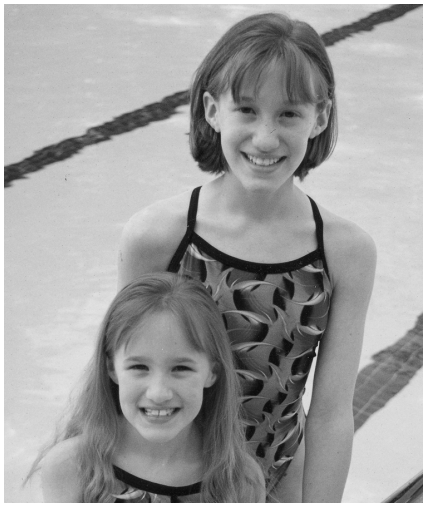
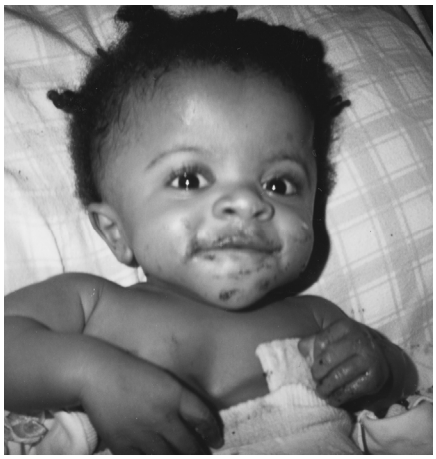
Guide to Osteogenesis Imperfecta





For Pediatricians and Family Practice Physicians

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Guide to Osteogenesis Imperfecta for Pediatricians and Family Practice Physicians

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"The problems faced by children with osteogenesis imperfecta and their families are complex and on several levels: anatomical, medical, adjustment to disability, and social. Some of these problems are formidable and may not be able to be completely solved…" (Cintas and Gerber, *Children with Osteogenesis Imperfecta: Strategies to Enhance Performance*, 2005)

Introduction

Osteogenesis imperfecta (OI) is a genetic disorder commonly known as brittle bone disease. Most physicians will see very few people with this disorder during their careers. This guidebook is therefore an introduction to OI and a reference to help medical professionals with clinical decision-making. It was prepared with the assistance of the Osteogenesis Imperfecta Foundation and specialists in the field of OI.

Recent research has expanded the information available about OI and its treatment. A list of sources of such information has been published at the end of this guide. (See "Resources," page 29.)

Definition

- OI is a heritable condition of connective tissue.
- In most cases, OI is caused by a dominant mutation in the COL1A1 or the COL1A2 genes that encode type I collagen. People with OI have less collagen than normal or a poorer quality than normal.
- Fewer than 10 percent of OI cases are believed to be caused by recessive mutations in other genes in the collagen pathway. Mutations in the genes for prolyl 3-hydroxylase (LEPRE1) and for cartilage-associated protein (CRTAP) have been identified.
- People with OI Types V and VI do not have evidence of mutations in the type I collagen genes.
- The hallmark feature of OI is fragile bones that fracture easily.
- OI affects both bone quality and bone mass.
- In some people, height, hearing, skin, blood vessels, muscles, tendons, and teeth may also be affected.
- OI is highly variable, ranging from a mild form with no deformity, normal stature, and few fractures to a form that is lethal during the perinatal period.
- Treatment availability is expanding.
- People with OI have lifelong medical issues, but they often lead healthy, productive lives.

Occurrence

- It is estimated that 25,000 to 50,000 people in the United States have OI.
- It is estimated that OI occurs once in every 12,000 to 15,000 births.
- OI occurs with equal frequency among males and females and across races and ethnic groups.

Role of the Primary Care Physician

- The physician can help a family place the child's case in perspective.

- He or she can develop a treatment plan to optimize quality of life, encourage peak bone mass development, and emphasize function, independence, and societal integration.
- The physician's office can be a medical home for the child, and the physician can coordinate care with a number of specialists.
- He or she can work with the family to ensure that all medical, psychological, social, developmental, and educational needs are addressed.

Life Span

- Life span varies with the type of OI. (See "Classification," page 5.)
- The mild and moderate forms of OI do not affect life expectancy.
- The progressively deforming OI Type III may reduce life span because of susceptibility to respiratory infection and cardiovascular compromise, but it is increasingly common for people to live into late middle age or their retirement years.
- The most severe form of OI, OI Type II, is also the rarest. It is frequently fatal during the neonatal period. The severe forms of recessively inherited OI are also frequently fatal. Treatments are being studied. They include respiratory support, and, in infants able to breathe without a respirator, the off-label use of bisphosphonates. (See "Drug Therapies – Bisphosphonates," page 15.) Some infants initially thought to have OI Type II are later identified as having severe OI Type III.

Genetics

- The majority of people with OI have a mutation in one of the two genes, COL1A1 or COL1A2, that encode type I collagen.
- More than 800 mutations have been discovered in the COL1A1 and COL1A2 genes, which are located on chromosomes 7 and 17.
- The less common moderate-to-severe forms of OI, Types V and VI, do not appear to involve mutations in a type 1 collagen gene. Specific mutations causing these types have not yet been identified. Candidate genes include those that help control bone development and organization. (See "Type V" and "Type VI," page 9.)
- Fewer than 10 percent of OI cases are believed to be caused by recessive mutations in genes in the collagen pathway. Mutations in the genes for prolyl 3-hydroxylase (LEPRE1) and for cartilage-associated protein (CRTAP) have been identified.
- There are some rare forms of OI for which the genetic cause is still unknown.

Inheritance

- In most families, OI is inherited in an autosomal dominant pattern.
- Often, OI is inherited from an affected parent.
- The mutation will usually be identical within families, but its expression (i.e., the degree of severity and the number of fractures, etc.) may differ among family members.
- Spontaneous new mutations are common, and they account for most cases of OI in children born to unaffected parents.
- New mutations can cause any type of OI, not just OI Type II or III.
- Poor nutrition, exposure to toxins in the environment, and drinking alcohol during pregnancy do not appear to cause these new mutations.

- Recessive inheritance patterns in OI have been described. They are associated with mutations in the genes for prolyl 3-hydroxylase (LEPRE1) and for cartilage-associated protein (CRTAP). One of the mutations in LEPRE1 has been found to occur especially in African-Americans and West Africans.
- Recessive OI and, in some rare cases, parental mosaicism for OI account for recurrence among siblings born to asymptomatic parents.
- Genetic counseling is recommended for asymptomatic parents of a child with OI before any future pregnancies. When a child's OI is caused by a dominant mutation there is a 2 to 5 percent chance with each future pregnancy that the child will have OI. When the cause was parental mosaicism for a dominant mutation, the chance of OI is 10 to 50 percent in each subsequent pregnancy. When a recessive mutation is involved, there is a 25 percent chance of OI with each future pregnancy.
- Genetic testing is available to possibly determine whether or not
  - a parent has a previously undiagnosed case of OI
  - a parent is a mosaic carrier of a mutation for a dominant form of OI
  - parents or siblings are carriers of a recessive form of OI.

Diagnosis, Clinical Features, and Classification

Diagnosis

- Diagnosis is primarily based on clinical evidence.
- It may be difficult to make a clinical diagnosis of the milder forms of OI in infancy and childhood.
- Referral to a specialist, such as a geneticist, orthopaedist, or endocrinologist who has clinical experience treating OI across the full range of OI types, may be necessary.
- Laboratory studies can rule out other conditions, provide information that is useful in medical management, and, in most cases, confirm the diagnosis through mutation identification.

