Childhood Motor Disorders provided a consensus statement defining and classifying the causes of hypertonia in childhood. The goal was to make communication more reliable between clinicians, to make diagnoses more accurate and clear, and to aid in appropriately identifying patients for medical and surgical interventions. Hypertonia was defined as abnormal resistance from a joint when a passive movement force is applied. Spasticity was more specifically defined as hypertonia with increasing resistance to external forces that increases with the speed of joint movement and varies with direction of movement, and/or resistance to the external movement that increases quickly above a threshold speed or angle. Spasticity and spastic hypertonia are considered interchangeable terms.

Pharoah POD, Platt MJ, Cooke T. The changing epidemiology of cerebral palsy. *Arch Dis Child Fetal Neonatal Ed* 1996;75:F169–73.

O'Shea TM, Preisser JS, Klinepeter KL, Dillard RG. Trends in mortality and cerebral palsy in a geographically based cohort of very low birth weight neonates born between 1982 to 1994. *Pediatrics* 1998;101:642–7.

Clark SL, Hankins GDV. Temporal and demographic trends in cerebral palsy—fact and fiction. *Am J Obstet Gynecol* 2003;188:628–33.

Sanger TD, Delgado MR, Gaebler-Spira D, Hallett M, Mink JW; Task Force on Childhood Motor Disorders. Classification and definition of disorders causing hypertonia in childhood. *Pediatrics* 2003;111:e89–97.

Table 1-1. Common Classifications of Subtypes of Cerebral Palsy

Subtype	Description	Comments
Spastic diplegia	Bilateral spasticity; lower extremities more affected. Poor lower extremity development. Often good command of upper extremities.	Can be normal neurologically. Seizures in about 20%. Diaper application can be difficult from spasticity due to adduction of hip. Classification historically defined inconsistently.
Spastic hemiplegia	Unilateral spasticity of arm/leg contralateral to brain lesion.	Asymmetric limb use; handedness by 1 year of age. Majority walk with an awkward gait. 13%–37% with cerebral infarct prenatally or perinatally.
Spastic quadriplegia	Spasticity involves all four extremities.	High rates of mental retardation and seizures. Oral motor deficits, many require gastrostomy tubes for feedings; high risk of aspiration.
Extrapyramidal	Distinct movements can be seen by 12–18 months of age. Athetoid dystonic posturing common.	Speech impairments can be severe; drooling, poor vocalization, explosive utterances. Intelligence normal in 78%.
Dystonia	Involuntary movement caused by sustained or intermittent muscle contractions, leading to repeated twisting motions and/or abnormal postures.	Exacerbated by attempted voluntary movement. Severity and presence may fluctuate over time.
Athetosis	Slow writhing extension, pronation, and supination of hands, fingers, feet, and toes.	
Chorea	Irregular spasmodic involuntary movements of limbs or facial muscles.	Can be associated with hypotonia.
Mixed	Includes symptoms of spasticity and extrapyramidal dysfunction.	
Hypotonic	Associated with decreased muscle tone.	Typically normal intelligence. Usually progress to other subtypes.

Spastic CP can be further divided by limb involvement, and includes mono-, di-, hemi-, tri-, and quadriplegia. Mono- and triplegia, involvement of one and three limbs respectively, are infrequent designations.

Spastic diplegia accounts for about 44% of CP cases and is described by bilateral spasticity, with the lower extremities affected more than upper. These patients often have good command of their upper extremities, but have poor lower extremity development and use their arms for locomotion. Historically, the definition of diplegia has changed significantly, causing some controversy. Some have defined diplegia as affecting all four limbs with the lower more affected, whereas others define it as spasticity of the legs only. Other more recent classifications describe spastic diplegia, which is not further delineated, in addition to another concurrent category of diplegia of upper limbs. Therefore, some authors recommend that the term diplegia not be used as they feel that diplegia and quadriplegia are difficult to separate, and a simpler classification applied uniformly would result in more valid and consistent epidemiologic data.

Spastic hemiplegia is described by unilateral spasticity of extremities contralateral to the brain lesion, and accounts for about one-third of spastic CP cases. Limb use usually becomes asymmetric by the age of 6 months, and hand preference is apparent by 1 year. Early locomotion involves pushing forward on the buttocks with assistance of the unaffected upper limb. The vast majority of these children will learn to walk by the age of 2, but typically with an

awkward gait. Figure 1-1 illustrates the typical posture of a patient with hemiplegia.

In spastic quadriplegia, the most severe form of spastic CP, all four extremities are involved. About 6% of patients with spastic CP are quadriplegic. These individuals have much greater functional impairment, including high rates of mental retardation and seizures, and a quarter of them require total care. Only one-third are ambulatory. Those unable to sit on their own by the age of 4 will likely not ambulate. Oral motor dysfunction is also characteristic of quadriplegia, and these patients are at increased risk of aspiration events, which can lead to frequent pneumonias.

A smaller number of patients exhibit extrapyramidal or dyskinetic movement disorders, including dystonia, athetosis, ataxia, myoclonus, and chorea. Chorea is manifested by irregular spasmodic, involuntary dancelike movements of the limbs or facial muscles. Athetosis consists of slow writhing movements with extension, pronation, and supination of the hands and feet and fanning of the digits. Choreoathetosis is a combination of the two. Myoclonus is described by shocklike jerks that can occur either with action, rest, or intention, but also as a result of external stimuli. These movements may or may not be synchronous and rhythmic, and may be generalized or focal. A combination of spasticity and movement disorders is termed mixed-type CP. Also, hypotonic CP is possible, but these children usually progress to the other CP subtypes.



Figure 1-1. Typical posture of a child with left hemiparesis. The arm assumes a position of internal rotation of the shoulder, elbow flexion, forearm pronation, wrist flexion, and thumb-in-palm. The leg shows hip adduction/flexion, knee flexion, ankle equines, hindfoot valgus, and metatarsal varus with hallux valgus. Reprinted with permission from Wake Forest University Orthopedic Press and Dr. LA Koman. Koman LA, Smith BP, Shilt JS. Cerebral palsy. *Lancet* 2004;363:1619–31.

Etiologies, Pathogenesis, and Risk Factors

Etiologies

When Little first described CP in 1862, he proposed that two of the dominant causes were neonatal asphyxia and birth trauma. Prolonged labors and difficult vaginal extractions that were typical in that era could have influenced this perception, which continued for the next century until contradictory data were provided. It was presumed that advances in obstetric care would all but eliminate CP, but as we have seen, there has been no decrease in the overall prevalence from the 1960s to the present.

Perinatal events account for only a small portion of the cases of CP. In more than 70% of cases of newborn encephalopathy, there is no evidence of intrapartum hypoxia, and isolated hypoxia accounts for less than 5% of moderate to severe newborn encephalopathy. Additionally, in less than 10% of cases of spastic CP is intrapartum asphyxia the possible cause of brain injury. Overall, more

than 90% of intrapartum hypoxia cases could not be the cause of CP, and in the remainder, signs consistent with hypoxia could have had antenatal or intrapartum causes. Therefore, data suggest that in a majority of cases, CP is caused by events occurring before labor onset or in the newborn after delivery.

In 1999, the International Cerebral Palsy Task Force published a consensus statement in an attempt to define the objective evidence needed to identify cases of CP that were caused perinatally. The task force identified three criteria necessary before intrapartum hypoxia could be considered as a cause of CP. They were 1) metabolic acidosis (pH less than 7.00 and base deficit greater than or equal to 12 mmol/L) in either intrapartum fetal, umbilical arterial cord, or very early neonatal blood; 2) early onset of moderate or severe neonatal encephalopathy in infants equal to or greater than 34 weeks gestational age; and 3) spastic quadriplegic or dyskinetic CP types. Neonatal encephalopathy is a syndrome characterized by altered neurological function in the near-term to term infant in the first few days after birth. Specific clinical manifestations include lethargy, coma, seizures, brain stem dysfunction, decreased tone, and decreased or absent reflexes. Spastic quadriplegia and dyskinetic CP are the only CP subtypes associated with intrapartum hypoxic events. Spastic quadriplegia is the more common of the two, but it is not exclusive to hypoxic events. Hemiplegia, diplegia, and ataxic CP have not been shown to be related to intrapartum hypoxia.

Five additional criteria that may suggest an intrapartum insult, but by themselves are not specific, include 1) sentinel hypoxic event immediately before or during labor; 2) sudden, sustained, and rapid fetal heart rate deterioration after the hypoxic event when the pattern was previously normal; 3) Apgar scores 0–6 for greater than 5 minutes; 4) early signs of multiple system involvement; and 5) early acute cerebral abnormality on imaging. Also provided were 13 factors that suggested a cause different from acute intrapartum hypoxia. Recently, this document was updated and included a fourth essential criterion that other identifiable etiologies be excluded, including coagulation and genetic disorders, trauma, or infectious conditions. Changes to the nonspecific criteria include the reduction of Apgar scores to 0–3 for greater than 5 minutes and the specification of a time frame of 72 hours for early signs of multiple system involvement.

Contributing Factors

Several risk factors or contributing factors have been identified for the development of CP, most of them antenatal as the fetal brain is particularly vulnerable to insults. These include prematurity, multiple gestation, low birth weight, and more recently intrauterine infection, maternal fever, and thrombophilia. Other associated factors include intrauterine growth retardation, antepartum hemorrhage, breech presentation, and congenital or chromosomal abnormalities. More recently, lower socioeconomic status has been linked to an increased risk of CP even when prematurity was

Hankins GDV, Speer M. Defining the pathogenesis and pathophysiology of neonatal encephalopathy and cerebral palsy. *Obstet Gynecol* 2003;102:628–36.

accounted for, and it is suggested that some of the etiologies of CP may be mediated by low economic status.

Pathogenesis

Cytokines may act as a final common pathway in the pathogenesis of brain injury in CP, and they may be produced after a variety of processes including infection, hypoxic-ischemic injury, reperfusion injury, and toxin-mediated injury. Intrauterine infection can contribute to inflammation. Elevated concentrations of cytokines secondary to infection have been proposed to increase the risk of neonatal brain injury and long-term deficits. Infants born to mothers with documented infection are more likely to develop periventricular leukomalacia. Periventricular leukomalacia is damage to white matter that usually occurs around 28–34 weeks gestational age. It can be described as white matter necrosis near the lateral ventricles that results in cyst formation and subsequent gliosis. Cystic periventricular leukomalacia has been shown to be an excellent predictor of CP, as 60%–100% of premature infants with the condition develop CP. A recent study found a 4-fold increase in the risk of CP in term and near-term infants born to mothers with chorioamnionitis.

It is not just infection, but the fetal response to infection that contributes to fetal brain damage. Proposed mechanisms include increased fetal cytokine concentrations, specifically interleukin-6 and tumor necrosis factor, altered placental gas exchange leading to hypoxia, and core temperature elevations, all of which can lead to direct damage to the developing fetal brain.

In addition to inflammation, more recent data has implicated coagulation disturbances. During pregnancy, balance in the coagulation cascade is lost, favoring procoagulant processes. Factor V Leiden mutations have been increasingly associated with CP. They favor activated protein C resistance and excessive thrombin generation. Recent data have shown a Factor V Leiden mutation in more than 25% of CP cases and less than 2% of controls. It is theorized that thrombi are dislodged from placental circulation and reach fetal circulation. However, a majority of these coagulation disturbances require the presence of another risk factor, such as inflammation due to infection, to produce thrombosis development. This in turn can lead to the development of periventricular leukomalacia.

Much recent research has been devoted to finding methods of preventing the development of CP. Administration of antenatal corticosteroids provides several benefits, including decreased neonatal mortality and decreased incidence of both respiratory distress syndrome and intraventricular hemorrhage, the latter in part by stabilization of the microvasculature of the developing nervous system. Intraventricular hemorrhage has been associated with periventricular leukomalacia, one of the best predictors of CP development. As a result, antenatal

corticosteroids are recommended for use at 24–34 weeks gestation when the mother is at risk of preterm delivery.

Meta-analysis of individual studies has also linked antenatal corticosteroids to a decrease in the risk of white matter damage, which is the primary risk factor in the development of CP after premature birth. This is especially true in the case of pregnancies complicated by fetal inflammatory response, infant hypothyroid conditions, and prolonged rupture of membranes. However, early (less than 96 hours) and delayed (longer than 3 weeks) administration of postnatal corticosteroids has been associated with an increased risk of CP. Animal data suggest that steroids may decrease brain size and cell numbers when given postnatally. Myelination and brain cell division may also be hampered, which could contribute to behavioral problems. Significant reductions in gray matter in premature infants was noted after dexamethasone administration. Behavioral data has also shown that spontaneous motility was decreased in infants who received dexamethasone treatment. Dexamethasone may be more likely than betamethasone to produce this effect because of its sulfite preservative.

Observational studies have shown a decreased incidence of CP when magnesium sulfate was given to mothers giving birth prematurely, but this finding has not been consistent. One recent randomized controlled trial was conducted to determine the benefit of magnesium sulfate at neuroprotective doses given to women with fetuses less than 30 weeks gestation in which birth was planned or expected within 24 hours. Primary outcomes were total mortality and CP corrected to age 2, and combined mortality and CP at 2 years. The incidence of CP and death or CP were lower in the magnesium group, but not significantly. There may be some clinical benefit to magnesium therapy because there was significant lowering of substantial motor dysfunction in the treatment group, but routine use is not recommended until these results can be confirmed by other trials.

Diagnosis

History, Physical, and Neurological Examinations

Diagnosing CP with certainty can be challenging, as noted by the fact that of the more than 5 children per 1000 diagnosed with CP at 1 year of age, only 2 retain the diagnosis at 7 years. An extensive required investigation for diagnosis includes a complete gestational and perinatal history and physical, neurologic, and developmental examinations. The physical examination should include an assessment of pelvis and lower extremity alignment while standing, spinal alignment, active and passive range of motion of the joints, tone or spasticity of the muscles, and any movement disorders or limb deformities.

Cerebral palsy may be suspected in an infant or young child who demonstrates abnormalities in reflexes,

Gibson CS, MacLennan AH, Goldwater PN, Dekker GA. Antenatal causes of cerebral palsy: associations between inherited thrombophilias, viral and bacterial infection, and inherited susceptibility to infection. *Obstet Gynecol Surv* 2003;58:209–20.

Baud O. Postnatal steroid treatment and brain development. *Arch Dis Child Fetal Neonatal Ed* 2004;89:F96–100.

Crowther CA, Hiller JE, Doyle LW, Haslam RR. Effect of magnesium sulfate given for neuroprotection before preterm birth: a randomized controlled trial. *JAMA* 2003;290:2669–76.

movements, and muscle tone. Delay in meeting major motor milestones is a significant early warning sign for the development of CP. Other signs that may be identified during examinations include toe-walking, fisting, handedness before the second birthday, scissoring of lower extremities, decreased head circumference growth rate, poor suck, irritability, and seizures. If there is evidence of disease progression, the diagnosis of CP can be ruled out. The algorithm in Figure 1-2 provides steps for the evaluation of a child suspected of having CP.

