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Proceedings Article

Abstracts from the 5th Baltimore Clinical Meeting on Osteogenesis Imperfecta

6th - 8th November, 2013, The Westin Baltimore-Washington International Airport

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Conference Coordinators:

Tracy Hart, Executive Director, the Osteogenesis Imperfecta Foundation, and Charlene Waldman

Introduction: An Update on Managing Clinical Issues in Osteogenesis Imperfecta

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Osteogenesis Imperfecta or brittle bone disease (OI) affects approximately 25 to 50,000 individuals in the US: it qualifies as a "rare disorder" under NIH guidelines. Until recently, OI has been associated with mutations affecting the synthesis of type I collagen alpha chains. However, interest in OI has surged as new technology has uncovered mutations affecting several genes, some of which are in the collagen metabolic pathway, while others are not. As a consequence, the number of OI clinical types has increased from the original types I-IV proposed by David Sillence in 1979, to 15 OI "types" currently listed in OMIM (Online Mendelian Inheritance in Man). The Sillence types are dominantly inherited; several of the recently described types are recessively inherited and are listed as new OI types based on the specific mutation rather than on distinctive clinical features.

However, while the genetics of OI has shown great progress, concern exists that the clinical approach to the individual with OI, child or adult, has tended to lag. Specifically, there is concern that useful information about the clinical management of the OI patient should be more readily available to the practitioner. To address this problem, The 5th Baltimore Clinical Meeting on Management Issues in Osteogenesis Imperfecta was held November 6-8, 2013, sponsored by the Charitable and Research Foundation and the Osteogenesis Imperfecta Foundation. The Proceedings presented here cover a variety of clinical issues related to the evolution of diagnosis and treatment in the management of the individual with OI.

Several overarching issues are worthy of comment:

- Although progress has occurred OI *in vitro* stem cell technology and DNA modification, data is lacking about stem cell engraftment and how to improve bone matrix *in vivo*. (D. Deyle, D. Rowe).
- In the realm of dental care, orthodontics may be required before and after orthognathic surgery to move the jaw so teeth can fit better or at all (J. Hartsfield).
- Hearing tests should begin at school age.
- Bone anchored hearing aids are clearly not an option for OI but cochlear implants can provide great results with modifications (D. Vernick, J. Pillion)
- Pregnancy in OI may be high risk for individuals with any cardiac dysfunction particularly those with diminished ejection fractions (D. Krakow)
- The association of skin disorders in OI requires additional study (A. Chien)
- Not only does valvular and aortic disease occur in OI, but arterial dissection may also occur (J. Shapiro).
- Structural cardiac dysfunction from abnormal collagen and the relationship of cardiac disease in OI similar to that in Marfan syndrome is discussed as is the surgical approach to the patient with OI vascular disease. (D. Judge, D. Cameron).
- Separating restrictive versus intrinsic pulmonary disease in OI is a challenge (R. Sandhaus)
- Management of constipation and abdominal pain can provide challenges for the individual with OI (J. Clarke).
- The orthopedic approach including issues related to rodding is presented (P. Sponseller, P Esposito, P Smith, P. Kahnuja).
- An approach to physical medicine and rehabilitation therapy which are underutilized in OI children and adults is presented (L. Drefus, C. Joseph).
- Treatment of OI children with intravenous bisphosphonate has had salutary effect in many children, decreasing fractures and pain and increasing mobility (F. Rauch, E. Rush). Although the administration of zoledronic acid, a very powerful bisphosphonate, is logistically easier than administering pamidronate, the effect of the two agents on fracture incidence is similar. Oral bisphosphonate agents have not been shown to be consistently effective in children (L. Ward). Not all children continue to respond to bisphosphonate therapy (J. Shapiro).

The Future of Stem Cell Treatment in OI

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Stem cells therapy is an attractive regenerative medicine approach to treating osteogenesis imperfecta (OI). Normal bone-forming cells could be transplanted into the bones of OI patients, replace the abnormal osteoblasts, produce normal collagen and improve bone function. We have demonstrated that adeno-associated viral (AAV) gene targeting vectors can disrupt the mutant collagen genes in mesenchymal stem cells (MSCs) which can then produce normal collagen and form bone. In addition, we have shown that a combination of gene targeting and induced pluripotent stem cell (iPSC) derivation can be used to generate a population of patient-specific, expandable, bone-forming cells with normal collagen expression. While these results are encouraging, many challenges including stem cell engraftment, cells for transplant, and methods of transplantation still remain before stem cell therapy can be used as an effective treatment for OI.

The Future of Stem Cell Treatment in OI

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Because advances in genetic engineering make the possibility of gene correction of an OI-causing mutation feasible, the question of how to deliver the corrected autologous cells back to the affected individual needs to be ad-

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dressed. Although there are numerous reports of systemic and local injection of mesenchymal derived cells leading to improved skeletal health, the direct demonstration that donor derived osteoblasts that are generating a donor derive bone matrix is still lacking. Our research group has been developing histological tools based on GFP reporter transgenic mice to directly answer these important questions. In a murine model system, the major observations we have made include:

1. Cells with osteoblast progenitor potential do not circulate either by direct injection, after bone marrow transplantation or from a parabiotic partner.
2. The cells that do circulate and become associated with the bone surface are myeloid in nature and many are TRAP positive.
3. The cells that attach and grow out from a bone marrow culture (not the non-adherent cells) do have *in vivo* osteogenic potential when directly injected into the marrow space.
4. The same cell will participate in a model of skeletal repair such as a calvarial defect or a long bone segmental defect.
5. When normal osteoprogenitor cells are transplanted into the marrow space of an OIM animal, the donor cells engraft and make a normal matrix in the regions that are populated by the donor cells.
6. Methods to enhance engraftment throughout the entirety of the endosteal bone need to be developed to make local cell therapy a realistic possibility.