The diagnostic process should include the following steps:
- a medical history, including pregnancy and childbirth information
- a family history
- a physical examination.

X rays: X-ray findings can include osteopenia (low bone density), fractures (new, subclinical, or old-healing), bowing of the long bones, vertebral compressions, and wormian bones in the skull sutures. Wormian bones, which are small bone islands in the skull where normally there is an intact sheet of bone, are seen in approximately 60 percent of people who have OI. They can also occur in infants with several other disorders.

Laboratory testing: Diagnostic tests are available for the dominant and recessive forms of OI. They include:
- Collagen molecular testing -- a deoxyribonucleic acid (DNA)-based analysis of COL1A1 and COL1A2 genes from a blood or saliva sample
- Collagen biochemical testing -- a protein-based analysis of cultured fibroblasts from a skin sample

- Separate studies that utilize a skin biopsy and sequencing of the genes for cartilage-associated protein (CRTAP) and prolyl 3-hydroxylase (LEPRE1) to test for the recessive forms of OI

Identifying an abnormality using any of the above tests establishes the diagnosis.

Regarding laboratory testing, it should be noted:

- It is estimated that greater than 90 percent of mutations that cause the dominant form of OI are detected with DNA analysis.
- Blood tests other than for those for DNA analysis are neither conclusive nor diagnostic for OI.
- Blood and urine tests can rule out conditions other than OI.
- A negative collagen test or DNA test result does not rule out OI.

Dual Energy X-ray Absorptiometry (DXA): The DXA bone mineral density test provides information about bone quantity, not quality. A low reading might be prognostic for a predisposition to fracture, causes of which include but are not restricted to OI. Bone mineral density may be lower than normal in people with any type of OI.

Bone Biopsy: When feasible, a biopsy of the iliac bone can identify all types of OI. A bone biopsy is invasive, requiring general anesthesia. Specially trained personnel must process the sample and read the slides. A child must weigh at least 22 pounds, or 10 kilograms, to be a candidate for the procedure. A bone biopsy may be obtained during orthopaedic surgery.

Clinical Features

OI is a highly variable disorder. A person who has it might exhibit only a few of the common characteristics. Some characteristics are age-dependent. They will not be seen in an infant or young child. Other characteristics are present only in certain types of OI. Furthermore, an infant or young child with a mild form of OI might not have bone deformity.

The clinical features of OI, in addition to fractures, may include the following:

- The sclerae might appear darker than normal, with a blue or gray tint. Although tinted sclerae are a frequently mentioned characteristic of OI, they are seen in only 50 percent of cases. Pale blue sclerae can occur in unaffected children up to 18 months of age. Intense scleral hue and/or its presence past the age of 2 years might warrant further evaluation for OI. In people who do have blue sclerae, the color intensity will vary. It may fade considerably as the child gets older.
- Dentinogenesis imperfecta, characterized by transparent, discolored, and fragile teeth that fracture easily, is evident in approximately 50 percent of people with OI, particularly in those with the severe forms. Dental abnormalities are usually apparent when the first tooth erupts. A child with healthy baby teeth will not develop dentinogenesis imperfecta. The condition tends to run in families.
- Bone malformations can include abnormal rib shape, *pectus carinatum* or *pectus excavatum*, curving of the long bones, vertebral compressions, spinal curves, scoliosis, mild kyphosis, and an abnormal skull shape.
- Osteopenia may be apparent on x ray or with bone density tests.

- The head circumference may be greater than average, or the head may appear large relative to the person's small body.
- The fontanels may close later than usual.
- Wormian bones are present in the skull in approximately 60 percent of people with OI.
- A triangular facial shape is characteristic in the more severe forms.
- Hearing loss may start in the young adult years. It rarely occurs earlier.
- The body may be disproportional. The length of the arms and/or legs, or the child's overall height, may be shorter than expected when compared with unaffected children. The child's torso may be short when compared with his or her arms and legs due to vertebral compression. The child may be barrel-chested.
- Infants may have a low weight for their age. Older children are frequently overweight for their size.
- The skin may feel soft and bruise easily.
- The joints may be lax and unstable and the feet may be flat.
- Most children with OI have decreased lean muscle mass and associated muscle weakness.
- Sensitivity to heat and cold, with increased sweating, may occur in some people with OI.
- Gross motor development may be delayed due to fractures and/or hypotonia. These developmental delays can include self-care deficits, delays in ambulation, and difficulty transferring from wheelchairs.
- The intellect is normal.
- In about 5 percent of all OI cases, exuberant callus formation – which usually follows a fracture or surgical procedure – indicates OI Type V.

Classification

Since 1979, OI has been classified by type according to a scheme developed by David Sillence, M.D. This system is based on mode of inheritance, clinical picture, and radiologic appearance. The OI type descriptions provide some information to the clinician and family about a person's prognosis, but they do not predict functional outcome. It is also important to note that the severity of OI ranges greatly; the different types of OI represent somewhat arbitrary cutoffs along a continuum. As a result, the severity of the disorder may vary significantly among people who have the same type. The OI classification scheme has continued to evolve as new information about OI is discovered.

Type I:

- OI Type I is the mildest and most common form of the disorder. It accounts for 50 percent of the total OI population.
- Type I manifests with mild bone fragility, relatively few fractures, and minimal limb deformities. The child might not fracture until he or she is ambulatory.
- Shoulders and elbow dislocations may occur more frequently in children with OI than in healthy children.
- Some children have few obvious signs of OI or fractures. Others experience multiple fractures of the long bones, compression fractures of the vertebrae, and chronic pain.
- The intervals between fractures may vary considerably.
- After growth is completed, the incidence of fractures decreases considerably.
- Blue sclerae are often present.

- Typically, a child's stature may be average or slightly shorter than average as compared with unaffected family members, but is still within the normal range for the age.
- There is a high incidence of hearing loss. Onset occurs primarily in young adulthood, but it may occur in early childhood.
- Dentinogenesis imperfecta is often absent.
- OI Type I is dominantly inherited. It can be inherited from an affected parent, or, in previously unaffected families, it results from a spontaneous mutation. Spontaneous mutations are common.
- Biochemical tests on cultured skin fibroblasts show a lower-than-normal amount of type I collagen. Collagen structure is normal.
- People with OI Type I experience the psychological burden of appearing normal and healthy to the casual observer despite needing to accommodate their bone fragility.
- The absence of obvious symptoms in some children may contribute to problems at school or with peers.
- Significant care issues that arise with OI Type I include gross motor developmental delays, joint and ligament weakness and instability, muscle weakness, the need to prevent fracture cycles, and the necessity of spine protection. (See "Behavioral and Lifestyle Modifications," page 13.) Children with OI and their parents will need emotional support at each new developmental stage. Family members should carry documentation of the OI diagnosis to avoid accusations of child abuse at emergency rooms.
- The treatment plan should maximize mobility and function, increase peak bone mass, and develop muscle strength. Physical therapy, early intervention programs, and as much exercise and physical activity as possible will improve outcomes.