Neurological Imaging

The determination of the etiology of CP is important and has a meaningful impact on prognosis, treatment, and supportive management of related conditions. Specific knowledge of causes or pathologies, whether occurring antenatally, perinatally, or postnatally, such as malformations, genetic disorders, or physical injury, can assist with identifying risk of recurrence of CP within families and susceptibility to acquired or genetic disorders, tailoring treatment options, and family counseling. Included among the several imaging techniques used to provide this information are cranial ultrasound, computed tomography, and magnetic resonance imaging.

Cranial ultrasound, which is noninvasive and relatively easy to perform, is the preferred method in high-risk preterm infants. It can identify periventricular white matter lesions that are associated with later morbidity and hemorrhages, although it is not as sensitive as magnetic resonance imaging. Computerized tomography is easily performed and less expensive. Newer high-resolution scans can identify calcifications that magnetic resonance imaging can miss. However, radiation exposure may be of concern with repeated scans. Magnetic resonance imaging has the advantages of better tissue-contrast resolution and no ionizing radiation or bone artifact. It is also more likely to identify an abnormality in children with CP, but is more expensive and requires sedation.

Neurological findings can be similar among all the CP syndromes, and causes are diverse. However, white matter lesions will typically result in spastic CP, whereas basal ganglia lesions result in extrapyramidal manifestations. Location of injury is important as it can help direct treatment choices. For example, genetic or mitochondrial disorders, kernicterus, and hypoxic-ischemic encephalopathy are associated with extrapyramidal CP, whereas pathologies such as periventricular leukomalacia and congenital human immunodeficiency virus infections are associated with spastic diplegia.

In 2004, the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society published a practice parameter for diagnostic assessment of the child diagnosed with CP or suspected of having CP. Recommendations include neurologic imaging for any child with CP in which an etiology has not been identified. Magnetic resonance imaging is preferred to computerized tomography because of a higher yield of abnormal scans

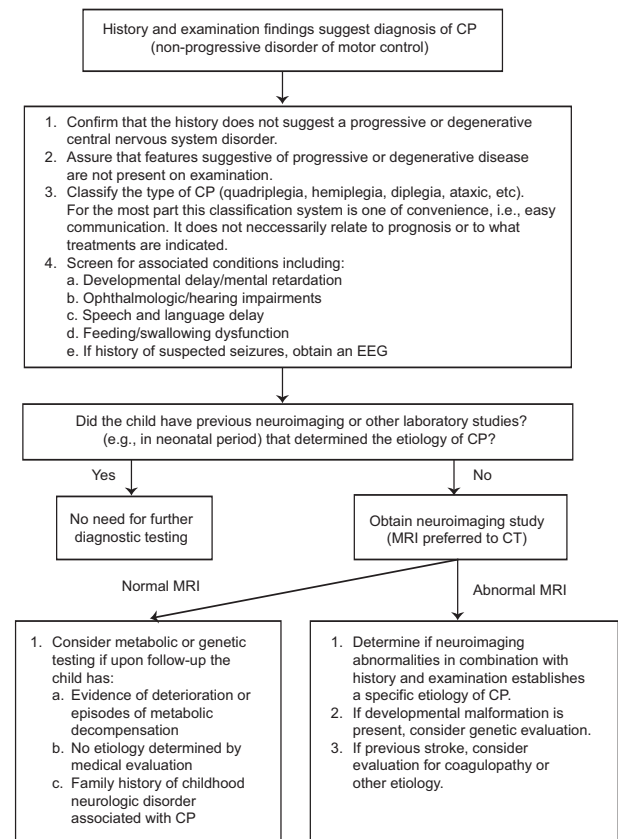


Figure 1-2. Algorithm for the evaluation of the child with CP.

Screening for associated conditions (mental retardation, vision/hearing impairments, speech and language delays, oral motor dysfunction, and epilepsy) is recommended. Neuroimaging (MRI preferred to CT) is recommended for further evaluation if the etiology of the child's CP has not been previously determined. In some children, additional metabolic or genetic testing may be indicated.

CP = cerebral palsy; CT = computed tomography; EEG = electroencephalogram; MRI = magnetic resonance imaging.

Reprinted with permission from Lippincott Williams & Wilkins. Ashwal S, Russman BS, Blasco PA, et al. Practice parameter: diagnostic assessment of the child with cerebral palsy; report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. *Neurology* 2004;62(2 of 2):851–63.

(90% to 77%) and a more reliable estimate of the cause and timing of the insult.

Neurologic imaging is the most predictive measure of CP pathogenesis in the term and preterm infant. Although muscle tone, reflexes, and examination are poorly predictive early in life, new research has shown spontaneous movements at this age to be predictive of CP. A General Movement tool has been developed to assess young infants with regard to the variability and complexity of spontaneous motor behavior. If definitely abnormal movements persist at 2–4 months post-term, CP is predicted with an accuracy of 85%–98%. Although long-term benefit of early intervention in these patients has yet to be verified, physical therapy or other modalities may be warranted.

Functional Assessment Tools

Several instruments have been developed to assess function, disability, quality of life, spasticity, and movement disorders. Function may be evaluated with the use of several global or function-specific tools (Table 1-2). Two major tools include the Gross Motor Function Measure and the Gross Motor Function Classification System, which were developed in an effort to measure children of all gross motor ability levels in clinical trials. The Gross Motor Function Classification System has become the tool used most often to classify the functional status of children aged 2–12 years. Investigations are ongoing to develop a similar tool valid for adolescents. The Pediatric Evaluation of Disability Inventory is often used as an outcome measure in clinical trials of pharmacotherapeutic interventions in patients with CP.

Movement tools include the Burke-Fahn-Marsden Scale of Dystonia and the Barry-Albright Dystonia Scale. The Barry-Albright scale was a modification of the Burke-Fahn-Marsden scale, but limitations still exist. Spasticity is commonly assessed using the Ashworth scale, which was first published in 1964 and revised in 1987 (Tables 1-3 and 1-4).

Disease Features and Complications

Spasticity

Spasticity is the most common abnormality in CP and can be characterized as having positive and negative symptoms. Positive symptoms of hypertonicity, hyperreflexia, dystonia and clonus can usually be ameliorated with treatment. Negative symptoms, including loss of motor planning and control, lack of endurance and

Table 1-2. Select Functional Assessment Tools in Cerebral Palsy

Tool	Description/Comments
Gross Motor Function Measure (GMFM)	Goal is to provide one measure for use in children of all ability levels and gross motor abilities in clinical trials. Assesses dimensions of 1) lying and rolling; 2) sitting; 3) crawling and kneeling; 4) standing; and 5) walking, running, and jumping. Used to assess efficacy of surgical, medical, or physical therapy interventions. Has been used in children under 2 years of age; scores may vary significantly depending on severity of disability.
Gross Motor Function Classification System (GMFCS)	Focused on disability and gross motor functional limitation, and based on GMFM. Five-level classification system with emphasis on self-initiated movement; sitting and walking primary observations. First generally accepted standardized system of classification of motor disability severity for practice and research. Most respected and used system to classify functional status of children aged 2–12 years; work ongoing for adolescent ages.
Burke-Fahn-Marsden Scale of Dystonia	First valid and reliable quantitative scale to assess torsion dystonias; primarily assesses movement related to function. Most useful for following course and response to therapy when serial assessments applied. Designed for primary torsion dystonia with no other history; children with dystonia from CP could have many other motor problems such as weakness, spasticity, or ataxia that could result in a higher score when dystonia is only a small part of movement disorder. Relatively insensitive to focal dystonia, because it is designed to assess degrees of generalized dystonia.
Barry-Albright Dystonia (BAD) Scale	Modification of Burke-Fahn-Marsden scale to include severity of posturing and involuntary dystonic movements. Excluded Burke scale components of provoking factors and disability as Barry-Albright patient population had dystonia at rest and with activity. Used in patients with dystonic CP, because other movement disorders not studied; not able to differentiate dystonia, athetosis, spasticity Overall score reliable, but not for individual body regions; role likely in multitool assessments.
Functional Independence Measure for Children (WeeFIM)	Assesses global functional independence of children with developmental disabilities; measure of disability, not impairment. Excellent correlation in age range of 6 months to 7 years; children with CP ages 2–12 years have been studied.
Pediatric Evaluation of Disability Inventory (PEDI)	Assesses functional skill level, self-care ability, mobility, and social function. Validity established for ages 6 months to 7 years; no patients with CP in study, but still applicable for global function assessment in CP. Used as outcome measure in interventional studies in patients with CP.

CP = cerebral palsy.

Table 1-3. Ashworth Scale for Assessment of Spasticity

Examination Results on Passive Movement of Limbs	Score
No increase in tone	0
Slight increase in tone giving a “catch” when the limb was moved in flexion or extension	1
More marked increase in tone, but limb easily flexed	2
Considerable increase in tone; passive movement difficult	3
Limb rigid in flexion or extension	4

Reprinted with permission from CMP Information, Ltd. Ashworth B. Preliminary trial of carisoprodol in multiple sclerosis. Practitioner 1964;192:540–2.

weakness, are more difficult to modify. Collectively, they are termed the upper motor neuron syndrome. A patient may describe the sensation as one of constant stiffness that varies greatly in intensity from day to day or moment to moment, and it can rapidly or gradually increase. Many factors can exacerbate spasticity such as pain, infection, fatigue, stress, lack of sleep, or environmental conditions such as temperature changes.

After injury that leads to a permanent static lesion in the cerebral motor cortex, an interruption of inhibitory suprasegmental inputs results in hyperactive segmental spinal reflex arcs, which result in spasticity. This loss of descending inhibitory input also increases gamma and alpha motor neuron excitability, which enhances spasticity. In addition, upper motor neuron injury results in poor muscle control and weakness due to decreased cortical input to reticulospinal and corticospinal tracts. In general, the greater the degree of spasticity, the less the degree of voluntary muscle control. Assessment of the degree of spasticity is done by manually moving limbs through the range of motion to cause passive stretch of muscles. Spasticity is then quantified using the Ashworth or modified Ashworth scales (Tables 1-3 and 1-4).

Children with spasticity do not always require treatment, as many children will rely on this increased tone to assist with ambulation or transfers. Management is goal-oriented and is focused on maximizing function and mobility, preventing contractures and subluxation, improving positioning and hygiene, and providing comfort.

Musculoskeletal Abnormalities

The constant increase in muscle tone resulting from spasticity leads to musculoskeletal complications, including contractures, subluxations, dislocations, and scoliosis. The mechanism of the effect of spasticity on the musculature of CP patients is not fully understood, but it appears that muscles undergo significant structural remodeling, which can include changes in tendon compliance and alterations in the actual muscle fibers. This spasticity, if prolonged, can lead to shortened muscle fibers and tendons, and contracture formation. The primary pathology is a lack of longitudinal growth of skeletal muscle, or muscle shortening leading to bony torsion and instability of joints. Normally, muscle growth occurs in an environment of regular stretching of relaxed muscle during physiologic loading. However,

Table 1-4. Modified Ashworth Scale for Assessment of Spasticity

Examination results on passive movement of limbs	Score
No increase in muscle tone	0
Slight increase in muscle tone, manifested by a catch and release or by minimal resistance at the end of the range of motion when the affected part(s) is moved in flexion or extension	1
Slight increase in muscle tone, manifested by a catch, followed by minimal resistance throughout the remainder (less than half) of the ROM	1+
More marked increase in muscle tone through most of the ROM, but affected part(s) easily moved	2
Considerable increase in muscle tone, passive movement difficult	3
Affected part(s) rigid in flexion or extension	4

ROM = range of motion.

Reprinted with permission from the American Physical Therapy Association. Bohannon RW, Smith MB. Interrater reliability of a modified Ashworth scale of muscle spasticity. Phys Ther 1987;67:206–7.

spasticity prevents relaxing of the muscle during activity, which leads to an imbalance in the growth of the muscle-tendon complexes and the long bones.

Nutrition and Growth Deficiencies

Nutrition and growth deficiencies are common in children with CP and have many causes. The most important causes are oral motor impairments and other gastrointestinal issues, such as reflux, that occur in 80%–90% of patients. Both oral dysphagia and gastroesophageal reflux reduce caloric intake and increase aspiration risk. They can be painful and result in food refusal. Children suffering from severe CP often are below the 3rd percentile for growth by age, whereas milder CP typically results in smaller growth delays.

Seizures

Estimates of the incidence of epilepsy in children with CP have ranged from 15% to 55% overall, compared with about 1% in the general pediatric population. Some forms of CP are more likely to be complicated by epilepsy, particularly those with more cortical pathologies such as quadriplegia (50%–94%), hemiplegia (33%–50%), and diplegia (16%–27%). The incidence in dystonic/dyskinetic CP is about 25%.

In patients with CP, the type of seizure present can be difficult to diagnose as it can be difficult to distinguish seizures from other involuntary movements such as dystonias or dyskinesias. Also, electroencephalograph changes may be present even without clinical seizures.

Studies attempting to correlate a seizure type with a CP type have not found any consistent patterns. Children with CP may be diagnosed with various seizure types such as partial, generalized tonic-clonic, myoclonic, and atonic, and epilepsy syndromes such as West and Lennox-Gastaut syndromes. Diagnostic procedures such as electro-

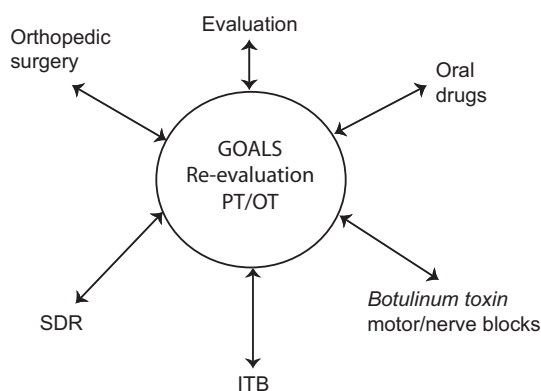


Figure 1-3. Schematic representation of the decision process for the treatment of spasticity.
 ITB = intrathecal baclofen; OT = occupational therapy; PT = physical therapy; SDR = selective dorsal rhizotomy.
 Reprinted with permission from BC Decker, Inc. Tilton AH, Maria BL (moderators). Consensus statement on pharmacotherapy for spasticity. *J Child Neurol* 2001;16:66–7.

encephalograph and magnetic resonance imaging are performed as they would be in the non-CP population.

The impact of epilepsy in CP can be significant. In functional patients, ambulation may be further impaired by seizure activity, and subclinical seizures may progress to loss of function in extremities.

Pain

Pain as a result of spasticity is a significant component of CP. It has tremendous impact on quality of life when one considers that life expectancy may include the sixth decade and beyond. The mechanism of spasticity-induced pain is not well understood. Misalignment of joints and the skeleton likely results in pain. It should be noted that pain itself can contribute to spasticity. Pain can be of a chronic nature due to postural issues, or more sharp and acute at the onset of muscle spasm. Pain may occur anywhere, but is more common and pronounced in the trunk and proximal extremities. It may be present at rest, particularly in those with contractures, but usually increases with movement, and typically will stay localized.