However, gene correction will probably have to be performed on iPS cells because the cell selection requirements of this technology will destroy the osteogenic properties of adult derived progenitor cells. The following illustrate some of the histological tools we have developed to test the effectiveness of corrected iPS cells for bone engraftment and bone matrix formation.

1. Mice capable of long-term human cell engraftment (NSG) have been modified to carry a GFP reporter to mark the murine contribution to a human cell transplant.
2. Adult human bone marrow stromal cells are capable of forming human bone in this model, but the cells lose their osteogenic potential with repetitive passaging.
3. Osteoblast-restricted GFP reporters can be inserted into iPS cells to clearly distinguish human and mouse bone that can form in a defect repair model.
4. Although patient specific bone and cartilage can be generated in the repair defects, the tissue does not remodel and become incorporated into the defect to the same degree as observed from human adult MSCs. Continued modifications of the *in vitro* cell culture protocol that generates the pre-implantation progenitor cells will be necessary. The objective is to obtain cells that resemble primary adult MSCs, which do appear to differentiate into a tissue that remodels and incorporates into host bone.

While these developments in genetic engineering and stem cell biology are encouraging, their eventual used in a human clinical setting is many years away. For the clinicians who see OI patients regularly, we hope that you will demand an unequivocal preclinical demonstration of feasibility before any plans for human studies are initiated.

Dental Issues, Emerging Research

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The pleiotropic effect of OI often involves the dentition and craniofacies, with approximately half of those with OI also having dentinogenesis imperfecta (DI). The incidence of DI is greater in the more severely affected viable class types (VI and III), which also tend to express the more severe effect on craniofacial growth. Denticles and abnormal dentin are constantly laid within the pulp. This process is rapid, and pulps of the DI teeth seem to achieve total obliteration before adulthood. There are other dental abnormalities in addition to DI, including impacted teeth. There is also a trend that cranial base anomalies are more common in patients who also have dentinogenesis imperfecta. The alteration in craniofacial growth starts with the cranial base, and extends to hypoplasia of the maxilla and relative prognathism of the mandible. This typically develops into a negative anterior overjet and a Class III malocclusion. Posterior open bites also occur, which are extremely resistant to treatment. Orthognathic surgery is possible to treat the skeletal malocclusion on a case by case basis. OI type I patients can receive orthodontic treatment as their treatment response to orthodontic forces is fairly similar to a non-affected population, and the extent of their malocclusion is also manageable in private orthodontic offices. Type III and IV with their more severe craniofacial deformities present much more complicated challenges. Bisphosphonate use may slow orthodontic tooth movement, but appear to present a very low risk of osteonecrosis of the jaws if dental extractions are indicated.

Osteogenesis Imperfecta and Pregnancy

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Understanding the appropriate management of pregnancy in women with osteogenesis imperfecta (OI) is of concern to both the individuals and their physicians. Historically, there was concern in the medical community over pregnancy outcomes in women of short stature due to high complication rates, whether the underlying genetic disorders could be passed on to their offspring, and management of delivery. Through experience and patient advocacy, increasing numbers of women with significant short stature due to numerous genetic disorders including OI have achieved successful pregnancy outcomes. Pregnancy causes numerous physiologic changes and adaptions that can exacerbate already stressed organ systems. Appreciation for normal physiologic changes should be understood and incorporated in the management of a pregnant woman with OI. For most patients with OI, cardiovascular pulmonary and skeletal systems may be adversely affected. There are also special concerns regarding appropriate intrapartum and delivery management as well as some rare complications that arise in OI and pregnancy.

Hearing Loss & Treatment in the OI Patient

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In this presentation, the natural history of hearing loss in osteogenesis imperfecta (OI) will be reviewed. It will be shown that while all types of hearing loss are found in patients with OI, conductive hearing loss is more commonly reported in younger patients with OI. Mixed hearing loss is more commonly seen with increasing age. However, sensorineural hearing loss has also been reported without any conductive involvement even in relatively young patients with OI. Fifty percent of people with OI over 50 years of age have a significant hearing loss. Examples will be shown of conductive, mixed and sensorineural hearing loss in patients with OI. The etiology of sensorineural hearing loss in OI can be related to changes in type 1 collagen which leads to changes in the inner ear structures. Abnormal bony formation leads to ossicular changes that cause a conductive hearing loss. Changes in the inner ear bony structures lead to local environmental changes that likely cause progressive sensorineural hearing loss. Treatment for hearing loss in OI includes a multiple pronged approach. Hearing aids and surgery are the major options depending upon the level and type of hearing loss present. Modifications to incorporate OI issues will be reviewed. Preliminary data suggest that in the future medication may play a role in prevention of hearing loss in OI.