Type II:

- OI Type II is the most severe form.
- At birth, infants with OI Type II have very short limbs, small chests, and soft skulls. Their legs are often in a frog-leg position.
- The radiologic features are characteristic and include absent or limited calvarial mineralization; flat vertebral bodies; very short, telescoped, broad femurs; beaded and often broad short ribs; and evidence of malformation of the long bones.
- Intrauterine fractures will be evident in the skull, long bones, or vertebrae.
- The sclerae are usually very dark blue or gray.
- The lungs are underdeveloped.
- Infants with OI Type II have low birth weights.
- Respiratory and swallowing problems are common.
- Macrocephaly may be present. Microcephaly is rarely present.
- Infants with OI Type II usually die within weeks of delivery. A few may survive longer; they usually die of respiratory and cardiac complications.
- OI Type II results from a new dominant mutation in a type 1 collagen gene or parental mosaicism. Similar extremely severe types of OI, Types VII and VIII, can be caused by recessive mutations to other genes. (See "Type VII" and "Type VIII," pages 9 and 10.)
- Genetic counseling is recommended for parents of a child with OI Type II before any future pregnancies.
- Significant care issues that arise with OI Type II include obtaining an accurate diagnosis,

getting genetic counseling, the family's need for emotional support, and management of respiratory and cardiac impairments. Infants with OI Type II who can breathe without a respirator and those with severe OI Type III may be candidates for off-label treatment with bisphosphonates. At this time, pamidronate (Aredia*) is the only bisphosphonate that has been studied in infants who have OI. Treatment research is ongoing. (See "Drug Therapies – Bisphosphonates," page 15.)

*Brand names included in this publication are provided as examples only, and their inclusion does not mean that these products are endorsed by the National Institutes of Health or any other Government agency. Also, if a particular brand name is not mentioned, this does not mean or imply that the product is unsatisfactory.

Type III:

- OI Type III is the most severe type among children who survive the neonatal period. The degree of bone fragility and the fracture rate vary widely.
- This type is characterized by structurally defective type I collagen. This poor-quality type I collagen is present in reduced amounts in the bone matrix.
- At birth, infants generally have mildly shortened and bowed limbs, small chests, and a soft calvarium.
- Respiratory and swallowing problems are common in newborns.
- There may be multiple long-bone fractures at birth, including many rib fractures.
- Frequent fractures of the long bones, the tension of muscle on soft bone, and the disruption of the growth plates lead to bowing and progressive malformation. Children have a markedly short stature, and adults are usually shorter than 3 feet, 6 inches, or 102 centimeters.
- Spine curvatures, compression fractures of the vertebrae, scoliosis, and chest deformities occur frequently.
- The altered structure of the growth plates gives a popcorn-like appearance to the metaphyses and epiphyses.
- The head is often large relative to body size.
- A triangular facial shape, due to overdevelopment of the head and underdevelopment of the face bones, is characteristic.
- The sclerae may be white or tinted blue, purple, or gray.
- Dentinogenesis imperfecta is common but not universal.
- The majority of OI Type III cases result from dominant mutations in type I collagen genes. Often these mutations are spontaneous. Similar extremely severe types of OI, Types VII and VIII, are caused by recessive mutations to other genes. (See "Type VII" and "Type VIII," pages 9 and 10.)
- Genetic counseling is recommended for asymptomatic parents of a child with OI Type III before any future pregnancies.
- Significant care issues that arise with OI Type III include the need to prevent fracture cycles; the appropriate timing of rodding surgery; scoliosis monitoring; respiratory function monitoring; the need to develop strategies to cope with short stature and fatigue; the family's need for emotional support, especially during the patient's infancy; and the off-label use of bisphosphonates. (See "Drug Therapies – Bisphosphonates," page 15.)
- It is also important to address difficulties with social integration, participation in leisure activities, and maintaining stamina.
- The treatment plan should maximize mobility and function, increase peak bone mass and

muscle strength, and employ as much exercise and physical activity as possible.

Type IV:

- People with OI Type IV are moderately affected. Type IV can range in severity from relatively few fractures, as in OI Type I, to a more severe form resembling OI Type III.
- The diagnosis can be made at birth but often occurs later.
- The child might not fracture until he or she is ambulatory.
- People with OI Type IV have moderate-to-severe growth retardation, which is one factor that distinguishes them clinically from people with Type I.
- Bowing of the long bones is common, but to a lesser extent than in Type III.
- The sclerae are often light blue in infancy, but the color intensity varies. The sclerae may lighten to white later in childhood or early adulthood.
- The child's height may be less than average for his or her age.
- Short humeri and femora are common.
- Long bone fractures, vertebral compression, scoliosis, and ligament laxity may also be present.
- Dentinogenesis imperfecta may be present or absent.
- OI Type IV has an autosomal dominant pattern of inheritance. Many cases are the result of a new mutation.
- This type is characterized by structurally defective type I collagen. This poor-quality type I collagen is present in reduced amounts in the bone matrix.
- Significant care issues that arise with OI Type IV include the need to prevent fracture cycles; the appropriate timing of rodding surgery; scoliosis monitoring; the need to develop strategies for coping with short stature and fatigue; the family's need for emotional support, especially during the patient's infancy; and the off-label use of bisphosphonates. (See "Drug Therapies – Bisphosphonates," page 15.)
- Family members should carry documentation of the OI diagnosis to avoid accusations of child abuse at emergency rooms.
- It is also important to address difficulties with social integration, participation in leisure activities, and maintaining stamina.
- The treatment plan should maximize mobility and function, increase peak bone mass and muscle strength, and employ as much exercise and physical activity as possible.

Microscopic studies of OI bone, led by Francis Glorieux, M.D., Ph.D., at the Shriners Hospital for Children in Montreal, have identified a subset of people who are clinically within the OI Type IV group but have distinctive patterns to their bone. Review of the clinical histories of these people uncovered other common features. As a result of this research, two types – Type V and Type VI – were added to the Sillence Classification. Regarding these types, it is important to note the following:

- They do not involve deficits of type 1 collagen.
- Treatment issues are similar to OI Type IV.
- Diagnosis requires specific radiographic and bone studies.

Type V:

- OI Type V is moderate in severity. It is similar to OI Type IV in terms of frequency of fractures and the degree of skeletal deformity.
- The most conspicuous feature of this type is large, hypertrophic calluses in the largest bones at fracture or surgical procedure sites.
- Hypertrophic calluses can also arise spontaneously.
- Calcification of the interosseous membrane between the radius and ulna restricts forearm rotation and may cause dislocation of the radial head.
- Women with OI Type V anticipating pregnancy should be screened for hypertrophic callus in the iliac bone.
- OI Type V is dominantly inherited and represents 5 percent of moderate-to-severe OI cases.

Type VI:

- OI Type VI is extremely rare. It is moderate in severity and similar in appearance and symptoms to OI Type IV.
- This type is distinguished by a characteristic mineralization defect seen in biopsied bone.
- The mode of inheritance is probably recessive, but it has not yet been identified.

Recessively Inherited Types of OI (Types VII and VIII):

- Two recessive types of OI, Types VII and VIII, were recently identified. Unlike the dominantly inherited types, the recessive types of OI do not involve mutations in the type 1 collagen genes.
- These recessive types of OI result from mutations in two genes that affect collagen posttranslational modification:
  - the cartilage-associated protein gene (CRTAP)
  - the prolyl 3-hydroxylase 1 gene (LEPRE1).
- Recessively inherited OI has been discovered in people with lethal, severe, and moderate OI. There is no evidence of a recessive form of mild OI. Recessive inheritance probably accounts for fewer than 10 percent of OI cases.
- Parents of a child who has a recessive type of OI have a 25 percent chance per pregnancy of having another child with OI. Unaffected siblings of a person with a recessive type have a 2 in 3 chance of being a carrier of the recessive gene.