Management of Spasticity

Management of spasticity is centered on achieving the goals of maximizing function, easing care, and preventing complications such as contractures, subluxation, and pain. The plan must include not only the patient, but also the caregivers who are primarily responsible for daily care and management of the patient. Re-evaluation of any intervention based on feedback of its effectiveness must be obtained (Figure 1-3). Further decisions are made with the patient's and caregivers' progress and needs in mind.

The choice from among the many options for spasticity management is influenced by age, presence of comorbidities, the ability of caregivers to implement treatment or follow up, and financial status. No matter

which methods are chosen, it is necessary to ensure that both patient and caregivers have realistic expectations.

Nonpharmacological Options

Physical and Occupational Therapy

In the past, physical and occupational therapy focused on decreasing deficits and impairments. Recently, however, World Health Organization efforts have generated increased interest in promoting function and participation. This new emphasis on improving a patient's ability to interact with his or her environment considers the environmental and personal factors affecting rehabilitation and therapy. It is essential to understand the specific motor disorder to guide the planning of physical and occupational therapy. Several different types of intervention are available. Whichever modality is chosen, it is recommended that the children and their families, in addition to the health care team, be involved in developing short-term and long-term goals.

Physiotherapy, Strength Training, and Orthotics

Regular stretching exercises are important in maintaining range of motion and preventing contractures. Ambulatory children typically stretch adequately with daily activities, but stretching regimens are prescribed to ensure benefit. A regular stretching program can provide decreased tone for hours, but is not effective for long-term spasticity reduction. Aerobic exercise is also beneficial. It can help reduce chronic pain, as well as improve strength, fitness, and motor function.

Patients with CP can participate in many sports, although some may require adaptation, such as "walker soccer" or sit-skiing. An added benefit is that many of these activities can be performed with peers in the community without therapist involvement. Other activities such as hippotherapy (use of horseback riding to improve balance and enhance movement patterns) are also beneficial in improving gross motor function.

The most appropriate duration and intensity of physiotherapy is unknown and may depend on the child and the severity of disease. Intensive physical therapy regimens have shown no significant benefit in outcomes compared with standard therapy. Strength training also increases strength and improves motor activity in patients with CP and is part of the physiotherapy regimen. A recent trial in independently ambulatory diplegic patients showed that a home-based strength-training program significantly increased muscle strength at 12 weeks in addition to a trend toward increased gross motor function such as standing, running, jumping, and stair climbing. Solid conclusions of the effect on activity and participation outcomes cannot be made as yet.

The main goal of orthotic devices is to prevent or correct deformities and to provide support to facilitate improvements in gait and skill development. Orthotic devices on the ankle and foot are most commonly used to treat equinus deformity (plantar orientation of foot due to gastrocnemius muscle complex spasticity). The devices improve the transition from sitting to standing and increase dorsiflexion when the foot strikes the ground. Hand, wrist, and knee orthotics may also be used during the day or throughout the night, depending on the child's tolerance.

Data from studies on the gastrocnemius and soleus muscle groups suggest that the devices need to be worn at least 7 hours/day.

As a result of the child's growth and general wear, orthotic devices usually need to be refabricated annually. Serial casting may also be used, which involves multiple cast applications over time in an effort to increase range of motion in joints, usually knees, elbows and ankles. Recent data in trials with botulinum toxin (BTX) found that casting and casting plus BTX were more effective for treating equinus deformity than BTX alone, which is in contrast to earlier studies. More research is necessary to determine serial-casting effectiveness with and without BTX, the most appropriate time to apply the cast, and the length of effect.

Neurodevelopmental Treatment

Neurodevelopmental treatment, developed in the 1960s, involves moving children through normal movement patterns so they experience the movements as they would normally occur. In part, they are placed in positions that inhibit normal reflexes, decrease muscle tone, and maintain a normal sequence of motor progression during tasks. A report published by the American Academy for Cerebral Palsy and Developmental Medicine concluded that data do not support the use of this intervention even though it is a common therapy method used by pediatric therapists world wide.

Conductive Education

In conductive education, trained conductors educate children on how to improve performance in motor control, mobility, and communication tasks. Minimal intervention is provided, and sufficient cognitive skills for comprehending directions are required. The focus is on making motor tasks a series of simple steps and problem-solving, and using musical rhythm to enhance learning. There is no evidence that conductive education is any more effective than traditional interventions or neurodevelopmental treatment.

Forced-use or Constraint-induced Movement Therapy

This method is used in patients with hemiparesis and involves restricting the use of the unaffected arm with a cast for 3–4 weeks while providing focused physical therapy on the affected arm. Randomized, controlled trials in children have shown significant improvements in motor skill scores when compared with conventional therapy, and improvements were sustained up to and beyond 6 months. Drawbacks include patients' potential lack of tolerance for prolonged casting and the time-intensive nature of the therapy (constraint therapy can also be performed by wrapping the unaffected limb during a focused physical therapy session and removing it after the session with subsequent assessment of the child for carryover). One study used 6 hours of intense therapy per day for 3 consecutive weeks. There is concern about the effect of prolonged casting on growth and development. Data in adult stroke victims, suggesting that much shorter therapy and cast-restraint times may also be effective, need to be confirmed in the pediatric CP population.

Therapeutic (Subthreshold) Electrical Stimulation

This procedure is the provision of subcutaneous or percutaneous electrical stimulation at low levels that do not cause muscle contraction. The stimulation is typically applied for at least 8 hours during sleep. Goals of therapy include improving strength, range of motion, and motor learning. Early reports and case series reported benefit, but two recent trials found no benefit in motor and ambulatory function or muscle growth compared with controls.

Assistive Devices

These devices include posture and seating support, wheelchairs, communication enhancers, computers, and other electronic devices. As with other therapies, the family and medical team must have clear goals in mind and must consider that needs will evolve over time, requiring changes in the types of devices used.

Surgical Therapy

Musculoskeletal Interventions

Although pharmacotherapy can delay the development of musculoskeletal complications of spasticity, most patients will eventually require orthopedic intervention. Indications for surgery include worsening deformities causing pain or inhibiting function, fixed contractures, joint subluxation or dislocation, scoliosis or kyphoscoliosis, and presence of deformities hindering delivery of care. Examples of procedures are tenotomy (surgical division of a tendon to relieve deformity caused by muscle shortening), osteotomy (cutting of a bone), tendon lengthening and transfer, and arthrodesis (surgical immobilization of a joint). These are often performed in combinations, but no data exist detailing the best combination or identifying a preferred procedure. Soft-tissue surgeries are usually delayed until the child is about 5 years of age when a mature gait pattern has developed. By not performing surgery in patients younger than 4, overcorrection is hopefully avoided. Any lengthened muscle will be weaker; therefore, physical therapy and rehabilitation are essential after orthopedic surgery.

The type of CP is a major factor that determines the orthopedic procedures performed. Patients with hemiplegia and diplegia often have the ability to ambulate. Typical procedures in these patients include fixed muscle-tendon contracture lengthening and tendon transfers involving muscle-tendon groups of the shoulders, arm, elbow, wrist, and hand, as well as the hip, hamstrings, calves, and Achilles. Patients with spastic quadriplegia develop the most severe skeletal complications. In addition to the upper and lower extremity deformities similar to those seen in other types of CP, hip displacement (35%–55% of patients compared with 1% and 5% in hemiplegia and diplegia) and spinal deformities are more common and progress rapidly. These musculoskeletal deformities may be especially difficult to cope with considering all the other comorbidities, such as seizures, lung disease, nutritional deficits, and osteopenia, that are more common in patients with spastic quadriplegia. Unfortunately, serious complications such as hip subluxation or dislocation are often not caught early because care focuses on all the other issues involved, thus limiting management options. The goal is early identification of abnormalities by frequent

screening and examination, which allows for correction with soft-tissue surgery and avoids the need for extensive reconstructive surgery.

Spinal deformity is also more common in patients with spastic quadriplegia, occurring in almost 75% of patients compared with 25% of all children with CP. Types of deformity include scoliosis, kyphosis, and lordosis, with scoliosis resulting in the most serious outcomes. Scoliosis progression may result in pain, problems with sitting, and potential dermal and cardiopulmonary complications. Spinal-fusion surgery is indicated in skeletally immature patients with curves greater than 40 degrees and in mature patients with curves of 50 degrees or greater. Although most patients and caregivers report satisfaction after the procedure, they are often not prepared for the ordeal. It is a highly invasive procedure, lasting up to 8 hours and resulting in prolonged anesthesia and extensive blood losses of up to 50%–100% of total volume. The many potential intraoperative and postoperative complications include dural tears, pneumothorax, cardiac arrest, ileus, superior mesenteric artery syndrome, sepsis, pneumonia, wound complications and infections, hardware infection or failure, spinal curve progression, decubitus ulcers, and respiratory distress syndrome.

Selective Dorsal Rhizotomy

Selective dorsal rhizotomy, performed since the 1980s, is a procedure in which posterior dorsal rootlets are transected in an effort to reduce lower limb spasticity, although reports of upper extremity spasticity reduction may also occur (Figure 1-4). Rootlets from L2 to S2 are electrically stimulated to determine which ones result in abnormal motor responses and qualify for transection. Typically, about 25%–50% of the rootlets are cut. In addition to reduction of lower extremity spasticity, rhizotomy combined with physical therapy has resulted in greater range of joint motion, improved gait, and improved function than with physical therapy alone. A meta-analysis of three trials concluded that children who had the most roots transected had the most improvement in function. Improved attention and cognition and increased disposition and physical comfort have also been associated with rhizotomy.

A recent prospective, nonrandomized trial comparing rhizotomy to orthopedic surgery showed that both interventions significantly improved gross motor function and Pediatric Evaluation of Disability Inventory scores. However, rhizotomy resulted in more pronounced effects on movements and motor skills for a longer time period postoperatively. In trials, complications are rare but can include sensory abnormalities, bowel and bladder dysfunction, back pain, and instability of the lumbosacral spine.

The best candidate for dorsal rhizotomy is a cooperative, motivated patient with pure spastic CP, diplegia, adequate strength, range of motion and balance with isolated muscle control and no fixed contractures, who is functionally limited by spasticity. The best age for the procedure is not known. Whereas some surgeons will perform rhizotomy on

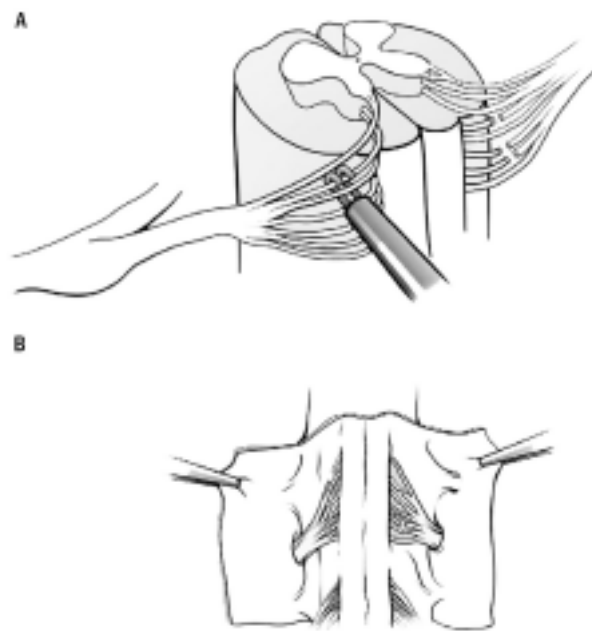


Figure 1-4. Schematic representation of the technique of selected dorsal rhizotomy.

A: After laminectomy, the dura is opened and the dorsal spinal rootlets are exposed. The rootlets are stimulated so that abnormal rootlet activity can be identified. B: a proportion of rootlets are transected.

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children as young as 2–4 years of age, others wait until after 6–8 years. Others suggest the best time is 3–8 years. Rhizotomy should not be performed in those with athetosis, ataxia, rigidity, dystonia, muscle weakness, overlengthened tendons, or severe joint contractures. In addition, further orthopedic procedures for shortened muscles or contracted joints will likely be necessary. Rhizotomy is an irreversible operation in which heightened caution is indicated.

Dorsal rhizotomy may be an effective intervention for the motivated, qualified patient who will participate in postoperative rehabilitation and physical therapy, although overall use of the procedure has decreased with the increasing use of intrathecal baclofen (ITB).

Hyperbaric Oxygen

There has been growing interest in the use of hyperbaric oxygen (HBO) for the treatment of children with spastic CP. It is theorized that the hypoxic-ischemic area in the brain may be metabolically or electrically reactivated by increasing plasma oxygen concentrations. This “penumbra” of viable but inactive neurons surrounding dead neurons is thought to be reactivated with HBO. (13) Metabolic changes of this nature have been demonstrated in stroke and traumatic brain injury, but have not been supported by current data on the static encephalopathy in CP.

A study published in 1999 reported improved fine and gross motor function and decreased spasticity in addition to other improvements reported by parents. However, the trial

13. Essex C. Hyperbaric oxygen and cerebral palsy: no proven benefit and potentially harmful. *Dev Med Child Neurol* 2003;45:213–5.

included only 25 patients, was unblinded and uncontrolled, was conducted at two separate centers with different protocols, and included some assessments that were subjective. Earlier case reports described benefits such as increased muscle flexibility and decreased seizures, but the evidence is anecdotal. Later trials were not able to confirm these results.

One trial randomly assigned 111 children aged 3–12 to more than 2 months of treatment with either HBO or slightly pressurized room air. Hyperbaric oxygen treatments consisted of 40 treatments of 1 hour of 100% oxygen at 1.75 atmospheres absolute while the control group received room air at 1.3 atmospheres absolute, the lowest pressure that could be detected. The primary outcome was gross motor function, with secondary outcomes of daily living performance, attention, memory, and speech. All outcomes improved during the course of the trial in both groups, with no differences between them. There was a significant difference in side effects, with 27 patients incurring 42 ear problems in the treatment group and 12 patients accounting for 15 ear problems in the control group.

Seventy-five of these patients met criteria for evaluation of neuropsychological effects, including attention assessment, memory, processing speed, and psychosocial functioning. Improvements were noted in both groups for self-control, auditory attention, and memory compared with baseline, but again there were no differences between the groups. In addition, based on a parent rating scale, the control group improved significantly in eight dimensions whereas the treatment group improved in only one.

There are several potential adverse effects associated with HBO, including ear pain or eardrum perforation and other ear complications, pneumothorax, oxygen-induced convulsions, respiratory distress, barotrauma, and myopia. Explosions and fires have occurred with the use of HBO. Oxygen is not flammable itself, but material will ignite and burn faster in its presence, and fireball explosions occur in a pure oxygen environment. In addition, use of the chamber is costly, and safety standards are not consistently met at operating centers.

Scant data are available to support the use of HBO in spastic CP, and many details need to be clarified, including the appropriate chamber pressure and the length and number of treatments. Despite the lack of benefit, some families have invested substantial time and financial resources in the hope of improving their child's condition.

Pharmacological Options

Oral Drug Therapy for Spasticity

Several oral drugs are available for the treatment of spasticity, and they are best used in patients with mild to moderate or global spasticity (Figure 1-5 illustrates the sites of action of common antispasticity drugs). Most studies of these drugs were done several years ago and used trial designs that were less rigorous than current standards and failed to address aspects of function. Also, most of these antispasticity studies were performed in adults. Therefore, use of these drugs in children is usually based on personal or clinical experience, and effectiveness in a specific patient dictates continued use. Table 1-5 lists typical dosing strategies for oral antispasticity drugs.