Osteogenesis Imperfecta and the Eye: Issues and Treatment

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Title: Osteogenesis Imperfecta and the Eye: Issues and Treatment

Purpose: To describe eye conditions in osteogenesis imperfecta (OI) and their medical and surgical treatments

Methods: 1) An internet based survey to record OI patient experiences of eye conditions was performed by the Kennedy Krieger Institute OI Registry (Jay Shapiro, MD, survey author); 2) A review of OI eye conditions from medical literature was performed.

Results: 409 of 2027 (20% response rate) OI patients in the OI Registry responded to the survey by April 6, 2013, including: 290 (71%) female; 119

(29%) male; 203 (50%) type I; 35 (9%) type III; 50 (12%) type IV; 6 (2%) type V; 2 (1%) type VI; and 111 (27%) unknown type. Mean age [± stdev] was 35 [± 20] years. 133 of 409 (33%) eye survey responses described eye or vision-related problems including [number (percentage of 409 total eye survey responses)]:

1. Loss of vision 41 (10%)
2. Refractive errors [myopia 17, hyperopia 4, astigmatism 15, contact lens use 1, presbyopia 1, Lasik correction 1] 39 (10%)
3. Glaucoma 10 (2%)
4. Cataract 9 (2%)
5. Keratoconus 7 (2%)
6. Macular degeneration 3 (1%)
7. Scleromalacia, Floaters - each 3 (1%)
8. Retinal or vitreous hemorrhage, Ambylopia, Light Sensitivity - each 2 (0.5%)
9. Retinal tears or detachment, ocular occlusion, dry eyes, oval shaped eye, high pressure, poor eyelid closure, chorioretinitis, retinal "thinning", eyelid ptosis, eye "paralysis", oculomotor nerve palsy, allergic conjunctivitis - each 1 (0.2%)

Ophthalmologist treatments for these conditions may include glasses (refractive errors, cataracts, amblyopia, scleromalacia), contact lenses (refractive errors, keratoconus), topical drops (dry eyes, allergic conjunctivitis), eye pressure lowering medications / laser / or surgery (glaucoma, ocular hypertension), corneal surgery including transplantation (keratoconus), Age Related Eye Disease Study (AREDS) vitamins (intermediate nonneovascular age related macular degeneration - ARMD), intravitreal injections of anti-vascular endothelial growth factor (anti-VEGF) agents or steroids (neovascular ARMD, retinal vein occlusion), retinal laser or vitrectomy (retinal and vitreous hemorrhage, retinal tear or detachment), eyelid surgery (some cases of poor eyelid closure and ptosis), strabismus surgery (certain cases of amblyopia, oculomotor nerve palsy), and patching (amblyopia). Ophthalmologist evaluations may be required to look for and treat underlying diseases that may cause eyelid ptosis (myasthenia gravis, thyroid eye disease, etc), oculomotor nerve palsy (thyroid eye disease, aneurysm, malignancy, etc.), and chorioretinitis (viral, bacterial, or fungal infection).

In the medical literature, a broad range of additional OI eye findings have been reported. Structural alterations in OI eyes include: 1) thin corneas, 2) thin/blue / gray sclera, and 3) decreased ocular rigidity; these vary according to OI genotype. Cases of corneal ectasias, anterior segment anomalies, ectopia lentis, progressive myopia, choroidal neovascularization, macular holes, optic neuropathies, and scleral rupture have been reported in OI. These may require corneal surgery including transplantation (corneal ectasia), aggressive glaucoma treatment (anterior segment dysgenesis), complex cataract surgery (ectopia lentis), anti-VEGF or photodynamic therapy (choroidal neovascularization), vitrectomy (macular hole), and surgical repair (scleral rupture).

Conclusions: OI patients may occasionally develop serious, blinding eye conditions. Annual and as needed (for any visual change) ophthalmologist evaluations are advised to rule out and treat serious eye disease. Glasses with strong frames are advised for better vision and protection from accidental trauma.

Gastrointestinal Issues and OI

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Osteogenesis imperfecta (OI) can be associated with increased gastrointestinal (GI) symptoms. There is limited data with regards to the frequency of GI symptoms in patients with OI, but this limited data suggests that constipation and abdominal pain may be more prevalent. The mechanisms which account for this increase are not entirely clear and are likely multifactorial. Numerous treatments for constipation exist including lifestyle modification, dietary agents, over the counter laxatives and prescription drugs (lubiprostone, linaclotide). Empiric therapy is recommended as the first step in care given the high prevalence of this symptom and the low yield of diagnostic work-up. Diagnostic testing can be employed in cases where the above treatments fail; however, this is a minority of cases. Dysphagia can also be observed in children with OI, although this appears to be less common and data regarding prevalence is minimal. In addition to the above, GI symptoms are commonly seen from medical therapy for OI - particularly with bisphosphonates and opiates, both of which can have significant GI side effects. People with OI can also suffer from any of a myriad of routine GI symptoms such as heartburn, regurgitation, diarrhea - which affect over 50% of the U.S. population at baseline. Finally, there is data to suggest that certain connective tissue diseases associated with joint laxity may have increased visceral sensation. While this has not been studied specifically in OI, it may account for some of the increased abdominal pain and may present options for treatment. At present, GI care is primarily supportive and data with regards to OI and GI interactions remain very scarce.