Type VII:

- Some cases of OI Type VII resemble OI Type IV in many aspects of appearance and symptoms.
- Other cases resemble OI Type II, except that infants have white sclerae, small heads and round faces.
- Short humeri and femora are common.
- Short stature is common.
- Coxa vara is common.
- OI Type VII results from recessive inheritance of a mutation in the CRTAP gene. Partial (10 percent) expression of CRTAP leads to moderate bone dysplasia. Total absence of the cartilage-associated protein has been lethal in all identified cases.

Type VIII:

- Cases of OI Type VIII are similar to OI Types II or III in appearance and symptoms except for white sclerae.
- OI Type VIII is characterized by severe growth deficiency and extreme under-mineralization of the skeleton.
- It is caused by absence or severe deficiency of prolyl 3-hydroxylase activity due to mutations in the LEPRE1 gene.

Additional Forms of OI

The following conditions are rare, but they feature fragile bones plus other significant symptoms. More detailed information on them can be found in *Pediatric Bone: Biology and Diseases*, Glorieux et al, 2003.

- **Osteoporosis-Pseudoglioma Syndrome:** This syndrome is a severe form of OI that also causes blindness. It results from mutations in the low-density lipoprotein receptor-related protein 5 (LRP5) gene.
- **Cole-Carpenter Syndrome:** This syndrome is described as OI with craniosynostosis and ocular proptosis.
- **Bruck Syndrome:** This syndrome is described as OI with congenital joint contractures. It results from mutations in the procollagen-lysine, 2-oxoglutarate 5-dioxygenase 2 (PLOD2) gene encoding a bone-specific lysyl-hydroxylase. This affects collagen crosslinking.
- **OI/Ehlers-Danlos Syndrome:** This recently identified syndrome features fragile bones and extreme ligament laxity. Young children affected by this syndrome may experience rapidly worsening spine curves.

Differential Diagnosis

- Other medical conditions that share some of the same clinical signs as OI include hypophosphatasia, juvenile Paget's disease, rickets, idiopathic juvenile osteoporosis, some inherited defects in vitamin D metabolism, Cushing's disease, and calcium deficiency and malabsorption.
- Premature infants are at risk for osteopenia during the first year of life.
- Ehlers-Danlos syndrome Types VIIA and VIIB, which are characterized by lax ligaments and loose joints, can also predispose a person to fractures.

Child Abuse

- It is estimated that 7 percent of children with unexplained fractures have an underlying medical condition.
- A child who has a pattern of fractures out of proportion to the reported traumas involved and no other signs of neglect should be evaluated for OI and other medical conditions. According to *Bone Health and Osteoporosis: A Report of the Surgeon General* (2004), "Pediatricians, orthopedists, emergency room physicians, and others who see children with fractures need to consider OI as a possible cause, particularly in cases involving multiple fractures or a family history of fractures."

- Referral to a geneticist, orthopaedist, or endocrinologist who has experience across the spectrum of OI variability may be necessary.
- Mild OI without family history appears similar to nonaccidental injury.
- OI is a clinical diagnosis. Negative results on molecular or biochemical tests do not exclude the condition because some forms of OI result from mutations in genes other than those tested for. Moreover, the tests do not identify all of the people with alterations in the tested-for genes. A positive test result does, however, indicate that a child most likely has OI.
- Family members should carry documentation of the OI diagnosis to avoid accusations of child abuse at emergency rooms.

Medical Management of OI

- Medical management will need to be customized to meet the needs of each child. Coordinated, interdisciplinary care is beneficial. More detailed information about a model interdisciplinary treatment program can be found in *Interdisciplinary Treatment Approaches for Children with Osteogenesis Imperfecta,* Chiasson et al, 2004.
- Specialists may include geneticists, endocrinologists, neurologists, orthopaedists, rehabilitation experts, and otolaryngologists. Speech therapy, nutrition counseling, psychological counseling, and access to adaptive equipment may also be necessary.
- Because OI can compromise respiratory health, parents appreciate it when their child is protected from exposure to other sick children, particularly during respiratory illness season, during visits to the doctor's office.

Role of OI Clinics and Research Programs

- A number of medical centers across the United States and Canada have OI clinics and/or research programs, often as components of genetics or bone dysplasia centers. A comprehensive list of centers and services is available. (See "Resources, Major Clinical Programs," and "Resources, the Osteogenesis Imperfecta Foundation," page 29).
- Children benefit from coordinated interdisciplinary care from physicians who are familiar with OI.
- Information from clinics should be shared with the primary care physician.

Development

- OI does not affect a child's ability to think and learn.
- A child's large-muscle development may be affected by fractures; muscle weakness; abnormal body size, shape, and proportion; misalignment of the long bones and joints; and pain.
- Most children with OI qualify for early intervention services and benefit from physical and occupational therapy.
- Some children require speech therapy to gain control of their oral cavity muscles.
- All children with OI benefit from safe physical exercise involving recreational and rehabilitative activities.

Growth

- Some types of OI are characterized by significantly short stature.
- Discrepancies in leg length can be caused by fractures or problems with growth plates. These discrepancies need to be evaluated by a gait specialist to prevent the child from losing the ability to walk.
- Hip or back pain due to poor alignment is common in all types of OI.
- In infants, especially those with OI Type III, the back of the skull can become flattened due to bone fragility. Lack of head control may also occur. (See "Preventing Head Flattening," page 22.)
- For additional information, consult the height and weight charts in Zeitlin et al, "Height and weight development during four years of therapy." *Pediatrics*, 2003.

Laboratory Findings

- Serum alkaline phosphatase levels may be elevated after a fracture.
- Hypercalciuria may be present in severely affected children. This should be evaluated. Treatment is not necessary unless the child produces kidney stones.
- Nephrocalcinosis may also be present in OI, but it has no impact on renal function.
- Aberrations in thyroid function are not associated with OI.

Treatments

Because there is no cure for OI, treatment focuses on minimizing fractures, the surgical correction of deformity, reducing bone fragility by increasing bone density, minimizing pain, and maximizing mobility and independent function.

Currently prescribed treatments include the following:

- behavioral and lifestyle modifications to avoid situations that may cause a fracture
- orthopaedic surgery
- scoliosis management
- rehabilitation, including water therapy and physical activity
- adaptive equipment and ambulation aids
- weight management.

Treatments currently being investigated include the following:

- oral and intravenous bisphosphonates
- growth hormone therapy.

The following treatments have been found to be ineffective and are no longer prescribed:

- vitamin C
- sodium fluoride
- magnesium
- anabolic steroids
- calcitonin.

Behavioral and Lifestyle Modifications

- Proper techniques for standing, sitting, and lifting will protect the spine.
- Activities that jar or twist the spine, such as jumping and games like crack-the-whip, should be avoided.
- As necessary, modify the home and school environment to accommodate short stature or low strength and to promote independent function.
- Maintain a safe environment. For young children this includes keeping the floor free of obstacles that could cause an accident.
- Develop healthy lifestyle diet and exercise habits to maximize peak bone mass, develop muscle strength, and avoid obesity.

Orthopaedic Management

- The goals of orthopaedic management include fracture care and the prevention or correction of bone deformities.
- Bracing, splinting, and orthotic supports all have a role in management.
- Intramedullary rodding with osteotomy is used to correct severe bowing of the long bones.
- Intramedullary rodding is also recommended for children who repeatedly break the long bone.
- Different types of rods (surgical nails) are available to address issues related to surgery, bone size, and the prospect for growth. The two major categories of rods are telescopic and nontelescopic.
- Telescopic rods are designed to lengthen during growth and thus postpone the need for replacement. Examples include the following:
  - Dubow-Bailey rod
  - Fassier-Duval rod.