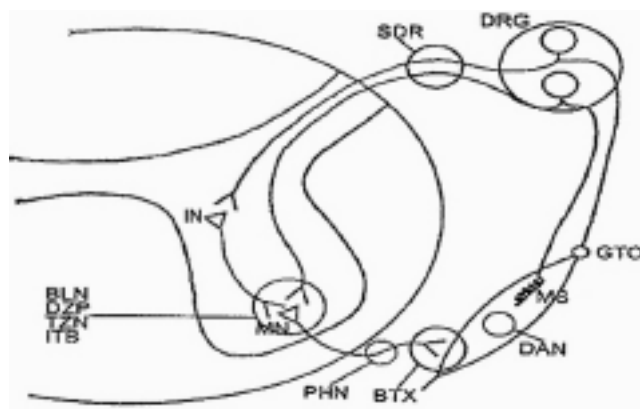


Figure 1-5. Segmental reflex arc with sites of action of interventions for spasticity management.

Sites of action: DRG = dorsal root ganglion; GTO = Golgi tendon organ; IN = spinal interneuron; MN = motoneuron; MS = muscle spindle. Treatments: BLN = baclofen; BTX = botulinum toxin; DAN = dantrolene; DZP = diazepam; ITB = intrathecal baclofen; PHN = phenol injection; SDR = selective dorsal rhizotomy; TZN = tizanidine.

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Baclofen

Baclofen is often used in the treatment of spasticity from spinal cord injury in adults. In our experience, it is the first-line therapy for children with spastic CP. It is structurally related to γ -aminobutyric acid (GABA) and can pass the blood-brain barrier into the central nervous system. Baclofen binds to the GABA_B receptor in the brain and spinal cord but has no activity at the GABA_A receptor. Activation of the GABA_B receptor is thought to decrease voltage-gated calcium channel conductance, which leads to a reduction in transmitter release. This hyperpolarization of neurons results in presynaptic inhibition in the spinal cord of monosynaptic and polysynaptic reflexes and a reduction in spasticity. Essentially, all activity is due to the L-isomer of baclofen, which may be the most effective formulation, but the only product available is a racemic mixture.

Baclofen is well-absorbed in doses up to 40 mg, but absorption is reduced as the dose increases. About 15% of the drug is metabolized and the rest is excreted unchanged in the urine. Therefore, drug interactions are rare. However, trazodone, fluoxetine, and sertraline have been reported to exacerbate spasticity, possibly by antagonizing the effects of baclofen.

Scant literature evaluating the use of baclofen in children with CP is available, although one double-blind, crossover trial in 20 children showed that baclofen was superior to placebo for reduction of spasticity. These authors recommended initial doses of 5–10 mg/day divided into three dosages for children 2–7 years of age, although higher doses may be used for older children. Other authors recommend starting at a lower dose of 2.5 mg/day, which can be titrated to 20–60 mg/day. Still others suggest that some patients may require up to 160 mg/day.

Data in press from our patient population under 18 years of age showed dosage ranges of 2–240 mg/day, with debilitating side effects exceedingly rare. Dose requirements tended to increase with time from the initial insult. Baclofen

Table 1-5. Dosing Recommendations for Oral Anti-spasticity Drugs

	Initial dosing	Comments
Baclofen	2.5–10 mg/day in up to three divided dosages	Lower initial dosing used in younger children. Typical daily maintenance dose 20–60 mg. Some patients may require 160 to more than 200 mg/day.
Dantrolene	0.5 mg/kg 2 times/day	Titrate to 3–4 times/day at about 1-week intervals. Maximum dosing 3 mg/kg 2–4 times/day.
Benzodiazepines (diazepam)	0.12–0.8 mg/kg in 3–4 divided dosages	With chronic dosing, tolerance and addiction is a concern. Primarily for short-term use (sleep aid or for night time spasms).
Clonidine	5–10 mcg/kg in 2–3 divided dosages	Titrate to effect; patients may eventually require frequent dosing. Usually less than 0.5 mg/day required but some require more than 1.5 mg/day.
Tizanidine	Established pediatric dosing not available 2–8 mg 2–4 times/day (adult)	Tablet-only dosage form, more expensive than clonidine.
Gabapentin	10 mg/kg in 3 divided dosages	Titrate about every 3 days to effect. Maintenance doses range from 25–50 mg/kg/day. Data in spastic cerebral palsy are lacking.

has been compared to diazepam. Both reduce spasticity, but baclofen is less sedating. More important, caregivers often find that interaction with children is made less challenging and more rewarding when baclofen is used.

Oral baclofen may produce adverse effects, including sedation leading to cognitive impairments such as confusion, memory loss, and attention deficits. Other reported adverse effects include weakness, ataxia, orthostatic hypotension, and dizziness, most of which are dose-related and tend to decrease with time. The effect of baclofen on seizure activity is unclear, as it has been reported to increase, decrease, or have no effect on the incidence. Abrupt discontinuation may lead to potentially severe withdrawal effects, including a rebound increase in spasticity, neuroleptic malignant syndrome, rhabdomyolysis, disorientation, hallucinations, and seizures. Fortunately, tolerance does not develop with this agent as it does with benzodiazepines.

Dosage form is often a consideration in children, especially those with CP who may have significant oral motor dysfunction. For those requiring a liquid formulation, several extemporaneous suspension recipes are available. If these are used, it is imperative to remind the caregiver to shake the suspension vigorously before each dose to avoid potential wide variation in concentration due to settling. The use of tablets is preferable, if possible.

Dantrolene Sodium

Dantrolene exerts its antispasticity effects by inhibiting release of calcium from the sarcoplasmic reticulum of skeletal muscle cells. This action prevents full muscle contraction after electrical excitation and results in generalized muscle weakness. Dantrolene has no effect on smooth or cardiac muscle. About 35% of a dantrolene dose is absorbed, and it is metabolized extensively in the liver by multiple pathways. Drug interactions are relatively few and not often of clinical significance in patients with CP. Use with verapamil may result in hyperkalemia and myocardial depression; use with estrogens may increase the incidence of hepatotoxicity; and use with other central nervous system

depressants may increase sedation. Also, dantrolene toxicity may be increased with monoamine oxidase inhibitors, phenothiazines, and clindamycin.

Data in adult studies showed a reduction in muscle tone. Performance and strength were not consistently altered, although small numbers saw improvement in activities of daily living. In children, dantrolene is superior to placebo in treating spasticity of CP, and the combination of dantrolene with diazepam has been reported more effective than either drug alone. Improved function while receiving long-term dantrolene therapy has also been reported.

Adverse effects of dantrolene include mild sedation, seizures, vomiting, diarrhea, severe constipation, and paresthesias. It should be used with caution in patients with impaired cardiac function or history of liver disease. The incidence of hepatotoxicity has approached 2%, and fatal hepatitis is about 0.3%; hepatotoxicity is more likely with prolonged dosing. Baseline liver function tests should be obtained before initiating therapy and periodically thereafter. Children with seizures may be receiving valproic acid, which can cause hepatotoxicity as well; many clinicians do not use these drugs concurrently. Therapy with dantrolene is usually initiated at 0.5 mg/kg 2 times/day, which is increased to 3–4 times/day at 4–7 day intervals. The dose is titrated to a maximum of 3 mg/kg per dose 2–4 times/day. A recipe for an extemporaneous preparation of a suspension is available. In our patient population, dantrolene is rarely used due to its relatively severe side effect profile.

Benzodiazepines

Benzodiazepines exert their effect by binding near GABA_A receptors, thus increasing the affinity of GABA_A for its receptors. Increased GABA binding results in an influx of chloride. This hyperpolarization leads to presynaptic inhibition and a reduction in monosynaptic and polysynaptic reflexes, likely due to a decrease in the release of excitatory neurotransmitters.

Diazepam is the drug in this class most commonly used for spasticity, although clorazepate and clonazepam are also

used. Diazepam is well-absorbed and distributes across the blood-brain barrier. It is metabolized in the liver to active metabolites (desmethyldiazepam and methyloxazepam), which are eventually excreted in the urine as glucuronidated oxazepam. The half-life of diazepam ranges from 20 to 50 hours in patients aged 2 years and over, and the half-life of metabolites may approach 100 hours. Diazepam is a substrate or inhibitor of several cytochrome P450 isoenzymes, but the primary drug interaction is the exacerbation of sedative effects with other central nervous system depressants. Erythromycin can decrease the metabolism of diazepam, and valproic acid may displace diazepam from protein-binding sites to potentially increase its sedative effects.

Diazepam has been evaluated in children with CP. Improvements were noted in spasticity, but some trials concluded that overall relaxation was responsible for much of the clinical improvement. There are several disadvantages to use of benzodiazepines. Common side effects include sedation, impaired memory and attention, ataxia, weakness, constipation, and urinary retention. In addition, tolerance to benzodiazepines develops and can lead to a physiologic addiction. Withdrawal is also a concern and is manifested by symptoms, including irritability, tremors, nausea, seizures, and insomnia.

Doses range from 0.12–0.8 mg/kg/day in 3–4 divided dosages. In our population, benzodiazepines are rarely used and are most often prescribed for short-term use as a sleep aid or to decrease nighttime spasms.

Centrally Acting α_2 -Adrenergic Agonists

Clonidine and tizanidine work in the spinal cord to reduce spasticity by hyperpolarizing motor neurons and reducing excitatory amino acid release. They have also been associated with the reduction of pain, which could contribute to their effects because pain is known to exacerbate spasticity. Clonidine is the primary adjunct to baclofen in our patient population. Clonidine is well-absorbed orally. It is metabolized to inactive metabolites, and about 50% of an oral dose is excreted in the urine unchanged. The half-life of clonidine in children is about 8–12 hours.

Aside from increased central nervous system depression when used with other sedating agents, drug interactions are usually not clinically relevant. β -Blockers can potentiate bradycardia when used with clonidine and could increase rebound hypertension associated with clonidine withdrawal. If clonidine is to be discontinued, the β -blocker should be discontinued before the clonidine taper begins.

Most literature on the use of clonidine or tizanidine in spasticity involves adult patients. Muscle tone has been reported to be reduced, but evidence of effect on function is lacking. Tizanidine has been shown to be similar in effectiveness to baclofen and diazepam for tone reduction. Clonidine dosing is typically initiated at 5–10 mcg/kg/day divided into 2–3 daily dosages, then titrated up as needed. Despite the relatively long half-life in children, many patients tolerate and require dosing up to 6 times/day.

Adverse effects of α_2 -adrenergic agonists include sedation, hypotension, gastrointestinal upset, depression, and liver enzyme elevations, which may be more common

with tizanidine. Despite the high doses of clonidine used in our patient population, little if any effect is seen on blood pressure. Rapid or abrupt discontinuation can result in rebound hypertension, tachycardia, palpitations, agitation and tremors.

Clonidine has been the most commonly used agent in our population. Although tizanidine is available in tablets only, dosage forms for clonidine include tablet, patch, and an extemporaneously compounded suspension. In addition, clonidine is much less expensive.

Gabapentin

Gabapentin exerts its effect by increasing the brain concentration of GABA, but it does not bind to GABA receptors. Absorption is rapid, and it is not metabolized. Drug interactions are minimal, although morphine and hydrocodone may elevate gabapentin concentrations. Also, concurrent ingestion of antacid preparations may decrease bioavailability of gabapentin by up to 20%.

Patients with multiple sclerosis have seen reductions in spasticity and increased comfort with gabapentin. In one report of facial spasm relief, symptoms returned on discontinuation. Neural pain relief was reported in a girl with CP, but other data in children are lacking.

Large, randomized trials of enteral anti-spasticity drugs, whether for monotherapy or combination therapy, do not exist to assist one in formulating a drug therapy plan. Clinician and patient experience may dictate therapeutic choices in many instances.

In our patient population, baclofen is the first-line drug when spasticity becomes significant enough to negatively affect activities of daily living or quality of life. It is at least as effective as other enteral drugs while having a relatively low side-effect and drug-interaction profile. Monotherapy is attempted first and is often satisfactory if spasticity is relatively mild. Dosing is commonly initiated as recommended above, and may be increased at about 3-day intervals.

Adjunct therapy with clonidine is initiated when baclofen has been maximized or when spasticity is severe enough to warrant use. In some patients with severe generalized spasticity, adjunct therapy is initiated well before baclofen has been titrated to high doses. Patients tolerate high doses of both baclofen and clonidine when required. Dantrolene can be considered for monotherapy or adjunct therapy and may be useful. However, with no strong data to suggest an increased efficacy over baclofen and clonidine, and due to its more severe side effect profile, dantrolene is generally avoided. If spasticity cannot be controlled with nonpharmacological options and enteral drugs, parenteral drugs, discussed below, are considered.

Drugs Used for Movement Disorders

Extrapyramidal CP is characterized by disorders of movement, including chorea, athetosis, dystonia, and myoclonus. Many drugs have been used for the treatment of these movement disorders (Table 1-6). Drugs typically used to manage dystonia are antiparkinsonian drugs, anticonvulsant drugs, antidopaminergic drugs, antidepressant drugs, and antispasticity drugs. Overall, fewer than 50% of patients will respond to these drugs.

Table 1-6. Drugs used in the Treatment of Movement Disorders in Cerebral Palsy

Movement Disorder	Drugs	Comments
Dystonia	Baclofen, carbamazepine, carbidopa/levodopa, clonazepam, lorazepam, reserpine, and tetrabenazine	Trihexyphenidyl may be most effective, but can require very high doses which are better tolerated in children; may work by other mechanisms than cholinergic blockade at high doses. Report of trazodone improving severe dystonia in two children. Esophageal reflux with posturing (Sandifer syndrome) can mimic dystonia; illnesses, fatigue, and stress may also exacerbate the dystonia.
Choreoathetosis	Baclofen, carbidopa/levodopa, clonazepam, fluphenazine, haloperidol, pimozone, reserpine, tetrabenazine, and valproic acid	Diazepam has shown some success in athetoid conditions. Tetrabenazine showed minimal clinical improvement in athetosis; was beneficial in a patient with non-CP related severe chorea unresponsive to several other drugs; not available commercially in the United States. Levodopa has resulted in increase in function although side effects are significant, including gastrointestinal upset, hypotension, and depression; improvement sustained with continued therapy.
Myoclonus	Baclofen, clonazepam, lorazepam, phenobarbital, and valproic acid	

CP = cerebral palsy.

Chorea and athetosis can present concurrently, and are treated similarly. Benzodiazepines have been used based on experience and convenience, but dopamine-blocking neuroleptic drugs tend to be the most effective despite their more extensive side effect profile. Myoclonus is commonly treated with anticonvulsants such as benzodiazepines, valproic acid, and phenobarbital, although baclofen may be effective in some patients. Treatment of extrapyramidal CP with neuroleptic agents could induce new dyskinesias or dystonia. Response to treatment of extrapyramidal CP is quite variable, and success is often found by trial and error. Some patients have improved when treatment for these disorders was tapered and discontinued.