Skin and OI

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The skin is important in protecting against external injuries and in the maintenance of internal homeostasis. It consists of three layers, the epidermis, dermis and the subcutaneous fat. A large component of the skin is comprised of collagen, located in the dermal layer. With mutations in genes encoding type I collagen seen in patients with osteogenesis imperfecta (OI), this leads to deficiencies in the quantity and structure of dermal collagen resulting in many of the cutaneous features found in OI. These findings include skin thinness, translucency, easy bruisability, impaired elasticity, atrophic scars, and elastosis perforans serpiginosa (EPS). Current management of cutaneous symptoms of OI involves gentle skin care, sun protection, off-label use of topical retinoids and targeted treatments for EPS and hyperhidrosis. The understanding of dermatologic manifestations in OI remains in its infancy. Further studies are needed to better understand the impact that OI has on the skin in order to improve treatment options. The Department of Dermatology at Johns Hopkins School of Medicine will be embarking on a clinical evaluation and survey study to gain a more comprehensive understanding of skin changes seen in patients with OI.

Pulmonary Issues and the OI Patient

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The lung is an underappreciated organ in osteogenesis imperfecta (OI). Likely, this relates to many more immediate problems confronting the clinician treating those with severe OI and the presumption of normal lung function in mild OI. Pulmonary disease is often ignored until breathing problems become severe. Still, the majority of those with moderate to severe OI die from or with pulmonary complications. Attention is usually directed to the structural abnormalities of chest wall, spine, and airways. There is a growing appreciation of the shared collagen abnormalities within bones and the lung parenchyma. Restrictive physiology predominates whether the primary problem is chest architecture or abnormal pulmonary collagen. Obstructive lung disease, sleep disordered breathing, chronic infection often with resultant bronchiectasis, and acute lung infections play significant roles as well. When these various contributions are combined with the difficulties of interpreting physiologic data in the face of short stature, scoliosis, and long bone abnormalities, the diagnosis and management of lung disease in OI can become quite difficult. This presentation will describe methods for successful evaluation of the effects of intrinsic lung disease and suggest ways to prevent pulmonary disease progression.

Osteogenesis Imperfecta and Heart Disease

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Although skeletal manifestations of Osteogenesis Imperfecta (OI) are the most readily discernible, cardiovascular diseases among people with OI are increasingly recognized as life-threatening and treatable manifestations. The exact prevalence of cardiovascular disease in OI is not known, but efforts to accurately discern these features are currently underway. Human population studies are informative, but longitudinal studies are inherently limited by rel-

atively small numbers. Because type I collagens are widely present in cardiac valves, ventricles, and vasculature, clinicians should be wary of several associated conditions, including hypertension, valve insufficiency, cardiomyopathy, aortic aneurysm, and arterial dissection. Inferential knowledge of potential cardiovascular complications of OI also arises from other heritable disorders of connective tissue, such as Marfan syndrome and vascular Ehlers Danlos Syndrome. Murine models with *Col1a1* and *Col1a2* mutations further support efforts to identify and understand the cardiovascular manifestations that are predicted to occur in people with OI. Although the pathophysiology of cardiovascular diseases in OI is poorly understood, similar phenotypic features in other heritable disorders of connective tissue suggest that extracellular collagens may regulate growth factor signaling. Symptoms that may indicate cardiovascular disease include chest pain, unexplained dyspnea, and palpitations. There are several ways to evaluate a patient with OI for cardiovascular diseases. Echocardiography is the most readily available method for imaging the heart and proximal aorta, and higher resolution studies with CT and MRI can also be used. Although no medical treatments are known specifically to improve the cardiovascular manifestations of OI, those used for other connective tissue disorders appear promising.

The OI Heart Protocol at the Kennedy Krieger Institute

Shapiro J, Melvin P, Judge D, Corretti M, Cameron D, Black J, Brennen C

Bone and Osteogenesis Imperfecta Dept., Kennedy Krieger Institute; and the Division of Cardiology, the Johns Hopkins University, Center for Inherited Heart Disease, the Heart & Vascular Institute, Johns Hopkins University and the Kennedy Krieger Institute, Baltimore, MD

Background: In response to a question about the frequency of aortic and valvular heart disease in the national OI Registry, 7.8% of 1800 respondents reported that they had experienced aortic or heart valve problems. This response has generated a study aimed at defining medical and surgical aspects of heart disease in children and adults with OI. This study involves individuals with an established diagnosis of heart involvement, it does not survey the incidence of heart lesions. While valvular involvement is recognized in OI, the occurrence of other cardiac or vascular disease is not well documented.

Methods and results: The OI Registry Heart Questionnaire was available to respondents. 48 individuals self-reported to the OI Registry questionnaire (27 females, 21 males; age range 1.2-75 years, x-age 47.8 years). 23 were type I patients, 19 type III, 4 type IV 1 type V and 10 were not classified. 42 % reported hypertension, 21 % had coronary artery disease. 54 % reported heart valve disease, 35 % reported mitral valve prolapse, 38 % reported a history of abnormal heart rhythm. 54 % reported valvular heart disease, 22 patients (46 %) reported a history of heart surgery (note patients pre-selected). 13 % reported aortic enlargement or aneurysm. 63 % of this group reported having scoliosis.

Dissection of peripheral vessels, although previously reported in individual cases, is not commonly recognized as a potential hazard in OI patients. This study now includes 4 individuals with OI, (3 type I, 1 type IV) with spontaneous dissections of carotid and/or iliac blood vessels. No common mutation is documented but the COL1A1 chain is involved in each.