  The Fassier-Duval rod is the only FDA-approved rod indicated for use in patients with OI.
- Nontelescopic rods do not expand. They need to be replaced if the child's bone lengthens and begins to bow. Nontelescopic rods may be the only option for children with very short, thin bones. Examples include the following:
  - Kirschner wires (K-wires)
  - Rush rods
  - Williams rods
  - elastic rods.
- Plates and pins or screws are not recommended for the surgical repair of fractures in children with OI. These devices create a short, stiff segment within the bone. The bone is likely to break above or below the plate. Pins and screws do not anchor well in OI bone, and long-term use can lead to thinning of the bone underneath the plate.
- Because immobilization reduces bone density and heavy casts can cause new fractures, orthopaedists with experience in OI recommend using the lightest possible casting materials, immobilizing for the shortest time possible, and limiting the use of the spica cast.
- Bones affected by OI mostly heal at the same rate as healthy bone.
- Delays in fracture healing, such as nonunions, can occur.

- Immobilization due to surgery may increase osteopenia and loss of muscle mass and functional strength. The recovery plan should include strategies for getting the child moving as soon as possible. Even children with mild OI will need physical therapy after fracture or surgery.
- Other surgical considerations include the following:
  - anesthesia risks related to dentinogenesis imperfecta, valvular heart disease, and hyperthermia
  - intubation difficulties
  - the risk of fracture during positioning for surgery
  - skin breakdown
  - the loss of strength due to immobilization.

Detailed information about orthopaedic management, including rodding surgery, can be found in *Interdisciplinary Treatment Approaches for Children with Osteogenesis Imperfecta,* Chiasson et al, 2004.

Musculoskeletal Issues

- Scoliosis is a serious issue for some types of OI. Considerations include the following:
  - The prevalence of spinal deformities among people with severe OI is high.
  - Spine deformities increase with age. Rapid progression is common, and curves should be closely monitored.
  - Bracing is of limited utility. It does not stop curve progression, and it may cause harm in more severely affected children. The use of customized braces for children with mild scoliosis and OI Type I is being studied.
  - A rapidly progressing curve may require fusion surgery.
- Kyphosis affects many children with OI.
- Compression fractures of the spine occur in all types of OI. Families need instruction in how to avoid spine-jarring activities and how to protect the spine.

Rehabilitation, Physical Therapy, Occupational Therapy, and Physical Activity

- Most children with OI benefit from physical activity programs.
- Treatment plans should promote and maintain optimal function. They should include early intervention, muscle strengthening, aerobic conditioning, and, when possible, protected ambulation.
- Infancy offers many opportunities to develop strength and avoid some of the deformities, such as torticollis, that are often seen in children with OI.
- Positioning is critical to avoid contracture and malformation. It is important not to leave a child with OI in a fixed position, either recumbent or sitting, for long periods.
- Immobilization reduces lean muscle mass and cardiovascular fitness, and it causes bone density to decline rapidly.
- Postfracture therapy is necessary to reduce the effects of immobilization on bone density and strength.
- The goal of physical therapy should be to improve function, fitness, and independent movement.

- Exercise should be prescribed based on the specific strengths and needs of each child. The focus should be on posture and stamina.
- Recreational activity can be a source of fun, socialization, and physical benefit to children with OI.
- Swimming and water therapy are highly recommended.
- A more detailed discussion of physical activity and OI can be found in *Children with Osteogenesis Imperfecta: Strategies to Enhance Performance*, Cintas and Gerber, 2005.

Drug Therapies – Bisphosphonates

The class of drugs called bisphosphonates are potent inhibitors of bone resorption. They are currently approved by the U.S. Food and Drug Administration (FDA) for the prevention or treatment of osteoporosis, Paget's disease of bone, and bone loss related to some cancers and cancer treatments. No drug in the bisphosphonate class has received an indication for use in the treatment of OI, but some physicians prescribe these drugs off-label for people with OI. Research started in the 1990's continues today into the use of these drugs in OI treatment and other bone diseases.

Bisphosphonate Research Summary:
Current knowledge about bisphosphonate use in OI can be summarized as follows:

- The benefits of bisphosphonates as reported in the medical literature include fewer fractures, improved bone density, normalization of diaphoresis, and pain reduction.
- The combination of bisphosphonates and physical therapy has been reported to increase mobility in people with OI.
- More severely affected infants and children seem to benefit the most from bisphosphonate treatment.
- The maximum benefit of bisphosphonate treatment appears within the first 3 to 4 years of treatment.
- The drug effect is growth dependent, so the younger the patient, the more striking the response.
- It is recommended that all children receiving a bisphosphonate be enrolled in an Institutional Review Board (IRB)-approved study and receive regular monitoring. When enrollment in an IRB-approved study is not possible, physicians are urged to correspond with the primary investigator of a study so that dosages and monitoring are appropriate for the child's age and type of OI.
- Most studies of bisphosphonate treatment for OI enroll children who have a diagnosis of OI Type III or IV or who have had four major fractures in 2 years, but the criteria vary. At this time, there is no evidence-based data to recommend treatment with bisphosphonates for people with mild OI and infrequent fractures.
- Bisphosphonate treatment can begin in early infancy, but severely affected infants may experience respiratory problems during the first infusion.
- Short-term side effects might include an acute phase reaction with flu-like symptoms after a first bisphosphonate infusion, gastrointestinal upset from oral bisphosphonates, and weight gain.
- Because of potential risks to the fetus, bisphosphonates are not recommended for women who are pregnant or who wish to become pregnant.

Areas for Additional Bisphosphonate Research:
Research is ongoing into a number of important topics related to bisphosphonate treatment for children with OI, as summarized below:

- Although increased bone mineral density is a frequent response to bisphosphonate treatment, not all treated people experience a subsequent decrease in fracture rate.
- The optimal dosing schedule and length of treatment have yet to be determined. Researchers are investigating the effects of lower dosages, drug holidays after 3 to 5 years, and a gradual program of tapering off.
- The long-term effects of bisphosphonates on the bones of growing children include thickening of cortical bone. This issue and others have not yet been fully studied. Issues currently being studied include thickening of cortical bone, risks related to long-term disruption of the bone turnover cycle, and the possible accumulation of bone microdamage.
- There is a need for more controlled studies of bisphosphonate treatment for OI to corroborate information from observational studies.
- Research on the following topics continues:
  - The possibility that buildup of bisphosphonates within the bone may result in hyperdense but fragile bones.
  - The causes of delayed osteotomy healing in some children during bisphosphonate treatment.
  - The increased fracture risk in untreated bone when treatment is stopped while a child is still growing.

Bisphosphonates and Osteonecrosis of the Jaw:
Osteonecrosis of the jaw (ONJ) has been reported in adults treated with bisphosphonates. Most cases involved patients with cancer diagnoses who received intravenous bisphosphonate treatment at dosages significantly higher than those used to treat OI. In many of these cases, dental surgery triggered the ONJ. To date, no cases of ONJ have been reported among children and teens treated with bisphosphonates. However, until more information is available, several precautions are suggested:

- When possible, schedule dental surgery prior to starting bisphosphonates.
- Consider a course of antibiotics prior to the dental surgery.
- Do not resume bisphosphonate treatment until after the surgical area has healed.
- It may be prudent to defer extractions of third molars until more information is available.