Parenteral Drug Therapy

Parenteral drug therapy for spasticity includes ITB, BTX, and phenol or alcohol. When administered intrathecally, baclofen is delivered directly to the spinal cord and is an option for those who have failed oral regimens or who experience intolerable side effects. This method of delivery often results in a decrease in the required daily dose and side effects, and can result in a greater reduction in tone than oral therapy. Botulinum toxin, phenol and alcohol provide neuromuscular blockade, or chemical denervation, which reduces muscle tone and the imbalance between agonist and antagonist muscle groups. The resting length of muscle is increased, which may decrease contracture development. With BTX use increasing, phenol and alcohol use has decreased significantly.

Intrathecal Baclofen

Intrathecal administration of baclofen provides the benefit of delivery of drug concentrations in the lumbar cerebrospinal fluid that are about 30 times higher than can be achieved with oral dosing. In some patients, the intrathecal dose required may be 1% that of the oral dose. In addition, because of the flow dynamics of cerebrospinal fluid, baclofen concentrations in the brain cerebrospinal fluid are about four times less than in the lumbar region.

This combination allows for improved control of spasticity and decreased side effects. Also, plasma concentrations in those receiving ITB are very low to undetectable. In addition to decreasing spasticity, goals of ITB therapy are to slow or prevent contractures, to improve comfort and positioning, and to ease the burden of care of nonfunctional patients.

Candidates for ITB include those with severe generalized spasticity (score greater than or equal to 3 in lower extremities on Modified Ashworth scale) for whom oral drugs or other measures have failed due to lack of efficacy or intolerable side effects. In addition, patients must be large enough to allow pump placement, which is typically around 15 kg or 4 years of age. A typical patient would be one for whom spasticity significantly affects the quality of life, but the spectrum of disability can be quite variable. Specific indications include any of the following when function, daily activities, or caregiver support are compromised: gait impairment with no significant weakness, upper and lower extremity spasticity, dystonia, and nonambulatory spastic quadriplegia. Contraindications include presence of infection at time of screening or scheduled implant, history of allergy to baclofen, patients who are not large enough to accommodate the pump, or inability to implant the pump 2.5 cm or less from the skin surface.

The implantable battery-powered device contains and delivers the drug from the pump reservoir through the catheter to the infusion site by a peristaltic action. The battery life is 4–7 years, and the pump, about the size of a hockey puck, is made of titanium. Earlier versions of the pumps had 10 mL and 18 mL capacities, and had a thickness of 21.6 mm and 27.5 mm respectively, and a diameter of 85.2 mm. The most recent pumps have 20 mL and 40 mL capacities with a thickness of 19.5 mm and 26 mm, respectively, and a diameter of 87.5 mm.

Patient Screening and Trial Dosing. Before the decision is made to implant a baclofen pump, patient screening and test dosing must be performed. Included in the screening is a thorough history and physical examination



Figure 1-6. Schematic representation of baclofen pump placement (side view).
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with spasticity evaluation, assessment of functional status, use of assistive or orthotic devices, history of antispasticity therapy, and an evaluation of the social support structure and financial situation. In addition, all persons involved must agree on a set of goals and expectations.

If it is decided that the patient is a good candidate, a test dose is administered by lumbar puncture. An initial dose of 50 mcg is delivered, and if no response is noted within 24 hours, subsequent doses of 75 mcg and 100 mcg are administered 24 hours apart. If no response is seen, the patient may not be an acceptable candidate, possibly as a result of a fixed contracture, and further evaluation may be necessary. If response is seen at any dose (a suggested 1-point drop for spasticity of cerebral origin and 2 points for spinal origin on the Modified Ashworth scale), implantation may be undertaken. Typically, the onset of action, peak effect, and durations of action are about 1 hour, 4 hours, and 8 hours after the bolus of the test doses, respectively. After each test dose, the patient must be monitored for signs of toxicity, such as drowsiness, dizziness, somnolence, respiratory depression, seizures, and loss of consciousness or coma. In an effort to save time, some clinicians will use higher initial doses of up to 100 mcg in larger patients, especially those already on high doses of oral baclofen, as larger doses may be required to see an effect.

The implantation procedure begins with the insertion of the catheter in the subarachnoid space, usually at the midlumbar level (L3–L4). In the past, the catheter would then be guided up to the lower thoracic vertebrae (T11), but now it may be as high as T5 or T4 or even between C7 and T2 to be in better position to control upper extremity

spasticity in quadriplegics. The catheter is then tunneled subcutaneously to the lower lateral abdomen where the pump is implanted inside a mesh pouch. The pump should not be inserted any deeper than 2.5 cm from the skin surface to allow access to the reservoir and access ports. The pump is connected to the catheter, and the pump is programmed with an initial bolus and continuous infusion rate. Figure 1-6 illustrates pump placement.

Dosing and Chronic Management. The initial daily dose is typically calculated by doubling the screening dose and delivering it continuously over 24 hours. Rate of delivery may be increased slowly as needed, but increases usually will not exceed 5%–15% in a 24-hour period. Dosages often increase then stabilize during the first 1–2 years of use. Requirements can vary significantly, ranging from less than 50 mcg/day to 1500 mcg/day or more. Some patients may require more than 2000 mcg/day.

The pump can be programmed noninvasively using a telemetry wand. It can be programmed to deliver a constant rate or variable rates to accommodate different functions during the course of a day, such as an increased infusion rate at bedtime due to nighttime spasticity or a decreased rate in the daytime hours to facilitate patient transfers or other activities of daily living. The wand also allows programming for the delivery and adjustment of bolus doses. The pump contains an alarm that sounds when the reservoir is low. The telemetry wand can then be used to determine the volume remaining in the pump, or to identify the problem that caused the alarm if the reservoir is not low. The pump will usually need to be refilled every 2–3 months, but intervals could be longer or as short as a few weeks depending on the dose requirement, size of the reservoir, and dose of baclofen used. Lioresal Intrathecal is supplied as a 500 mcg/mL or 2000 mcg/mL solution for refills, and 50 mcg/mL for screening.

Benefits and Cost of Therapy. Intrathecal baclofen was first developed in the 1980s, and in the 2 decades since then a large body of literature about its use has developed. Early studies focused on patients with spinal cord injury or multiple sclerosis, followed by trials focused on patients with spasticity of cerebral origin from traumatic and hypoxic brain injuries and CP. Several trials of patients with spasticity of spinal origin showed that ITB significantly decreased spasticity, reduced pain, and improved function, which led to benefits such as the ability to work and fewer sick days, improved cognitive and academic performance, improved hygiene and reduced requirements for urinary catheterizations, and improved locomotion. Nursing care became easier in many instances.

The effects tended to be more pronounced in the lower extremities, which could be due to severe motor deficit or cerebellar syndrome, or perhaps a consequence of lower thoracic placement of the pump catheter, although some authors suggest catheter location has little influence on effect. Trials in patients with spasticity of cerebral origin showed similar results. Other benefits identified include a reduction in joint contractures, improved healing of decubitus ulcers, improved range of motion and motor skills, and an easing of nursing care of nonfunctional patients. Many recent publications describe benefits of

ITB in patients with CP. Improvements include decreased spasticity, functional improvement in activities of daily living (although not in all patients), increased ambulation, increased ease of caregiving, decreased pain, decreased surgical requirement in those planned to receive surgical intervention, increased caregiver satisfaction including meeting of goals, and decreased oral spasticity drug requirement. Other benefits of ITB therapy include fewer side effects, greater dosing flexibility due to the ability to program specific doses, increased endurance, greater alertness, improved nutritional status, and increased quality of life.

The cost burden of ITB is greatest in the first year. Initial cost for implantation, including screening, surgery, and pump, approaches \$20,000–\$25,000, although this can vary at different institutions based on contracts. The annual cost of drug refills can approach \$1,000. The pump will need to be replaced every 4–7 years, which will approach \$20,000. Nevertheless, analyses show that other costs are reduced, including those for attendant care, other spasticity drugs, disability income, and hospitalization costs. After the first year, a decrease in use of resources may be seen. A recent cost/benefit analysis suggested that the baclofen pump is likely an appropriate intervention for those with severe spasticity who are bedridden or wheelchair-bound, and who have significant pain or skin breakdown.

None of the data on ITB use in spasticity are generated from randomized, controlled trials. In addition, the most appropriate methods for objective assessment of effect are unclear. The spectrum of patients in the studies have varied considerably, from ambulatory patients with hemiplegia or diplegia to quadriplegics completely dependent on caregivers in every aspect of life. Clearly, more research needs to be performed to accurately identify the patients who will benefit the most from this costly therapy. However, given the amount of literature showing positive results and the overwhelming majority of caregivers reporting satisfaction with this intervention, ITB will continue to be an important part of managing spasticity.

Complications and Precautions. Serious adverse events are rare. However, several potential complications and precautions are related to the surgery, the pump or catheter, or the drug itself (Table 1-7). Overdose is possible due to programmer error, but dose failure and withdrawal are more common. Withdrawal can occur due to failure to refill the reservoir, pump failure, or catheter withdrawal, kinking, or breakage. “Spaghetti” catheter occurs when the catheter crumples at the bottom of the spinal cord. Abrupt baclofen withdrawal can result in serious morbidity and mortality. In

2002, a box warning was added to the product labeling, which described withdrawal presenting with high fever, altered mental status, rebound spasticity and muscle rigidity, which in rare cases progressed to rhabdomyolysis, multiple organ system failure, and death. Symptoms typically begin within hours to a few days. The most common reasons reported for abrupt discontinuation of baclofen included catheter malfunction, low drug volume, and end of battery life. Patients must be educated to notice initial signs of withdrawal, such as a return of spasticity to baseline, pruritus, hypotension, and paresthesias.

Of interest, in our practice central nervous system symptoms were witnessed in a patient who, previously on high-dose oral baclofen, received a baclofen pump after which oral baclofen was discontinued. When low-dose oral baclofen was resumed, the symptoms resolved. Possibly, intrathecal delivery of baclofen achieved lower concentrations near the upper spinal cord and brain, and resulted in withdrawal. Therefore, it may be prudent to avoid abrupt discontinuation of all oral baclofen after implantation of the pump.

The most common complications include catheter-related problems such as dislodgment, kinking, disconnection, seromas, cerebrospinal fluid leaks, and infections. The most common drug-related adverse effects include hypotonia, somnolence, headache, nausea and vomiting, and paresthesia. Some data suggest that complications requiring intervention may be more common in mixed-type CP, younger and smaller patients, nonambulatory patients, and those with gastrostomy tubes. However, more research is needed to clearly identify those at greatest risk for complications. Several other issues that are related to ITB must be taken into account in everyday life and are discussed in Table 1-7.

Botulinum Toxin

Pharmacology. Botulinum toxin is produced by the spore-forming anaerobic bacteria *Clostridium botulinum*. There are seven toxin subtypes (A, B, C, D, E, F, and G), but only A and B are commercially available. The toxin is composed of a 100-kilodalton heavy chain and a 50-kilodalton light chain. The toxin is a single longer, low-potency chain until it is internalized into the cytosol of cells on the presynaptic terminal where it is cleaved into its two units. Vesicles containing acetylcholine normally fuse with the neuronal cell membrane at the nerve terminal with the help of a synaptic fusion apparatus called SNARE proteins, and subsequently release the acetylcholine into the synaptic cleft. However, the light chain of the BTX selectively cleaves the fusion proteins, and the SNARE complex does

Butler C, Campbell S. Evidence of the effects of ITB for spastic and dystonic cerebral palsy. *Dev Med Child Neurol* 2000;42:634–45.

Fitzgerald JJ, Tsegaye M, Vloeberghs MH. Treatment of childhood spasticity of cerebral origin with intrathecal baclofen: a series of 52 cases. *Br J Neurosurg* 2004;18:240–5.

Remy-Neris O, Tiffreau V, Bouilland S, Bussel B. Intrathecal baclofen in subjects with spastic hemiplegia: assessment of the antispastic effect during gait. *Arch Phys Med Rehabil* 2003;84:643–50.

Awaad Y, Tayem H, Munoz S, et al. Functional assessment following intrathecal baclofen therapy in children with spastic cerebral palsy. *J Child Neurol* 2003;18:26–34.

Albright AL, Gilmartin R, Swift D, et al. Long-term intrathecal baclofen therapy for severe spasticity of cerebral origin. *J Neurosurg* 2003;98:291–5.

Sampson FC, Hayward A, Evans G, Morton R, Collett B. Functional benefits and cost/benefit analysis of continuous intrathecal baclofen infusion for the management of severe spasticity. *J Neurosurg* 2002;96:1052–7.

Table 1-7. Complications, Precautions, and Considerations Regarding Intrathecal Baclofen Pump Therapy

Complication	Comment
Surgical	
Infection	Can occur at pump insertion site in mesh pocket or at catheter; can track from pump to catheter and can result in meningitis. May require pump removal.
Inaccessible port	Possibly due to pump being inserted too deeply or upside down.
Procedural complications	Cerebrospinal fluid leak, bleeding, spinal cord damage, pump damage due to improper handling, anesthesia or medical complications, pocket seroma, hematoma or erosion, reservoir contamination.
Pump/catheter	
Pump failure	Most commonly due to catheter problem; battery expiration also possible but prevented by alarm system. Pumps have been reported to flip requiring manual flipping or surgical correction.
Catheter complications	Baclofen delivery may be hindered by kinked, disconnected, dislodged, or “spaghetti” catheters; may precipitate withdrawal.
Drug	
Overdose	Programmer error, not pump malfunction; can result in somnolence, hypotonia, respiratory depression or failure, loss of consciousness, or coma.
Drug side effects	Weakness, sedation, confusion, dizziness, ataxia, nausea, hypotension, paresthesia, and headaches; less common than with oral administration and typically responds to dose reductions. Weight gain, which is not unexpected because up to 40% of energy expenditure is due to spasticity; may be beneficial by improving soft tissue cover of the pump. Increased seizure frequency; likely due to increased weight gain and subsequent decrease in antiepileptic serum concentrations; not associated with new-onset seizures.
Elective Replacement Indicator (ERI)	Pump emits sound when is nearing end of service (EOS); must schedule replacement as EOS will occur in 90 days and the pump will stop.
Patient activities	Avoid contact sports or strenuous exercise that may jar, twist, stretch or impact the body; catheter may be damaged or dislodged.
Environment	Pressure and temperature changes may result in changes in infusion rates. As temperature increases above 37°C flow rate increases, and rate decreases below 37°C; at clinically relevant temperatures, variation is less than 5%. Altitudes above 500 meters result in increased flow rates; variation is about 5% at 4500 meters, although lower atmospheric pressure has been known to deliver in excess of 14% of programmed rate; no adverse consequences known as a result of this phenomenon. Hyperbaric conditions (above 2.0 atmospheres absolute) can damage the pump; if hyperbaric therapy must be administered, the pump should be filled to capacity.
Identification card	Patients must carry Medtronic Patient Identification Card at all times to show to security personnel and health care professionals.
Pump manipulation	Patients should avoid unnecessary manipulation that may result in catheter complications that could lead to drug or CSF leaks; potential for under or over doses; referred to as “Twiddler’s Syndrome.”
Refill	Patients must be reminded to appear for scheduled refills to avoid withdrawal risks or pump failure.
Implant site	Patients must keep the site clean and dry and protected from pressure, which could result in infection or erosion through the skin.
Radiological issues	High-output ultrasonic devices such as lithotripsy should not be used. Magnetic resonance imaging temporarily stops the pump motor rotor during exposure, but should resume normal function on termination; pump rate should be verified after the procedure. Magnetic resonance imaging can result in increased local temperatures near the pump; unlikely that the patient will experience uncomfortable warmth. Image of magnetic resonance imaging scan will be distorted with dropout areas around the pump. Radiation such as cobalt 60 or gamma radiation can damage the pump.

not form, preventing vesicles from fusing to the terminal. Consequently, neuromuscular transmission does not occur, resulting in flaccid paralysis and muscle weakness even though production and storage of acetylcholine and electrical conduction proceed normally. Reversal of this process takes about 3–12 months. Nerves begin sprouting and after 1 month are able to cause muscle contractions, followed by a return of vesicle turnover and regression of the sprouts.