Medical records have been obtained for 5 adult patients who died prior to planned surgery or shortly post- surgery. Patients were 33, 34, 67 years, and two were age 69. One died postoperatively with surgery for aortic dissection, one patient died prior to planned surgery for mitral insufficiency and two patients, each age 69 years, died following surgery for combined mitral, aortic or tricuspid valve involvement.

Measurements of carotid artery intimal thickness and endothelial cell responsivity in OI adults is normal to-date.

Conclusion: The true incidence and characteristic of cardiac/vascular disease in OI remains to be defined. Standards for medical and surgical assessment of children and adults with OI also remain to be defined.

Cardiovascular Surgery in Osteogenesis Imperfecta Patients

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Cardiovascular manifestations of osteogenesis imperfecta include aortic aneurysm, aortic dissection, and valvar regurgitation, primarily aortic and mitral. Surgical experience with these lesions has been limited, but multiple reports have emphasized high mortality and high rates of complications, particularly postoperative hemorrhage and periprosthetic leak. Modern experience at the Johns Hopkins Hospital with 6 patients undergoing mainly aortic valve replacement +/- mitral and aortic root replacement for symptomatic valvar regurgitation has provided a more promising outlook: no operative mortality, no paravalvar leaks, and no reoperations for bleeding. Furthermore, there have been no clinically significant rib fractures or problems with sternal healing. The challenges have related mainly to compromised pulmonary function due to chest wall deformity and the obstacles of physical rehabilitation in the wheelchair-bound patient. OI patients with clinically important aortic or valvar lesions should be offered surgical therapy, though may require care at specialized centers with experience in treatment of connective tissue disorders.

Basilar Invagination

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The terms basilar impression, cranial settling and basilar invagination, have frequently been used in error interchangeably. Basilar impression refers to the upward migration of the cervical spine into the cranial vault resulting in compression of the brainstem and upper cervical spinal cord. Cranial settling and basilar invagination are subgroups of basilar impression. The distinction between the two comes from where the deformity arises. Cranial settling arises from an abnormal articulation between C1 and C2, and consequently C2 telescopes through C1 and causes the basilar impression. Basilar invagination (BI) results from deformation of the basi-occiput, and the entire cervical spine telescopes into the skull base. In basilar invagination, the C1-2 relationship is normal. This deformation of the skull base can be seen in osteogenesis imperfecta (OI), and is thought to arise from repeat micro-fractures and healing. BI can be seen in 25-71% of patients with OI. It is most commonly seen in type III OI (observed in 15-33% of patients). Not all OI patients with BI are symptomatic. The symptoms can include headaches, myelopathy, cranial neuropathies, and hydrocephalus. Treatment of BI in OI can slow the progression of the symptoms, but most likely cannot halt them altogether. Surgical intervention for BI involves a posterior occipital-cervical instrumented fusion and a decompressive procedure. The decompressive procedure can be in the form of indirect decompression (traction) or direct decompression (bony resection). Ventral decompressive procedures are extensive and carry significant morbidity profiles. Given the morbidity of surgical intervention, and given the fact that surgery is aimed to slow, but not halt, the progression of the BI, surgery is reserved for progressive symptomatic basilar invagination.

When to Perform IM Rod Fixation in Children With OI

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There have been steady advances in the treatment of long bone deformities in children with osteogenesis imperfecta. The use of bisphosphonates and other medical agents has improved bone density and musculoskeletal pain, but we are still far short of being able to provide normal bone density, modeling, function, and quality of life. Some of the skeletal issues which remain can be improved with surgery, while others cannot. An outline of the potential benefits and implications can help families arrive at a reasonable decision about whether or not to undergo surgery for OI-related bone deformities.

Indications: The two general categories of problems which benefit most from surgery include frequent fractures (despite optimum medical treatment)

and severe bowing which compromises function. Frequent fractures are often psychologically difficult for children and families. They occur at unpredictable times and prevent full incorporation of the child in school and physical activities. Femur fractures are particularly disabling. Fractures which heal with residual bow are particularly prone to further fractures due to the residual stresses on the bone. Tibia fractures are slightly less disabling. After several fractures, many families will choose to have surgery to realign and prophylactically stabilize the bones. Studies by Esposito, Plotkin, Cho, and others have shown that this strategy is typically successful. Telescoping rods are able to provide event-free duration of 4-5 years in most cases. The author's preference is to address all "problem" bones in one or both extremities at a surgical setting if conditions are satisfactory. Rod fixation at the time of fracture is sometimes a worthwhile strategy but this is often unpredictable and does not always allow full implementation of a comprehensive strategy.

There is also increasing recognition that upper extremity stabilization is beneficial to function. The humerus and ulna can be stabilized using current techniques.

The ideal age for surgery comprises a wide range. Typically deferral of extensive reconstruction until the age of 4-5 allows the use of rods which are large enough and strong enough to provide the promised benefits and last until the juvenile/adolescent period. Sometimes earlier surgery is called for but in this case usually it is best to address just the problem area and not a more comprehensive reconstruction.

Techniques and tips: The Fassier-Duval rod is the most versatile and comprehensive system of telescoping rods available. It allows whole-bone stabilization through minimally-invasive approach if bone diameter is satisfactory. The instrumentation is highly refined. The key technical steps are to plan out the areas of osteotomies carefully to minimize the number necessary. Select the largest diameter rod which the bone can accommodate, in order to last as long as possible.