Additional resources regarding bisphosphonate treatment for children with OI include *Effective Practices in Clinical Care for Osteogenesis Imperfecta* (OI Foundation, 2007) and *Interdisciplinary Treatment Approaches for Children with Osteogenesis Imperfecta* (Chiasson et al, 2004).

Drug Therapies – Growth Hormone

- Researchers at several medical centers are studying growth hormone treatment for OI.
- Results have been variable.
- At this time, there are no standard guidelines for use.

Drug Therapies – Teriparatide (Synthetic Parathyroid Hormone)

- Teriparatide (Forteo) is not appropriate for children due to the risk of bone cancer. It is being studied as a treatment for adults.

General Clinical Findings and Implications for Medical Management

Cardiovascular

- The incidence of congenital malformations in children with OI is similar to that in the unaffected population.
- The cardiovascular manifestations most often seen in people with OI include aortic valve disease and mitral valve prolapse.
- Valve replacement has been successfully performed in people with OI.
- Specific mutations in collagen genes may predispose people to aortic aneurysm.

Connective Tissue

- Increased capillary fragility causes a tendency to bruise easily.
- Decreased platelet retention and reduced factor VIII R:Ag has been noted in people with OI.
- The skin of people with OI is stiffer and less elastic than normal. People with OI may be prone to scars from sutures.
- People with OI have reduced muscle strength. The problem may be significant in people with the moderate and severe forms of OI.
- Laxity is common in OI. It can lead to frequent sprains and dislocations of the hips, shoulders, and radial heads.
- Flat feet are common in OI.
- Hernias may be present at birth. They occur more frequently in people with OI than in unaffected children.

Endocrine

- Growth hormone deficiency is rare among children with OI.
- A hypermetabolic state is common in OI. Symptoms include the following:
  - excessive diaphoresis
  - increased oxygen consumption
  - elevated thyroxine levels.
- Young women with OI may start menstruating later than unaffected women.

Eyes and Vision

- Scleral thickness is normal in OI Type I.
- The sclerae may be thin in the other types of OI.
- Scleral color is related in part to lucency, but it is also related to the way the abnormal matrix of the sclera scatters certain light wavelengths.
- Corneal thickness is reduced in all types of OI.

- Arcus corneae may be seen in children with OI Type I, but it does not seem to be associated with hypercholeserolemia.
- The reported incidence of myopia is higher in people with OI than in the unaffected population.

Gastrointestinal

- Constipation is common in OI.
- Protusio acetabuli (pelvic malformation) and pelvic deformities contribute to constipation in severely affected children.

Hearing

- Due to structural and bone abnormalities of the ear bones, people with OI often develop hearing loss by the third decade of life.
- Other abnormalities that can affect hearing include lopped pinna, notching of the helix of the pinna, rosy flush of the medial wall of the middle ear, and vestibular problems.
- The pediatrician should regularly check the hearing of a child with OI.
- A formal hearing assessment by a specialist who has experience in evaluating children should take place at age 3 or 4 years, or before starting school. The child should thereafter be assessed every 3 years.
- Children with borderline hearing may need yearly testing.
- A family history of hearing loss and frequent sinus and/or ear infections may predispose a child with OI to early hearing loss.
- Children and families will benefit from instruction about techniques that can protect their hearing.

Medication

- Titrate medication dosage to a child's weight, not age, even with older children and teens.
- Some nonsteroidal anti-inflammatory drugs have been linked to retarded bone healing after fracture.
- Minimize the use of drugs that contain steroids because of their negative effect on bone metabolism. (They can cause secondary osteoporosis.)

Neurological

- Basilar invagination of the skull may be seen in children with the more severe forms of OI. Basilar invagination is a potentially fatal complication of OI. Its incidence is unknown. Several studies suggest that when symptoms are present, they do not always worsen.
- Hydrocephalus has been reported in some children with severe forms of OI. An enlarged head may not be a sign of true hydrocephalus, and it may not require shunting.

Nutrition

- Children with OI need a balanced diet that contains adequate water, fiber, calcium, and vitamin D calibrated to their age and size.

- To help them avoid obesity, children with limited mobility may benefit from nutrition counseling.

Pain

- It is a myth that children with OI feel less pain than other patients.
- Bone pain can be significant and chronic.
- Acute fracture care should include adequate pain relief.
- Infants and children with chronic and acute pain, especially from femur fractures, will often require pain medications more powerful than ibuprofen for short periods of time.

Renal Involvement

- Hypercalciuria is common in moderate and severe OI. Kidney stones affect only an estimated 20 percent of people with OI who have the condition.
- High-dosage calcium supplementation may contribute to kidney stones.

Respiratory Function

- Decreased chest volume and deformities may lead to restrictive pulmonary disorder in severe cases of OI.
- Pulmonary complications can occur due to rib fractures, kyphoscoliosis, muscle weakness of the chest wall, heart valve disorders, and chronic bronchitis or asthma.
- Lung collagen abnormalities have a negative impact on lung function.
- Respiratory complications, including pneumonia, are a significant cause of death among the OI population, especially among those with OI Type III.
- Supplemental oxygen, bilevel positive airway pressure, or bronchodilators for asthma may be indicated.
- Even when not caused by OI, lung problems can be more severe in people who have OI of any type.
- People with OI of any type have higher rates of asthma and pneumonia than people who do not have OI.

Teeth

- Approximately 50 percent of children with OI have dentinogenesis imperfecta.
  - The severity of dentinogenesis imperfecta is not related to the severity of the child's skeletal issues.
  - The severity may differ among affected members of the same family.
  - Primary teeth are always more significantly affected than permanent teeth.
  - Caps may be required to prevent the primary teeth from breaking.
- Malocclusion is common.
- Orthodontic treatment is possible.
- Orthognathic surgery may be necessary due to hypoplastic maxilla and changes in the position of basal bones.

General Health Care Issues

- The general health care needs of people with OI are the same as in the general population.
- Typical childhood illnesses can be expected.
- Take precautions to avoid causing a fracture when performing physical examinations.
- Medication dosages should be titrated to body weight, not age, even in young adults.
- Ear infections may be more common in children with OI than in their unaffected peers. These infections should be treated to prevent hearing damage.

Obtaining a Blood Pressure Measurement

- Blood pressure cuffs may cause fractures in people with OI.
- Do not use an automatic blood pressure cuff.
- If possible, avoid taking the measurement on an arm that has repeatedly fractured or is bowed.

Immunizations

- There are no contraindications. Children with OI can receive the same immunizations as unaffected children.
- Some children with OI, due to respiratory compromise and the risk of cough-induced rib fractures, may benefit from pneumonia and influenza vaccination.

Respiratory Infections

- Children with any type of OI have a general predisposition to respiratory infections.
- Respiratory infections may be more serious in children with OI Type III.

Cardiopulmonary Resuscitation

- There are no contraindications for cardiopulmonary resuscitation.
- Adjust the force for compressions to achieve desired depth.
- Children with OI are likely to require less forceful compressions than unaffected children.

Screenings

- Routine screenings for vision and hearing are appropriate.
- By the time a child with OI is age 10, additional hearing testing by an audiologist with experience evaluating children may be required. Baseline audiologic testing before entry into school has been recommended.
- Scoliosis screening should start at an early age.
- Bone density testing may be required if the child participates in a research protocol. A baseline test as a young adult or when a new course of treatment is started is informative.

Weight

- Weight should be closely monitored because obesity presents additional challenges to the skeleton.