In addition to muscle weakness and tone reduction, BTX is thought to have other effects. Pain relief may be the result

of decreased muscle activity and contraction, but other mechanisms may include the inhibition of the release of substance P, which plays a significant role in inflammation and pain perception. Data from studies in patients with dystonia and spasticity have shown that pain reduction is one of the greatest benefits of therapy. Also, evidence suggests that afferent input to the central nervous system is decreased, causing decreases in excitability and restoring intracortical inhibition.

Pharmacodynamics. There are three available preparations of BTX: two are type A (Botox and Dysport)

Koman LA, Smith BP, Balkrishnan R. Spasticity associated with cerebral palsy in children: guidelines for the use of botulinum A toxin. *Paediatr Drugs* 2003;5:11–23.

Table 1-8. Available Botulinum toxin Preparations

	Botox (type A)	Dysport (type A)	Myobloc (type B)
Dosage form	100 units/vial	500 units/vial	2500, 5000, and 10,000 units/vial (5000 units/mL)
	Vacuum-dried for reconstitution with preservative-free saline for injection	Freeze-dried for reconstitution with preservative-free saline for injection	Liquid preparation, may be diluted with preservative-free saline for injection
Storage	Unopened vials at 2–8°C up to 2 years	Unopened vials at 2–8°C up to 1 year	Unopened vials at 2–8°C up to 21 months
	Use reconstituted vial within 4 hours ^{a,b}	Use reconstituted vial within 8 hours ^b	Use opened vials within 4 hours
Approximate potency ^c	1 unit	4 units	40–50 units
Non-toxin protein content	20 units/nanogram	40 units/nanogram	100 units/nanogram
Typical administration concentrations	25–100 units/mL	500 units/mL	5000 units/mL
Available in United States	Yes	No	Yes
Approximate cost	\$490–560 per 100 units	NA	\$500 per 5000 units

^aDue to concern about sterility because there is no preservative; studies have shown that the reconstituted toxin remains effective for at least 2 weeks.

^bStore reconstituted vials at 2–8°C.

^cAn approximate Botox:Dysport ratio of 1:4 may be appropriate for comparison of local muscle effect, but for systemic effects a 1:2 ratio may be more appropriate; an accurate equivalency for Myobloc has not been established; additional data suggest that toxin doses are not interchangeable based on simple ratios.

NA = not available.

and one is type B (Myobloc). There are several important differences between these products, and literature is often nonspecific regarding dosage forms used. It is imperative to interpret dosages with caution (Table 1-8). Botox is the only type A preparation available for use in the United States.

Potency of BTX is expressed as mouse units determined by the amount of toxin needed to kill 50% of specific genetic mouse strains. Potency ratios of Botox: Dysport: Myobloc are about 1 unit:4 units:40–50 units. However, the assays for potency are specific to each manufacturer; clinically there are no simple equivalencies, and so dosing must be based solely on the preparation used. Botox and Dysport are not interchangeable.

Both BTX type A and B have similar onset of action, and their dynamic effects are dose-dependent. Declines in action potential are seen about 1–3 days after injection, and the peak effect occurs in 1–3 weeks. Clinical effects from type A typically last for 3–4 months, but may vary from less than 1 month to up to 6 months and beyond. The effect is most pronounced in the first weeks, then it plateaus and declines for the duration of activity. Although the clinical response from type B is similar to type A, maximum paralysis at 2 weeks is less pronounced and recovery tends to occur much more quickly with type B. Although electrophysiologic studies show significant decreases in amplitude for 3 months after injection, the clinical response does not always persist that long. Factors contributing to the duration of response include dose and delivery, dilution, and the type of muscle injected.

Appropriate Use. Botulinum toxin is currently used in children with CP to treat spasticity and focal dystonia, both of which are commonly present together. Recent trials have shown BTX to be effective in reducing drooling. It is most frequently used in patients with a small number of specific

muscle groups that require tone reduction. Greater than four large spastic muscle groups typically dictates the use of systemic therapy such as oral drugs or ITB. However, even in these patients, BTX can be used as part of an overall treatment plan.

Younger patients, aged 1–5 years, may see more benefit in lower extremity spasticity than patients older than 5 years, who see more benefit in upper extremity spasticity. Initially, patients under 18 months of age did not receive BTX because of concerns about potential long-term effects on development. However, continued experience has shown that BTX use can be effective in children much younger than 1 year. Earlier intervention may be more effective because much motor development occurs during this time. Ideally, there should be enough strength in the muscles that they will tolerate weakening; those with weak muscles initially may see a decrease in function. Although BTX may help prevent contractures from developing, it will not benefit static contractures.

Dosing regimens have evolved with experience and have been developed by consensus. Empiric dosing ranges from 1–6 units/kg of body weight per muscle. This dosing has been effective, but it may be more appropriate to base the dose on the number of neuromuscular junctions per muscle in addition to the muscle mass. Muscle mass, number of muscles to be injected, overall status of the patient, baseline muscle strength, severity of joint deformity, and age of the patient need to be considered in determining the most appropriate dose. Early studies used total doses of 4–8 units/kg. However, the current recommended maximum total body dose per visit of 15 units/kg is well-tolerated. There are reports of even higher doses being used in multiple muscle groups without significant complications

while significantly increasing the duration of action. Table 1-9 provides a guideline for dosing Botox in children with CP.

There are several administration techniques for intramuscular delivery. The most common for locating and injecting easy-to-access musculature such as the gastrocnemius, biceps, and hamstrings is to palpate the muscle manually with the muscle under passive stretch or relaxed. Locating smaller and deeper musculature may require ultrasound or electromyography before injection. Electromyography can also be particularly useful to differentiate spastic nontarget muscles. Local anesthesia is typically required for electromyography and can be accomplished with 2.5% lidocaine and 2.5% prilocaine (EMLA cream) or 4% lidocaine (ELA-Max). Anxiolysis with drugs such as oral midazolam may be required for some patients. Some centers use ethyl chloride as a local coolant just before and during the injection, and care must be taken not to freeze the needle, which could prevent delivery. General anesthesia is rarely needed.

Not all patients will respond to BTX, and lack of efficacy can be due to fixed contracture, injection of the wrong muscle, subtherapeutic dosage, excessive weakness of the injected or antagonist muscles, inappropriate goals, or

formation of antibodies. If no reason for failure can be identified, increasing the dosage is appropriate.

Several trials have evaluated the effect of BTX in lower extremity spasticity, and a smaller number of trials have evaluated the effect of BTX in the upper extremities. A meta-analysis of randomized controlled trials in patients treated for lower extremity spasticity estimated that about 25% more patients would show improvement with BTX than with placebo or casting alone, although recent trials have shown casting or combination therapy to be more successful than BTX alone.

A majority of studies evaluated equinus foot deformity caused by spasticity in the gastrocnemius and soleus muscles. Consistent improvements were seen in active range of motion and gait. Larger muscle groups have also been evaluated. Administration of BTX to hip adductors before surgical release was beneficial and at the same time facilitated postoperative analgesia and reduced opioid and sedative requirements. Studies of effectiveness for upper extremity muscles have also shown benefit, including decrease in tone at the elbow and wrist, increased range of motion of the elbow, thumb, and fingers, improvement in outcome scores such as the Pediatric Evaluation of Disability Inventory, and grip strength.

Table 1-9. Dosing Guidelines for Botulinum toxin type A (BOTOX) for Cerebral Palsy in Children^a

Clinical Deformity	Muscle Groups	Dose (units/kg)	Usual No. of Injection Sites
Upper extremity			
Shoulder internal rotation adduction	Subscapularis	1-4	2
	Pectoralis major	1-4	2
	Latissimus	1-4	2
Elbow flexion	Biceps	1-4	2
	Brachialis	1-4	2
Forearm pronation	Pronator teres	1-3	2
	Pronator quadratus	1-2	2
Wrist flexion	Flexor carpi radialis	1-4	2
	Flexor carpi ulnaris	1-4	2
Finger flexion	Flexor digitorum superficialis	1-2	2
	Flexor digitorum profundus	1-2	2
	Flexor pollicis longus	1-2	2
Thumb-in-palm	Adductor pollicis	1	2
	First dorsal interosseous	1	2
Lower extremity			
Scissoring	Adductor longus	1-4	2
	Adductor magnus	1-4	2
	Adductor brevis	1-4	2
	Gracilis	1-2	2
Hip subluxation	Iliacus	2-3	2
	Psoas major	2-4	3
Crouched gait			
Hip flexion	Iliacus	2-3	2
	Psoas major	2-4	2
Knee flexion	Semimembranosus	1-3	2
	Semitendinosus	1-3	2
	Biceps femoris	1-3	2
	Rectus femoris	1-3	2
	Medial gastrocnemius	1-3	2
Equinus foot	Lateral gastrocnemius	1-3	2
Varus hindfoot	Posterior tibialis	1-4	2

^aGuideline provides starting point and may require adjustment for specific patients; Dysport dosing is different and should be determined by the clinician as a conversion from Botox has not been verified.

Reprinted with permission from Wolters Kluwer Health and Adis International. Koman LA, Smith BP, Balkrishnan R. Spasticity associated with cerebral palsy in children: guidelines for the use of botulinum toxin. *Pediatr Drugs* 2003;5:16.

Lower extremity use has shown more consistent and dose-related improvement than upper extremity use. There are several proposed reasons, including more activity after injection with the lower extremities (i.e., walking) and difficulty in measuring outcomes in upper extremities. In addition, patients with hemiplegia learn to not use the affected upper limb and primarily use the unaffected limb, potentially decreasing use after injection. The resultant change in muscle tone without physical therapy or use fails to maximize the benefit of treatment.

The use of BTX in dystonia and other movement disorders is also supported in the literature. There are case reports of children with focal dystonia associated with pain, generalized dystonia, and blepharospasm who benefited from BTX injections. One study in children with dystonic CP showed significant improvement in skilled hand movements and foot posture, and the onset and duration of effect were similar to those treated for spasticity. It is clear that BTX results in improving objective measurements such as tone, strength, and range of motion, but the effect on function is less clear, especially in severe impairment. Table 1-10 summarizes selected recent trials of BTX in the lower and upper extremities.

Adverse Effects. Botulinum toxin has a relatively mild side-effect profile when doses do not exceed the recommended maximum. Commonly reported side effects range from 8% to less than 1% and include pain on injection (most common), muscle soreness, bruising, greater than desired weakness in injected and adjacent muscles, dysphagia, rash, incontinence, pneumonia, constipation (improved and worsened), diarrhea, gastroenteritis, fever, respiratory infection, somnolence, convulsions, abnormal gait, and accidental injury or falls.

Similar rates for many of these side effects were reported in placebo groups, indicating that they are likely typical of the disease in children. The incidence of accidental injury or falls has been one of the most disparate between BTX and placebo, likely due to greater than desired weakness and/or spread to adjacent muscles. Diffusion to other muscles is dependent on dose, volume, dilution, and number of injections. Abnormal gait may also be explained by drug diffusion. The incidence of convulsions or seizures is similar to placebo, which is representative of one of the more common complications of CP. Dysphagia is of particular concern because it can lead to aspiration pneumonia and serious morbidity. Patients who receive BTX in the neck or head area should be monitored closely. However, in trials in which BTX was injected into salivary glands to decrease drooling, no significant side effects were noted.

Antibodies to BTX type A develop in less than 5% of adult patients, and are thought to occur even less frequently in children. Factors increasing the likelihood of antibody formation include shorter time between injections, higher doses, and booster injections. The lowest dose and the longest interval required to achieve the desired clinical effect should be used. Nontoxin protein content also contributes to antibody formation. Botox contains less nontoxin protein than Dysport and Myobloc (Table 1-8).

More recent Botox preparations have lower protein content, and this formulation should be less antigenic. If a patient develops antibodies to type A toxin, he or she may respond to type B. However, not all patients will respond to type B. Although it has been used in children, no peer-reviewed trials in spastic CP have been published, the duration of action may be shorter, and resistance to type B may occur even faster than to type A.

Contraindications and Precautions. Contraindications to the use of BTX include known hypersensitivity to any component of the dosage form, which includes human albumin. Patients with peripheral motor neuropathic diseases such as amyotrophic lateral sclerosis or neuromuscular junction disorders such as myasthenia gravis may experience significantly increased systemic effects. Severe dysphagia can result, which could lead to aspiration and severe respiratory distress, requiring the use of feeding tubes. Administration of aminoglycosides concurrently could potentiate the effect of the toxin.

Alcohol and Phenol

Alcohol and phenol have been used for treating spasticity for several decades. At high enough concentrations, they work by denaturing proteins and cause tissue destruction in the injected area. Both drugs have shown benefit in treating spasticity due to CP.

Alcohol injection to children has been associated with a decrease in spasticity with gait improvement while maintaining strength of the muscle, although the duration of effect was only 1–6 weeks. Other studies using alcohol for treatment of nerves such as the obturator (hip adductor spasticity), musculocutaneous (arm flexion), tibial (ankle-foot spasticity) and sciatic (knee flexor spasticity) nerve found benefit; some studies reported benefit for several months.

Phenol has also produced significant decreases in spasticity with duration of effects lasting 3–18 months. One study compared phenol motor point blocks to BTX type A in patients with foot deformity after stroke. Both drugs were effective in reducing spasticity, and effects were similar at 12 weeks; however, BTX was more effective at 2 and 4 weeks, and phenol was associated with more adverse effects.

Despite the effectiveness, lower cost, and potential long duration of alcohol and phenol, there are drawbacks to their use that have made BTX the most common method of neuromuscular blockade. Conscious sedation or general anesthesia is typically required, especially in children, because of the significant pain associated with alcohol and phenol injection. In addition, the technical expertise for administration may far exceed that required for BTX. Complications of alcohol or phenol injection can be severe and include prolonged skin irritation and muscle soreness, dysesthesia, peripheral nerve palsies, muscle necrosis, and vascular complications such as peripheral edema and deep vein thrombosis. Even so, alcohol and phenol could be used in conjunction with BTX as a component of overall spasticity management, and they could have a greater role in patients unresponsive to BTX. Table 1-11 provides a brief comparison of the two agents.