It is critical to have center-positioning of both the top and bottom threaded portions of the F-D rod. This requires careful fluoroscopic visualization. It is better to do an extra osteotomy (closer to the epiphysis) if necessary to achieve durable centering and position of these rod ends.

Each region has special technical requirements. For the proximal femur, it is important to start the entry in the center of the trochanter, which is posteriorly located. This allows more permanent fixation and also best correction of the anterior bow. The threaded portion should be seated in cartilage but not cross the apophysis. Awareness of the large amount of un-ossified cartilage in young children is helpful in determining proper seating of the tip. For the distal femur, it is critical to be centered on the lateral view. The author prefers to use the largest threaded portion which can fit the bone. Sometimes the interlocking option is preferred to prevent migration over time. An arthrogram can be helpful in knowing how much un-ossified cartilage is present in order to prevent protrusion in the joint. When fixing the femur in children, it is helpful to minimize the natural tendency of the feet to "roll" laterally. This then results in retroversion of the femur and the typical outward orientation of the femur seen in most patients with OI. It can be minimized with the use of a cast or brace for approximately a month until rotational stability is achieved.

The proximal tibia requires an intra-articular start. The usual tendency is to start anteriorly, which then predisposes to an anterior bow of the tibia. The small height of the upper tibial epiphysis requires the smaller threaded portion to be used. The distal tibia must also be centered, otherwise the ankle will go into valgus as is commonly seen in OI. The interlocking option is best for this area. The tip of the pin should be bent to avoid prominence.

The proximal humerus requires an entry as close to the acromion as possible. Osteotomy in the mid-shaft of the humerus requires exposure of or knowledge of the position of the radial nerve. Sometimes this is covered in callus or scar and may be tethered. The distal humerus has no good option for an "anatomic" alignment with positioning of the Fassier rod but some varus will result from its position in the capitellum. The ulna is amenable to rod fixation but the distal threads will need to be cut to fit within the epiphysis at the wrist.

Near maturity, fracture rates decline significantly. If rod fixation is needed, non-telescoping options should be considered.

Complications: Non-union is still seen in children. Adequate immobilization is needed if the bones are thin. Allograft can help with union as well.

Failure of engagement of the rod tips will result in migration and eventually later fracture. Sometimes it is best to intervene early if repositioning is necessary.

Rod bending is a technically challenging problem. They impair elongation and predispose to non-union. It is rarely possible to manipulate these in a "closed" fashion, as the rod will rotate and usually not straighten to a functional degree. Usually rod exchange is needed. The best strategy is to maximize the length of the female portion of the telescoping rod so that further bending is prevented.

Humeral Osteotomies in Osteogenesis Imperfecta

Esposito Paul
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Initial Experience with percutaneous IM nailing of Humeri in the Pediatric Osteogenesis Imperfecta Population

Purpose: To report a single center surgical experience treating humeral deformity and fractures in children with Osteogenesis Imperfecta.

Methods: A retrospective chart review of children with OI treated with percutaneous intramedullary fixation between 2005 and 2012 with greater than one year follow up was performed. All patients by one pediatric orthopaedic surgeon using an intermedullary devices including Fassier-Duval rod, Rush rod, K wires or the male portion only of the FD rod.

Results: Seventeen patients underwent internal fixation of a total of 36 humeri. Internal fixation of the 36 humeri included the use of twenty-one FD rods, six FD rod revisions, four Rush rods and four male only portion of the FD rod. In addition, one patient with an atrophic non union following a fracture was internally fixated with an FD rod initially but subsequently required medial and lateral plating with grafting. Complications included posterior migration of the distal rod, proximal migration or bending of the rod. Five of the 36 humeri required revision. The two bent FD rods incurred deformation at the interface between the male and female portion of the rod.

Conclusion: Intramedullary fixation using multiple modalities including FD rodding in lower extremities for OI has been shown to be an efficacious surgical treatment. IM fixation and correction of deformity demonstrates a reasonable option to improve comfort and function in children with recurrent fractures and or deformity secondary to Osteogenesis Imperfecta.

Scoliosis in Osteogenesis Imperfecta

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Spinal deformities are frequent in Osteogenesis Imperfecta (OI). We designed a study to describe the behavior of spinal curvature during growth in OI and establish the relationship to disease severity, mobility status, and medical treatment with bisphosphonates. The medical records and radiographs of patients with OI were retrospectively reviewed. Severity was classified by the modified Sillence classification and also by the Functional Mobility Score (FMS). For each participant with scoliosis, serial curve measurements were recorded throughout follow up.

One hundred and fifty-seven patients with scoliosis associated with OI were identified, a prevalence of 50%. Scoliosis prevalence (68%) and progression rate (6 degrees per year) were the highest in the most severely affected group of patients, those with modified Sillence type III. An intermediate group, modified Sillence type IV, demonstrated intermediate values (54%, 4 degrees per year). The mildest group of OI patients, modified Sillence type I, had the lowest prevalence (39%) and rate of progression (1 degree per year). The FMS 50 meter score was also predictive, with those using a wheelchair showing increased curve prevalence and progression. Early treatment, before age 6, with bisphosphonate therapy in type III OI decreased the progression rate by 3.8 degrees per year, which was statistically significant. We were unable to show a benefit of bisphosphonate treatment on curve behavior in other types of OI or at an older age.