- Nutrition counseling may be beneficial, especially for children with short stature and reduced ambulation.

Infant Care

Bedding

- A standard crib mattress is most suitable.
- Waterbeds and soft bedding should not be used.
- A gel pad may be necessary to protect the back of the skull.

Diapering

- When diapering an infant with OI, do not lift the infant by the ankles. It could cause a fracture.
- Slide one of your hands under the infant's buttocks to lift him or her and use the other to remove and replace the diaper.

Exercise and Physical Activity

- A program of graduated physical activity is necessary during infancy.
- Bath time allows children with OI to experience movement in a comfortable environment.
- Carrying an infant with OI on a pillow is no longer recommended.
- Infants should be repositioned frequently during the day. Beneficial positions for an infant with OI include being held, carried, held on a caregiver's shoulder, and side lying.
- Detailed information about appropriate activities and safety precautions for infants is discussed in *Children with Osteogenesis Imperfecta: Strategies to Enhance Performance* (Cintas and Gerber, 2005).

Feeding

- Breast milk is an excellent source of calories for most infants, including those with OI. Babies without severe OI should be capable of breastfeeding.
- Some babies with OI display a weak sucking reflex and may require small, frequent feedings.
- Infants with severe forms of OI may have difficulty breathing and/or swallowing which will impair their ability to eat.
- The combination of small stature, feeding problems, and slow growth may be mistaken for failure to thrive.
- Burping an infant with OI should be done very gently, with soft taps, and possibly with padding over the hand, or by gently rubbing the baby's back.
- Older infants and toddlers may require a food program designed by a clinical nutritionist or an oral motor therapist to help them make the transition to soft foods.

Constipation

- Medications, excessive perspiration, and pelvic malformation can contribute to a tendency toward constipation.

Handling Suggestions

- When handling an infant with OI, all movements should be slow, methodical, and gentle.
- Never push, pull, twist, bend, apply pressure to, or try to straighten an infant's arms or legs.
- Infants with OI should not be picked up under the axillae or around the rib cage. Such actions can cause rib fractures. Instead, you should support the infant's head and trunk with one hand, while your other hand supports the buttocks.
- When holding an infant with OI, keep your fingers spread apart to provide a wider base of support and an even distribution of support pressure.
- When lifting the baby for feeding, dressing, or diapering, apply support to the broadest possible area along the buttocks, back, and head.
- Infants with fractures may be immobilized with a cast or splint to reduce motion and provide stabilization. Such infants must not be placed prone on their stomachs because suffocation can occur.
- Care should be taken when changing the infant's clothing, bedding, or bandages to protect his or her arms, wrists, fingers, legs, and ankles.
- When dressing the infant, bring garments over the infant's limbs; do not pull the limbs through sleeves or pants' legs. Pulling, twisting, or getting a limb caught in clothing can cause fractures.
- It is important that babies with OI receive affection and that they are held and touched by their parents and other caregivers.
- Infants can be carried against the caregiver's shoulder. The caregiver should bend down to pick up the infant from a flat surface rather than bring the infant all the way up to adult height before positioning him or her against the caregiver's own trunk and shoulder. Regularly alternate which shoulder you use to support the infant to encourage the infant to develop different neck muscles.
- Once infant has achieved head and neck control, he or she can be carried facing forward, against the caregiver's chest. Place one hand around the child's chest and another under the buttocks.

Preventing Head Flattening

- All infants with OI have soft skulls.
- To prevent skull malformations, every effort should be made to reduce pressure on the back of the head. The following strategies are beneficial:
  - Put gel pads under the infant's head when he or she is on her back.
  - Position the infant in a propped, side-lying position.
  - Frequently change the infant's position throughout the day.
  - Carry the infant on your shoulder or in an approved sling carrier.
  - Avoid leaving the infant in a car seat for long periods.
- Helmets have been used in some infants who have OI, but they are not universally recommended. In severely affected infants, the additional weight of a helmet may make the already challenging task of gaining head and neck control even more difficult.

Pain

- Pain due to fracture, particularly femur fracture, must be controlled. Infants may need stronger medications than acetaminophen or ibuprofen.

- Infants and children experiencing chronic pain may be fussy, which should not be confused with colic, and they may resist moving the sore body part or appear lethargic.
- Infants cannot localize the pain; fussiness may be a sign of fracture.
- Splinting or wrapping a suspected fracture offers relief.
- Aches can be relieved by a warm bath.

Car Seats

- An approved car safety seat geared to the child's weight and his or her ability to sit up is appropriate.
- A padded washable cover for the seat is a good idea, but it is unsafe to add extra padding that was not provided by the seat manufacturer.
- Other important car seat features include a well-padded harness and a head-hugger support pillow.
- Some hospitals or local Easter Seals centers loan car seats to children who are in a spica cast. Some standard car seats can also accommodate a spica cast.
- Some severely affected infants with OI may require a car bed.

Psychological, Emotional, and Social Support

- Coping with and adjusting to having a child with OI is stressful for families. The stress of having a baby with a serious medical condition can strain the family's resources and lead to postpartum depression in the mother.
- Getting in touch with other parents of children with OI can provide emotional support. (See "Resources, the Osteogenesis Imperfecta Foundation," page 29.)
- Families will need referrals to a variety of medical specialists.
- At different times, families will need referrals to social service and resource organizations in the community.
- Siblings of the affected child also may need support.
- Addressing issues regarding self-esteem, sexuality, and peer integration is important for the overall health of the older child or teenager with OI.
- The mental health issues of children with OI are similar to those of other children with chronic health conditions. They include the following:
  - depression
  - the fear of an early death
  - the fear of strangers
  - anxiety in crowds.

School

- Families may need assistance providing a child's school with information about OI. Such information should include the following:
  - OI does not cause an intellectual deficit.
  - The school's physical environment may need to be adapted for the child with OI.
  - The physical education program may need to be adapted for the child with OI.

- It is important to let teachers and school administrators know that while the child has a chronic medical condition, he or she still has the same need for intellectual development and social interaction as other students.
- The physician may be asked to comment on whether an aide is needed and whether certain school activities, such as those related to the physical education program, are safe for the child with OI.
- Children with OI need an Individualized Education Program or a 504 plan that can be adapted as changes are called for.
- Teacher resources include a teacher's guide for the book *Jason's First Day!* (OI Foundation, 2004) and a brochure and DVD titled *Plan for Success* (OI Foundation, 2006, 1999).

Transition to Adult Care

- Like other older children and teens, children with OI need age-appropriate information about sexuality and childbearing.
- Information about the benefits of making healthy lifestyle choices – such as not smoking, not abusing alcohol, and maintaining a healthy weight – are as important for young people with OI as for their unaffected peers.

Physicians can help young people with OI transition from pediatric to adult care by taking the following steps:

- Encourage older children to be their own advocates. They can speak to health care providers directly and provide their own medical history.
- Provide the family with a referral list of physicians in the community who are familiar with OI. (See "Resources, the Osteogenesis Imperfecta Foundation," page 29.)
- Be aware of insurance requirements so your office can work with the family to facilitate a transition between insurance carriers, if necessary.