Table 1-10. Recent Studies of Botulinum toxin in Cerebral Palsy

Trial	Patients	Interventions	Outcome	Comments
Lower extremity				
Corry, et al. J Pediatr Orthop 1998;18:304–11	20 ambulatory children (2–9 years) with foot equinus who were candidates for casting.	Randomized to casting or BtA injection. Assessments before treatment and at 2 and 12 weeks. Botox 6–8 units/kg. Dysport 15 units/kg.	Significant tone reduction at 12 weeks in treatment group, not casting group, and relapse at 12 weeks much greater in casting group. Dorsiflexion increased at 2 weeks in both; increased in treatment group at 12 weeks and relapsed in casting group.	Gait dynamics equally improved. Fewer side effects in treatment group. BtA shown as effective as casting for management of equinus. Any potential differences in those receiving different toxin preparations not addressed.
Koman, et al. J Pediatr Orthop 2000;20:108–15	114 ambulatory children (2–16 years) with foot equinus.	Double-blind, randomized trial of BtA versus placebo. Assessed at baseline, 2, 4, 8, and 12 weeks. Botox 4 units/kg.	Lower extremity function significantly better in BtA group at all follow-up. Ankle dorsiflexion significantly better in BtA group at 4 and 12 weeks.	Adverse events 17% in BtA group, 4% in placebo group; all mild to moderate. No serum antibodies detected.
Ubhi, et al. Arch Dis Child 2000;83:481–7	40 ambulatory children (2–16 years) with foot equinus.	Double-blind, randomized trial of BtA versus placebo. Assessed at baseline, 2, 6, and 12 weeks. Dysport 15 units/kg for hemiplegics, 25 units/kg for diplegics.	Significant gait improvement at 6 and 12 weeks in BtA group. GMFM walking dimension improved at 12 weeks in BtA group. No change in passive dorsiflexion.	Adverse events mild. First controlled trial to show improvement in ambulation.
Barwood, et al. Dev Med Child Neurol 2000;42:116–21	16 children (2–10 years) to receive adductor release due to risk of hip dislocation.	Double-blind, randomized trial of BtA versus placebo. BtA administered 5–10 days before procedure. Postoperative assessment of pain scores, nausea, vomiting, sedation, vital signs, analgesia requirement, complications, length of stay, and readmission at 3 months. Botox 8 units/kg.	Significant reduction in total opioid and sedative requirement. Significant postoperative pain reduction. Hospital stay significantly reduced.	No readmissions in BtA group, three in placebo group (2 due to home pain control issues) BtA found useful for augmenting pain control after hip adductor release and may have application in other situations as pain may be due in large part to spasticity.
Baker, et al. Dev Med Child Neurol 2002;44:666–75	125 ambulatory children (2–9 years) with foot equinus.	Double-blind, randomized trial of BtA versus placebo. Assessed at baseline, 4, 8, and 16 weeks. Dysport 10, 20, or 30 units/kg or placebo.	Significant improvement of dynamic component or difference between passive and active gastrocnemius muscle lengths. Improvement in subjective functional measurements by parents and investigators.	GMFM not significantly changed. 20 units/kg most effective dose. Adverse effects mild, resolved within 2 weeks.
Russman B, et al. Dev Med Child Neurol 2002;44(suppl 91):8	37 ambulatory children (3–9 years) with foot equinus.	Randomized, prospective trial of BtA versus BtA plus casting versus casting plus placebo. Assessed at baseline, 3, 6, 7.5 months, and 1 year. Botox 4 units/kg.	Both BtA plus casting and placebo plus casting showed improvements in ankle kinematics, but BtA alone did not.	Results conflict with earlier studies that showed BtA was at least as effective or superior to casting; more investigation necessary.

Table 1-10. Recent Studies of Botulinum toxin in Cerebral Palsy (Continued)

Trial	Patients	Interventions	Outcome	Comments
Glanzman A, et al. Dev Med Child Neurol 2002;44(suppl 91):33	55 children with spasticity and plantar flexion contractures (mean age 7 years).	Retrospective study of BtA versus casting versus BtA plus casting. Botox 2.5 units/kg.	Both BtA plus casting and casting alone resulted in significantly increased range of motion compared with BtA alone.	Results conflict with earlier data; contractures in this population may have contributed to lack of effect in BtA-only group.
Upper extremity				
Fehlings, et al. J Pediatr 2000;137:331–7	30 children (2.5–10 years) with hemiplegia.	Single-blind, randomized trial of BtA plus OT versus OT alone. Assessed at baseline, 1, 3, and 6 months. Botox 2–6 units/kg to at least one of either biceps, volar forearm or adductor pollicis muscles.	Significant change in Quality of Upper Extremity Skill Test at 1 month, only moderate at 3 and 6 months. Significant improvement on parent completed self-care domain of PEDI score.	Modified Ashworth scores not significantly different. Passive range of motion not significantly different. No significant adverse effects.
Hurvitz, et al. Arch Phys Med Rehabil 2003;84:444–54	9 children (7–16 years) with asymmetric upper extremity function due to spasticity.	Open-label clinical trial. Assessed at baseline, 2, 4, 6, 12, 18, and 24 weeks. Botox 50–100 units/muscle at biceps, triceps, flexor carpi radialis, flexor digitorum profundus, flexor carpi ulnaris, pectoralis, pronator teres, brachialis, or brachioradialis.	Spasticity decreased, passive range of motion increased but was not statistically significant. No change in functional assessment with PEDI scale. Transient improvement in motor control tasks; more complicated tasks required more time for effects.	Very small number of subjects, unblinded. BtA in addition to task training may increase effectiveness.
Yang, et al. Am J Phys Med Rehabil 2003;82:284–89	15 children (4–13 years) with spastic CP.	Open-label trial. Assessed at baseline, 6 and 12 weeks. Botox 1–2 units/kg per muscle after 3 months PT/OT.	Significant decrease in spasticity. Improvement in fine motor skills. Self-care capability improved but not until after 6 weeks.	Significant decrease in caregiver assistance. No significant adverse effects. Small number of subjects, unblinded.

BtA = botulinum toxin type A; CP = cerebral palsy; GMFM = Gross Motor Function Measure; OT = occupational therapy; PEDI = Pediatric Evaluation Disability Inventory; PT = physical therapy.

Pain Management

The numerous modalities for treatment of spasticity and improvement of function have not been adequately studied for effectiveness in pain relief. Most efforts are aimed at decreasing spasticity as unrelieved pain can result in decreased activity and lead to respiratory, cardiac, gastrointestinal, immunologic, neurologic, and musculoskeletal complications.

Pain management begins with nonpharmacological modalities, with efforts focusing on minimizing stimuli that can lead to spasticity and pain. These efforts include thorough bowel and bladder care, prevention and treatment of skin problems such as pressure sores, use of relaxed clothing, and dysphagia management. Posture and position can be addressed with training, seating, sensory feedback, and the use of splints, braces, or casts. Physical therapy, particularly stretching, and strengthening of antagonist muscles may be of benefit. Mechanical pain relief with the

application of heat or cold, electrotherapy, and hydrotherapy may also be used.

Although these treatments can be effective, they may take an inordinate amount of time. For example, it has been suggested that 3 hours of stretching per day might be necessary, and very few programs could provide this. Thus, pharmacological therapy will likely be required. If a stimulus is identified that may cause injury or inflammation, nonsteroidal anti-inflammatory drugs or opioids may be used. Tricyclic antidepressants may be of benefit when analgesics fail. Selective serotonin reuptake inhibitors should be avoided due to their potential to exacerbate spasticity by inhibiting baclofen. Anticonvulsant drugs, particularly carbamazepine and gabapentin, have also been used for pain.

However, spasticity control is the most important method of pain management. Drugs include those already discussed, including baclofen, dantrolene, clonidine and tizanidine, and diazepam. When oral drugs fail or side effects become

Table 1-11. Comparison of Alcohol and Phenol

	Alcohol	Phenol
Mechanism of action	Protein denaturing, tissue destruction.	Protein denaturing, tissue destruction.
Effect	5%–10% local anesthetic. Higher concentrations result in nonspecific protein destruction. Range of concentrations used clinically is 35%–60%; some have used 50%–100% successfully.	<1% local anesthetic. 1%–7% all neural tissues affected. Range of concentrations used clinically 3%–6%; 0.25–0.5 mL of 5%–6% solution suggested to completely denervate a muscle.
Technique	Motor point or intramuscular injections with electrical stimulation. Requires conscious sedation or general anesthesia.	Motor point blocks in muscle belly or motor nerve blockade with electrical stimulation; open nerve block with direct visualization. Requires conscious sedation or general anesthesia. Some methods require additional skill and technological assistance.
Adverse effects	Pain, muscle discomfort, vascular complications, chronic dysesthesia, permanent peripheral nerve palsies, and systemic intoxication.	Pain, muscle necrosis, dysesthesia, peripheral edema, deep vein thrombosis, and spinal cord infarction.

intolerable, peripheral nerve or motor point blocks with alcohol or phenol, BTX, or ITB may be initiated. Surgical procedures such as selective dorsal rhizotomy, neurectomy, tenotomy, myotomy, and tendon transfer may be required.

Seizure Management

Seizures are far more common in individuals with CP than in the healthy population, especially in those with quadriplegia, and they may be induced by genetic, prenatal, perinatal, and postnatal events. Seizures may be difficult to control in severely affected individuals. In general, seizure disorders complicate care and increase the burden for caregivers, and may make it more difficult to allow supervision by someone other than the primary caregiver.

Once they manifest, seizures are likely to recur, so treatment is usually not delayed. Phenobarbital is used most often in the neonatal patients with CP, and valproic acid is an effective first-line therapy in older infants and children. Caution should be taken in those receiving dantrolene for spasticity because of the increased risk of serious hepatotoxicity when used concurrently with valproic acid. It is also prudent to rule out metabolic disorders such as urea cycle or carnitine metabolism defects, which could be exacerbated by valproic acid. Still, because of its broad-spectrum activity and ease of use, valproic acid can be very effective.

Other “first-generation” drugs such as carbamazepine and phenytoin are sometimes used. However, phenytoin is generally avoided due to difficult-to-control pharmacokinetics and decreased bioavailability when given with enteral formulas (which these patients frequently receive). When valproic acid fails, other drugs such as lamotrigine, gabapentin, and topiramate may be used. Drugs such as oxcarbazepine and levetiracetam may be useful for patients with CP, but little data are available. Once diagnosis is confirmed, aside from initiating therapy with valproic acid, management with antiepileptic drugs is similar to managing epilepsy in general. Please refer to the epilepsy chapter for more detailed discussion.

Management of Nutritional Complications

Nutritional and Growth Deficiencies

Almost one-third of children with CP are underfed and malnourished, and those with severe disease often have linear growth below the 3rd percentile. Muscle mass is decreased as a result of reduced growth rates and also because of disuse. This decrease is true even though energy expenditure is typically decreased due to less physical activity. In addition to reduced growth rates, consequences of poor nutritional status include increased surgical morbidity, decreased bone density, slower healing of decubitus ulcers, and death.

Many factors are associated with nutritional deficiencies, but oral motor impairment, which occurs in up to 90% of children with CP and which can be especially severe in quadriplegia, is the most important. Features and symptoms of oral motor impairment include dysphagia, temporomandibular joint contractures, hypoxemia, discomfort, choking, coughing, apnea, tachypnea, and vomiting and aspiration as a result of gastroesophageal reflux. Anatomically, common abnormalities include hypopharyngeal hypotonia, supraglottic edema associated with reflux, and tracheobronchomalacia.

Dysphagia and oral motor impairment contribute to inadequate nutritional status by making mealtimes difficult, prolonged, tiresome, and unpleasant. Children with CP are often offered less food, and they consume about 50% that of controls. Nonnutritional factors also play a role and include muscle wasting from immobility, reduction in or lack of weight bearing, and joint contractures and scoliosis, which can render growth measurements inaccurate.

Gastroesophageal reflux may be a significant contributor to feeding and nutrition problems. Studies have found rates of reflux greater than 70% in children with CP who present with failure to thrive, food refusal, low-volume feedings, and vomiting. In addition, reflux results in smaller caloric intake, increases aspiration risk, and can be painful, which further increases food refusal. Most children receive

pharmacological therapy for reflux, typically with histamine-2 receptor antagonists or proton pump inhibitors and metoclopramide. Also, baclofen may decrease reflux by inhibiting transient lower esophageal sphincter relaxation.

Role of Gastrostomy Feedings

Children who are unable to maintain adequate nutrition with oral feedings may require tube feedings, either with nasogastric or gastrostomy tubes. Nasogastric tubes are appropriate for short-term interventions. When used long-term, they are associated with undesirable appearance, nasal discomfort, irritation of the larynx, aspiration, and tube displacement. They can also contribute to oral aversion and slow the development of oral feeding skills.

Gastrostomy tubes are a better option for long-term feeding. In general, gastrostomy is indicated in patients with CP who suffer from dysphagia resulting in poor nutrition, aspiration with respiratory complications, and poor fluid intake. Gastrostomy is also indicated for patients who refuse medication and for whom oral feedings result in undue effort or stress. Oral feedings may continue in conjunction with gastrostomy tube feeds.

The literature does not provide firm conclusions about the efficacy of gastrostomy. Data from cohort studies suggest that outcomes may be poorer in those who receive gastrostomy feedings versus those who are orally fed, including death, decreased global health and physical test scores, increased incontinence, and family reports of greater impacts on time and emotions due to worry about the child's health. However, the gastrostomy groups tended to have more severe disease than the orally fed groups, and in one trial the risk of death was greatly reduced when confounders were accounted for. In essence, these studies could not determine whether the gastrostomy or the increased severity of disease resulted in worse outcomes compared with orally fed children.

Other data suggest that tube feedings result in increased growth, improved nutritional status, reduction in aspiration symptoms, improved general development, improved social interaction and disposition, decreased difficulty in feedings, and increased caregiver satisfaction. However, some parents felt that gastrostomy feedings decreased satisfaction by removing interaction during meal times.

Complications of gastrostomy are not uncommon and may be major or minor. Rates of major complications have ranged from 17% to 39% in some reports and include bowel obstructions, gastrointestinal ulcerations and bleeds, and peritonitis. Minor complications are more common and have been reported to occur in up to 95% of patients. They include cellulitis and leakage at the ostomy site, granuloma formation, vomiting, retching, tube blockage and dislocation, dumping syndrome, diarrhea, and constipation.

Fundoplication, often performed with gastrostomy to help control reflux, has been associated with high complication rates postoperatively such as persistent retching. Gastrojejunal tubes have been compared to gastrostomy with fundoplication, but further study is needed

to determine if complications are lessened. Other concerns include the delivery of nutrients in enterally fed patients. In general, children with CP have decreased caloric need. When feedings are based solely on caloric need, patients may not receive sufficient nutrients such as calcium, phosphorus, and vitamin D. Thus, intake of macronutrients and micronutrients should be monitored along with caloric intake.