The prevalence of scoliosis is much higher in OI than the general population. Progression rates of scoliosis in children with OI are variable depending on severity of OI. High rates of progression in types III and IV OI contrast with type I OI, which follows a more benign course. Bisphosphonates initiated before age six can modulate curve progression in type III OI.

Joint Replacement in Osteogenesis Imperfecta

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Total joint replacement for the treatment of degenerative arthritis is a life altering surgery with excellent long-term outcomes. In patients with osteogenesis imperfecta, the procedure can be extremely challenging and presents a number of pitfalls not present in routine total joint replacement. This unique patient population presents with bone quality and deformities that are not common in routine total joint replacement surgery. Long bone deformity from previous fractures may preclude the use of standard implants and may require additional procedures or techniques. Bone quality may lead to intraoperative fractures. Retained hardware from previous procedures may also complicate the surgery. Ligamentous laxity has serious implications for the stability of hip and knee replacements, and this needs to be identified and may require revision joint replacement implants.

Only those surgeons with specialty training in complex and revision procedures should undertake these procedures. While arthroplasty improves the quality of life in those afflicted with osteoarthritis, the longevity of the prosthesis in this patient population remains unknown. The move in North America towards cementless or biologic fixation may have differing outcomes in patients with OI.

Child Abuse and OI - Clinical and Legal Issues

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The presence or even suggestion of Osteogenesis Imperfecta in a child can complicate the process of identifying and prosecuting child abuse cases. It is increasingly important to explore the relationship of OI to child abuse injuries. This presentation begins with three case presentations involving OI and allegations of child abuse, discussing what role OI played in the outcome of each case. We will then discuss the path of a child abuse case from medical diagnosis through the criminal justice system. We will then consider a recent abusive head trauma/shaken baby syndrome criminal case in which the defense was one of OI and minor trauma. In this case, the child tested positive for a genetic mutation reported only once in a patient who had clinical OI. We will discuss the challenges that OI presented in this case and the ultimate outcome of the trial.

OI and Rehabilitation

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Rehabilitation plays a crucial role in patient and family education, strengthening, and in advancing mobility from birth into adulthood. A key to success is an interdisciplinary team approach working together towards the goal of improving mobility and promoting independence. As a physical therapist, this can be a challenging population to treat and predict changes across the years due to the variability within the Type of OI, high risk of fractures, and bone deformity. Individuals with OI commonly experience multiple fractures, muscle weakness, and skeletal deformities which challenge mobility and function throughout their lifespan. The purpose of this lecture is to inform participants of current rehabilitation research and discuss the role of physical therapy in the interdisciplinary care of individuals with OI throughout the lifespan, including changes in functional mobility.

The ICF model can guide therapists in treatment planning in the areas of structure/function, activity, and participation to work towards meeting the patient and family goals. Commonly used functional outcome measures include: PODCI, GMFM, Gillette FAQ, PEDI, BAMF, Six minute walk test, Timed up and Go, Timed sit to stand, and/or the CAPE. Individuals with OI from childhood into adulthood are aware of their limitations and play a key role in guiding the progression of their therapy. In adults with OI, pain associated with aging and/or the loss of function plays an emotional toll, this may lead to weight gain further impairing one's function. Therapy plays a role in adapting ADL's and recreational activities to promote fitness and prevent loss of function through the life span.

Rehabilitation exercise programs should focus on active/dynamic self-stretching of tight muscles such as: hip flexors, hamstrings, gastroc, and/or pectoralis; and strengthening of commonly weak muscles including: hip abductors/extensors, trunk, scapular muscles, and ankle plantar flexors. For adults, therapeutic activities that help with pain reduction are also essential. Rehabilitation includes knowledge of general OI precautions, patient and family education, strengthening, functional mobility, and ways to promote aerobic fitness in individuals with OI across the lifespan.

Current Medical Treatment of Osteogenesis Imperfecta in Childhood

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Patients with severe osteogenesis imperfecta (OI) frequently receive intravenous bisphosphonates as an adjunct therapy to physiotherapy, rehabilitation and orthopedic surgery. This treatment is associated with rapid relief from bone pain, absence of new vertebral fractures, reshaping of previously fractured vertebral bodies and a lower number of long-bone fractures. Rapid bone mass changes occur through modulation of growth-dependent processes. Consequently, intravenous bisphosphonates are much less effective in adults with OI. Even though pamidronate has been studied in most detail, newer intravenous bisphosphonates, such as neridronate and zoledronate, are easier to administer and are increasingly used in pediatric OI.

The bioavailability of oral bisphosphonates is low and variable, but the ease of administration and potentially lower costs make this approach appealing. However, we found that oral alendronate in the treatment of severe pediatric OI had no significant effect on long-bone fracture rates despite marked increases in spine bone density. In contrast, a recent randomized controlled trial in children with mostly mild OI found that oral risedronate was associated not only with the expected increase in spine and total body bone density, but also with a 40% and 50% lower number of fractures overall. There was, however, no difference in the frequency of new vertebral fractures.

The optimal treatment regimen (i.e. dose and duration) and the long-term consequences of bisphosphonate therapy in children are currently unknown. Given these uncertainties, treatment with bisphosphonates during growth should be reserved for children with OI who have significant clinical problems, including vertebral compression fractures or long-bone deformities. Medical therapies other than bisphosphonates play a minor role at present.