Research

- Ongoing research is exploring the use of bisphosphonates for infants, children, and adults with OI. (See "Resources, Major Clinical Programs," page 29.)
- Growth hormone therapies, especially for OI Type I, are being studied in animals and in humans in limited clinical trials.
- Gene therapies are also being studied.
- The NIH studies the natural history of OI in individual patients. The NIH also sponsors a series of research protocols in OI. (See "Resources, Major Clinical Programs," page 29.)
- The OI Registry, a joint project of the OI Foundation and the OI Clinic at the Kennedy Krieger Institute in Baltimore, Maryland, is a confidential database of information about people who have OI. Registry participants are volunteers. This database is available to researchers who obtain Institutional Review Board and registry approval. Parents can register a child with OI in this project by contacting the OI Foundation. (See "Resources, the Osteogenesis Imperfecta Registry," page 30.)
- Additional basic and clinical research is ongoing at different centers around the world, including those participating in the Linked Clinical Research Center program sponsored by the OI Foundation and the Children's Brittle Bone Foundation.

Myths

Myth: A baby with OI should always be carried on a pillow and discouraged from moving.
Fact: Although there are handling techniques and precautions, it is in the child's best interest to be held and touched and to explore independent movement to the greatest extent possible. Immobility increases bone loss and decreases muscle mass, leading to weakness, bone fragility, and more fractures.

Myth: Fractures caused by OI can be easily distinguished from those caused by child abuse.
Fact: Children with OI can have all types of fractures, including spiral, rib, skull, incomplete, and displaced fractures. Distinguishing OI fractures from child abuse requires a thorough assessment by a medical professional who is familiar with the full range of OI characteristics.

Myth: OI only affects the bones.
Fact: Though fragile bones are the hallmark of OI, other medical problems, including loose joints, early hearing loss, brittle teeth, respiratory problems, and easy bruising, are also part of the disorder.

Myth: OI is a childhood disorder; people grow out of it by their teens.
Fact: OI is a genetic disorder that is present throughout a person's lifetime. The frequency of fractures may decrease after puberty, when growth stops. Later, it may increase again in women with the onset of menopause and in men due to age-related changes in their endocrine system.

Myth: People with OI are diagnosed at birth.
Fact: OI Type I, the most common and mildest form of OI, is rarely diagnosed at birth unless a parent has OI. In fact, some very mild cases are only diagnosed when a person has a child with OI Type I, and a review of the person's medical history reveals a pattern of fractures and other features of OI. OI is primarily a clinical diagnosis. Collagen studies and/or DNA analysis can identify the mutation and confirm the clinical diagnosis. Negative results on these tests do not eliminate the diagnosis of OI.

Myth: People who have OI cannot have children.
Fact: OI does not affect fertility. Many men and women who have OI have children. Some women who have OI may experience pregnancy complications due to skeletal problems. It is important that all young people with OI receive information about their condition and reproductive health.

Myth: All children of a parent who has OI will have OI.
Fact: When one parent has a dominantly inherited type of OI, there is a 50 percent chance with each pregnancy that the child will have OI. There is a 50 percent chance that the child will not have OI. In the rare instances where OI is transmitted as a recessive trait, parents are healthy carriers and their children have a 25 percent chance to be affected and a 50 percent chance to be carriers.

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Resources

Major Clinical Programs

OI Program at the NIH, Bethesda, MD
For information regarding clinical trials at the NIH, call (301) 496-0741 or e-mail oiprogram@mail.nih.gov.

OI Program at the Kennedy Krieger Institute, Baltimore, MD
This program is the largest OI clinic in the United States. It offers interdisciplinary care for children and adults and is associated with Johns Hopkins Hospital. For information, call (443) 923-2704.

OI Interdisciplinary Clinics at the Shriners Hospitals for Children (United States and Canada)
For information about Shriners Hospitals in the United States and Canada, visit www.shrinershq.org.

For information regarding OI treatment or clinical trials at the Shriners Hospital for Children in Montreal, Canada, contact (514) 282-7158 or visit the Web site at www.shriners-genetics.mcgill.ca. This hospital has a large treatment and research program for children.

The OI Foundation's Directory of OI Clinics provides profiles of more than 40 clinics, bone dysplasia programs, and research institutions in the United States, Canada, and England. (This directory is available in print from the OI Foundation or you can view it on the Foundation's Web site at www.oif.org.)

The Osteogenesis Imperfecta Foundation

- The mission of the OI Foundation is to improve the quality of life for people affected by OI through research to find treatments and a cure, education, awareness, and mutual support.
- The OI Foundation provides education materials for families and health care providers. Many of the topics mentioned in this guide are covered in greater depth in other publications. Call or visit the foundation's Web site for a list of current publications.
- The OI Foundation offers an "Information on Demand" service. Trained staff members provide medically verified answers to thousands of questions a year. Physicians can also be put in touch with a member of the Foundation's Medical Advisory Council if a consultation is requested.
- The OI Foundation has links to OI family associations in countries outside the United States.
- Primary care physicians may wish to register by phone or e-mail for a no-charge subscription to the OI Foundation quarterly newsletter, *Breakthrough,* and to receive monthly e-news letters.
- Contact the OI Foundation:
  - Telephone: (800) 981-2663 or (301) 947-0083
  - E-Mail: bonelink@oif.org
  - Web site: www.oif.org

- Many of the OI Foundation's publications and materials can be viewed and printed from the Web site. These materials also can be ordered from the OI Foundation through the Web site store or by calling or e-mailing the foundation. New materials are added on a regular basis.

The Osteogenesis Imperfecta Registry

People who have been diagnosed with OI can volunteer to join the OI Registry. This confidential database is jointly sponsored by the OI Foundation and the OI Clinic at the Kennedy Krieger Institute. The registry's purpose is to maintain patient contact information, to collect information descriptive of OI, and to encourage research. For more information, visit the OI Foundation's Web site or the OI Clinic at the Kennedy Krieger Institute's Web site at www.osteogenesisimperfecta.org.

Community Organizations and Resources – Web Sites

- American Academy of Pediatrics – www.aap.org
- Easter Seals – www.Easter-Seals.org
- Family Voices – www.familyvoices.org
- National Dissemination Center for Children with Disabilities (NICHCY) – www.nichcy.org
- Air Charity Network – www.aircharitynetwork.org, or call (877) 621-7177.

Biochemical and DNA-Testing Providers

The length of time before you receive results and the cost per test varies. Contact the providers below for more information.

National Institutes of Health, Bethesda, MD
Bone and Extracellular Matrix Branch
Collagen testing for dominant and recessive mutations for children and families in an NIH study
Phone: (301) 496-0741
Web site: www.oiprogram.nichd.nih.gov
E-mail: oiprogram@mail.nih.gov or bemb@mail.nih.gov
Testing offered on a case-by-case basis.

University of Washington, Seattle, WA
Collagen Diagnostic Laboratory, Department of Pathology
Collagen testing and DNA sequencing
Phone: (206) 543-0459
Web site: www.pathology.washington.edu/clinical/collagen

Tulane University, New Orleans, LA
Matrix DNA Diagnostics Laboratory
DNA sequencing
Phone: (504) 988-7706
Web site: www.som.tulane.edu/gene_therapy/matrix/matrix_dna_diagnostics.shtml

Baylor College of Medicine, Houston, TX
Medical Genetics Laboratories
Testing for Recessive OI (DNA Analysis – CRTAP Sequencing)
Phone: 1-800-411-4363
Web site: www.bcm.edu/geneticlabs

Athena Diagnostics, Inc., Worcester, MA
DNA analysis
Phone: (800) 394-4493
Web Site: www.AthenaDiagnostics.com

Shriners Hospital for Children, Montreal, Canada
Genetics Unit
Collagen testing and DNA analysis for patients
Phone: (514) 282-7158
Web site: www.shriners-genetics.mcgill.ca

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