Although no firm conclusion can be made regarding the benefits and risks of gastrostomy feedings, it is a common, well-accepted practice in patients with CP. The procedure is relatively safe, nutritional status generally improves quickly, and caregivers usually see benefit. Thus, for patients who meet criteria and for patients and caregivers who desire the intervention, gastrostomy placement can be a valuable intervention.

Social and Developmental Issues

Bladder and Bowel Function

Urinary tract dysfunction is a relatively common phenomenon in children with CP (almost 25% of those aged 4–18 are reported to be incontinent) and adults with CP. Bladder dysfunction results from spasticity of skeletal muscles, as well as the detrusor muscle, which causes contraction of the bladder and small, frequent voids. Other related problems include urinary urgency, frequency, retention, and infection. Anatomical defects in the urinary tract are not common, and evaluation of patients without significant symptoms or infections is not warranted. The most severe bladder dysfunction occurs in quadriplegics with poor intellectual capacity; less than 40% are continent by age 6. These children cannot determine when they need to void and/or cannot communicate it, and they often have difficulty getting to the bathroom and in a proper position to void in a timely manner. It may be necessary to modify toilet seats or clothing or add handrails to assist in toileting.

Constipation is a common, potentially severe bowel complication and can contribute to nutritional deficiencies. Prompt resolution is important and may be achieved with the use of laxatives and enemas. A child with a propensity for constipation should have a diet with high-fiber content, have adequate fluid intake, and may require the addition of stool softening agents such as docusate sodium. Most patients benefit from a regular bowel program, which includes attempts about 30 minutes after meals. Glycerin or bisacodyl suppositories may be useful. This regular pattern may allow some children to achieve a high level of bowel control.

Drooling

Drooling can be a significant problem, not only for health reasons, but also for social reasons. It has been estimated that anywhere from 25% to 33% of all patients with CP

Sleigh G, Brocklehurst P. Gastrostomy feeding in cerebral palsy: a systematic review. *Arch Dis Child* 2004;89:534–9.

Samson-Fang L, Butler C, O'Donnell M; AACPD. Effects of gastrostomy feeding in children with cerebral palsy: an AACPD evidence report. *Dev Med Child Neurol* 2003;45:415–26.

Table 1-12. Miscellaneous Supportive Therapies

Indication	Dosing and/or Administration
Drooling	
Glycopyrrolate	40–100 mcg/kg per dose by mouth 3–4 times/day 4–10 mcg/kg per dose IM/IV every 3–4 hours
Scopolamine	1.5 mg transdermal patch (change every 72 hours)
Constipation	
Bisacodyl	5–10 mg/day by mouth (5–15 mg for those > 12 years) 5–10 mg/day per rectum
Glycerin	Pediatric or adult suppository daily as needed
Lactulose	7.5–30 mL/day
Milk of Magnesia	5–60 mL/day
Docusate sodium	Children: 10–150 mg/day in 1–4 divided dosages Adolescents and adults: 50–400 mg/day in 1–4 divided dosages
Polyethylene glycol	1 g/kg/day in 2 divided doses
Urinary incontinence	
Oxybutinin	5 mg by mouth 2–4 times/day

IM = intramuscularly; IV = intravenously.

drool to some extent. Drooling is the result of a loss of coordination of the orofacial and head and neck muscles, palate and tongue, allowing excessive accumulation of saliva. Other contributors include dysphagia and the inability to close the lip and jaw. It is not related to excessive production of saliva. Complications include aspiration, poor hygiene, speech difficulty, tissue softening, and infection, in addition to the social stigma.

There are several management options, but they are often only temporarily successful. In some cases, behavior-modification strategies using alarms are helpful. Anticholinergic drugs such as glycopyrrolate and scopolamine may be effective in decreasing flow of saliva, but side effects such as dry mouth, restlessness, somnolence, blurred vision, and confusion often limit their usefulness. Operative procedures have been used. Denervation may be successful early, but drooling typically will return to baseline. Salivary ducts may be ligated, rerouted, or removed, but these procedures may lead to an increase in aspiration, discomfort, or accelerated tooth decay.

Recently, injections of BTX into the parotid and submandibular glands have been shown to decrease salivary flow rates. In clinical trials, BTX was significantly more effective in reducing flow, was as effective at reducing clinically significant drooling, and caused significantly fewer side effects than transdermal scopolamine. However, the percentage of responders was significantly lower in the BTX group. In addition, general anesthesia was required for BTX administration. More investigation is required to determine the most appropriate patients and dosing regimens for BTX. Table 1-12 provides dosing for common supportive therapies for drooling, constipation, and urinary incontinence.

Fractures

Almost all children with moderate to severe CP will have some degree of osteopenia, defined as a bone mineral density Z-score of -2 or lower. The most common site of fracture is the femur. Fractures can be the result of osteopenia coupled with long-term rigidity, leading to contractures, hip dislocations, falls, or seizures. Contributing factors are poor nutritional status including vitamin D deficiency and use of anticonvulsants. Nonambulatory, non-weight bearing patients may suffer the most significant losses in bone density, and rickets complicated by fractures is not uncommon. Vitamin D and calcium supplementation, especially in those receiving antiepileptic drugs, may help reduce fracture rates.

Family Issues

Impact of Diagnosis

When CP is suspected, and other processes such as metabolic or genetic defects or nonaccidental trauma have been ruled out, it is important to discuss the diagnosis with the family at that time. Families are far more likely to be satisfied with early disclosure and will be better able to cope and understand the diagnosis if they are involved from the start, and if the term CP and the implications of the diagnosis are carefully explained.

The initial questions of parents and families usually relate to how severe the disease will be and whether or not their child will walk. Some data suggest that in children who develop adequate head control by 9 months of age, sit by themselves by 2 years of age, and crawl by 30 months of age, independent ambulation is more likely. This is in contrast to those not meeting these respective milestones by 20 months, 36 months, and 61 months, who will be less likely to ambulate. However, in a vast majority of cases, accurate prognosis is difficult regarding ambulation, cognition, and language skills. Most experts suggest 2 years of age as the minimum age to assign a diagnosis of CP, and it may be appropriate to withhold diagnosis until later than that. Still, a preliminary diagnosis provides parents with referral to resources such as early intervention programs, supplemental security income, Medicaid, and comprehensive multidisciplinary care services.

A diagnosis of CP will have lifelong consequences. Families need time and support as they begin to acknowledge that their child is not “normal.” In our experience, with support from the health care team, other available resources, and support networks, families often deal effectively with the difficulties involved and develop a rewarding and meaningful lifetime experience.

Issues in Daily Care

Care of patients with CP, especially for those with quadriplegia who are completely dependent on caregivers for all activities of daily living, can be extremely demanding. Needs of children with severe disabilities are significantly greater than those of unaffected children and do not lessen with age. Investigations have shown that the stress of day-to-day care is extremely difficult to cope with

and can affect the health of the caregiver. One study identified in primary caregivers significant increases in health problems such as distress, emotional and cognitive problems, back problems, headaches, ulcers, arthritis, pain, and other chronic physical ailments. Strong family relationships, strong caregiver interest in learning about CP, and therapy and social service assistance can all help lessen the burden of care and improve the child's quality of life.

Financial burdens are also significant. Multiple organ systems may be affected as children age, and the chronicity of the morbid conditions of CP results in these patients being three times more likely than the normal population to require hospitalization. It is estimated that the average lifetime cost of caring for a patient with CP is about \$500,000. In addition, the families' decreased ability to work for wages due to the heavy care demands results in lower income compared with other families, despite no difference in education level. Medicaid and other community and educational resources are available to help ease the cost burden.

Early intervention in patients with CP is key to maximizing their development and ability to function in society. Children receiving structured, family-centered early intervention require fewer special education services in later years. In the 1970s laws were passed that required special education and other services for persons with disabilities, which assisted in provision of these programs. The Americans with Disabilities Act and the Individuals with Disabilities Education Act require that states provide statewide comprehensive multidisciplinary programs for infants and young children and their families.

A multidisciplinary team determines program eligibility based on physical, cognitive, communication, social, emotional, and adaptive skill sets. As children age, they may continue to be eligible for programs such as special preschool programs or other educational services. The Individuals with Disabilities Education Act provide benefits through 21 years of age. The Rehabilitation Act, passed in 1973, requires states to ensure that impaired students receive services necessary for all needs to met just as nondisabled students' are. Primary care physicians can assist by informing families of locally available services. Web sites can also be valuable resources for the health care team and families (Table 1-13).

Quality Of Life and Life Expectancy

Quality of life is dependent on many factors, including severity of disease and functional limitations, psychological and social status, environment, and availability of resources. Despite the potential devastating nature of CP, most children with CP are able to live at home, attend regular schools, and take part in many community activities. Adults with CP typically are able to lead independent lives, as about 60% are able to ambulate with or without assistance. However, about one-third continue to live with their parents, who may not be able to maintain the same level of care as they age.

Outcomes can be difficult to predict. Some patients with a particular type of CP may be minimally affected, while another with the same diagnosis may suffer from multiple complications and likely have a worse outcome.

Life expectancy is variable, determined primarily by the severity of disease. Some, such as those mildly affected by hemiplegia, have essentially a normal life span, while those with devastating disease may have only a 50% chance of reaching age 20. Specific predictors of decreased life expectancy include mental retardation severity (inability to speak, identify voices, or interact), physical disability (poor mobility, inability to crawl or roll over, inability to feed self), requirement of tube feeding, incontinence, and the presence of a severe seizure disorder. In the most severely affected individuals, respiratory complications such as infection and aspiration are the leading causes of death.

Conclusion

There is no cure for CP and no current strategies available to prevent it, so most investigation is directed at best management of the condition and its effects, especially spasticity. Several nonpharmacological and pharmacological therapeutic options exist, and all may be effective. However, patients and family dynamics are quite different. Any modality chosen to maximize the quality of life for the patient and family must be based upon teamwork and goal-setting between the health care team, the patient, and the caregivers.

Table 1-13. Selected Web-based Resources for Health Care Professionals and Families

Organization	Web site ^a (All accessed December 14, 2005)
American Academy for Cerebral Palsy and Developmental Medicine	www.aacpdm.org/index?service=page/Home
United Cerebral Palsy Association	www.ucp.org
The Cerebral Palsy Network	www.thecpnetwork.net/firms.com
Pediatric Stroke Network	www.pediatricstrokenetwork.com
Special Olympics	www.specialolympics.org
MUMS National Parent to Parent Networks	www.netnet.net/mums
National Family Caregivers Association	www.nfcacares.org
Disability Rights Education and Defense Fund	www.dredf.org
Americans with Disabilities Act Home page	www.ada.gov

^aMost Web sites have links to other pertinent sites.

CP = cerebral palsy.

Annotated Bibliography

1. MacLennan A. A template for defining a causal relation between acute intrapartum events and cerebral palsy: international consensus statement. *BMJ* 1999;319:1054–9.

This consensus statement, developed by the International Cerebral Palsy Task Force and supported by 16 professional organizations from around the world, was motivated in part by the accumulation of data contradicting the opinion that perinatal asphyxia was a frequent cause of cerebral palsy. It is now accepted that the majority of cases of cerebral palsy are caused by insults in the prenatal and postnatal periods. In addition, many signs of perinatal asphyxia can be mimicked by other conditions. Therefore, the task force developed criteria for identifying when the development of cerebral palsy may be caused by acute intrapartum hypoxia. The three general criteria identified as necessary were metabolic acidosis, severe or moderate neonatal encephalopathy, and development of spastic quadriplegia or dyskinetic cerebral palsy. Five additional nonspecific criteria were factors that suggest a perinatal insult. Thirteen factors were listed of which, if any one factor were present, the likelihood of a perinatal insult causing neurological damage would be significantly decreased. In addition to providing assistance to health-care community with research, this consensus statement has also provided the legal system with a guideline to assist in determining the probability that an insult incurred during labor resulted in the development of cerebral palsy or other neurological sequelae.

2. Murphy N, Such-Neibar T. Cerebral palsy diagnosis and management: the state of the art. *Curr Probl Pediatr Adolesc Health Care* 2003;33:146–69.

This comprehensive review is an excellent resource not only for those unfamiliar with cerebral palsy, but also for those with clinical experience. After a review of definitions, epidemiology, cerebral palsy subtypes, risk factors, and diagnosis, the authors discuss other issues related to cerebral palsy based on age. Each section is prefaced with a short case, followed by a discussion of points that are most important and common in that particular age group. The authors discuss topics affecting cerebral palsy patients through infancy to adulthood, including neuromotor development, nonpharmacological interventions, nutrition, social issues, and advocacy. Both oral and parenteral drug therapy are discussed, although less thoroughly than other sources. The chronological presentation of complications makes this article particularly useful.

3. Wu YW, Escobar GJ, Grether JK, Croen LA, Greene JD, Newman TB. Chorioamnionitis and cerebral palsy in term and near-term infants. *JAMA* 2003;290:2677–84.

This case-controlled study of 109 children with moderate to severe spastic or dyskinetic cerebral palsy and 218 controls from a cohort of more than 230,000 infants born at 36 or more weeks' gestational age was conducted to determine to what extent, if any, clinical chorioamnionitis increased the risk of cerebral palsy. Children in the cerebral palsy group were identified from an electronic database and confirmed by a pediatric neurologist. Analysis showed that clinical chorioamnionitis was present in 14% of cerebral palsy cases, and 4% of controls. Independent risk factors identified for the development of cerebral palsy included chorioamnionitis, intrauterine growth restriction, maternal black ethnicity, maternal age older than 25 years, and nulliparity.

Chorioamnionitis was associated with four times the risk of cerebral palsy in term infants. The authors hypothesized that chorioamnionitis may contribute to cerebral palsy development by causing increased fetal cytokines, inflammation of placental membranes, decreased blood flow and gas exchange, core temperature elevations secondary to maternal fever, and direct infection of the fetal brain and meninges. Significantly, according to the authors, the results suggest that chorioamnionitis causes birth asphyxia. Limitations of this study included multiple comparisons, potential unidentified confounders, and the fact that the cerebral palsy group was not examined by the investigators.

4. Tilton AH. Injectable neuromuscular blockade in the treatment of spasticity and movement disorders. *J Child Neurol* 2003;18(suppl 1):S50–66.

This excellent review covers the three major methods of neuromuscular blockade for the treatment of spasticity: alcohol, phenol, and botulinum toxin (BTX). In addition to pharmacology, uses, and efficacy, patient evaluation, techniques of administration, drug preparation and dosage, and treatment failure are also discussed. This article is a good reference for all clinicians, and an excellent resource for those who are unfamiliar with BTX.

5. Katz RT. Life expectancy for children with cerebral palsy and mental retardation: implications for life care planning. *NeuroRehabilitation* 2003;18:261–70.

Health care providers may be asked by patient advocates to assist in the planning for long-term needs of severely affected individuals, and estimating the life expectancy of these patients is an important part of that process. With that in mind, the author comprehensively reviews the literature pertaining to the life expectancy of children with cerebral palsy and developmental disabilities. The author summarizes the results of several studies and provides discussion in the text with several tables organized by age or life expectancy, severity of disability, and functional limitations. The large amount of data reviewed is concisely summarized at the end of the article in five important points regarding life expectancy in this patient population.