Current Treatment of OI in Children and Adults

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The Osteogenesis Imperfecta clinic at Children's Hospital and Medical Center is a multidisciplinary clinic where evaluations and visits are completed within a 1-2 day period. Patients who travel from outside the Omaha metro area generally have radiology studies such as DEXA and audiometric testing the day prior to their clinic visit. On the day of their visit, patients meet with genetics/metabolism, orthopaedic surgery, physical therapy, occupational therapy, dentistry, nutrition, social work, and our research coordinator.

The medical aspects of the visit concern both skeletal and extraskeletal manifestations of OI. Most patients in our clinic are treated with intravenous pamidronate with a small number who are treated with zoledronate. Dosing and intervals are decided by patient and parent reports of pain, incidence of fractures, and improvement in bone mineral density. Nonskeletal aspects of routine OI care include growth and nutrition, gastrointestinal complaints such as constipation and functional abdominal pain, cardiovascular problems such as valvular disease, as well as sleep and respiratory problems.

Most patients who are treated with pamidronate are on the low dose (4.5

mg/kg/year) "Omaha protocol" or a similar variant thereof. Use of zoledronate in our clinic has mainly been isolated to patients who come to the clinic on a stable dose, or those who have exhibited previous nonresponse to pamidronate (defined as failure to decrease fracture rate, insufficient improvement of chronic bone pain, or increase of bone density of spine or femur of less than five percent in two consecutive years).

Femur Fractures Associated with Intramedullary Rods in Osteogenesis Imperfecta: Relation to Pamidronate Therapy

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Bisphosphonate treatment of children with OI has been successful in reducing fracture incidence, improving vertebral morphometry with growth and reducing musculoskeletal discomfort. However, concerns about the adverse effects of prolonged bisphosphonate treatment have surfaced both in patients with osteoporosis as well as in children and adults with osteogenesis imperfecta. This report addresses the occurrence of femur fractures in the presence of intramedullary rods in children treated with pamidronate.

Case Presentations: This 6-year-old boy has type I osteogenesis imperfecta. He was treated for 4 years with intravenous pamidronate, recently at 6 month intervals. On July 13, 2012, he experienced a fracture to a femur which was rodded which caused the rod to bend. The patient sustained a right tibial fracture in January of 2013. He had a femur fracture on 04/21/2013, another fracture in the right femur on 06/16/2013, and a refracture on 08/1/2013.

16-year-7-month-old boy presumed type III osteogenesis imperfecta. This problem is resorption around the bone compounded by the presence of nonunion at the site of osteotomies particularly in the left femur and in the right humerus. This patient had been treated with pamidronate infusions from 2001 to 2006. There was an awareness during orthopedic surgery that the bone was becoming more brittle. In addition, it appeared that the bone was rejecting or extruding the rods and that there was considerable absorption in bone around the rod particularly in the left femur.

In 2012, Hegazy et al: reported on 72 with patients with OI, ages 2-18 years, who had femoral osteotomies and intramedullary rod fixation and had been treated with long term (>5 years) pamidronate[1]. 5 had subtrochanteric and one had mid-diaphyseal stress fracture with minimal or no trauma. 4/6 had low vit D levels at the time of fracture. None of the fractures were located at stress riser locations, i.e., the tip of implant or metaphyseal growth lines. By contrast, Harcke et al. questioned the location of fractures at either the proximal or distal ends of metaphyseal pamidronate bands[2]. Of 53 patients treated with pamidronate, only 14 sustained fractures after treatment. Radiographs were available for 11 patients, showing 19 fractures. Because 63 % of these fractures were located at a junction with pamidronate bands but not within the bands, the authors proposed stress risers as the mechanism where bone mineral density abruptly changed as a result of the cyclic administration of pamidronate. A similar mechanism involving distal femur fracture susceptibility was proposed by Glorieux and Rauch[3]. Nicolaou et al., examined fracture patterns in 133 patients with moderate or severe OI currently treated with oral residronate or IV pamidronate, duration x= 6.1 years (3.1-9.4 years). 11/133 patients had 16 femoral fractures documented on imaging studies. In 10 of the 16 fractures femora had a telescopic rod *in situ*[4]. In non-treated historical controls, 73 % also had fractures in rodded bones but the fracture incidence was not compared with the treated group. Bilateral atypical subtrochanteric fractures were reported in a 64 year old woman with OI treated with pamidronate for 3 years and zoledronic acid for 2 years[5]. Similarly, a unilateral atypical fracture of the femur shaft associated with cortical thickening occurred in a 75 year old woman with OI treated with alendronate for 3 years[6]. These reports in children and adults share prolonged exposure to bisphosphonate, usually in excess of 5 years. It is estimated that as many as 10% of bisphosphonate treated individuals with intramedullary rods could fracture around the rod. However, at this time a direct relationship to pamidronate cannot be defined. Contributing factors such as vitamin D deficiency or marked depression of bone turnover have not been evaluated. Resorption of bone around the rod and subsequent rotation of the bone around the rod may permit the occurrence of stress fractures which then propagate. Because these appear to be recurrent events, early recognition is required to consider treatment modification to lessen involvement of the same or other rodded extremities.

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