

Thoracic Insufficiency Syndrome

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Abstract:

Thoracic insufficiency syndrome (TIS) is defined as an inability of the thorax to support normal respiration and lung growth. The majority of alveolar development occurs in the first 5 years of life and rapid growth during this phase of life can quickly worsen chest and spine deformity for children with early onset scoliosis (EOS). Advances have been made in the care of these patients with the orthopaedic focus on increasing thoracic volume to allow space for continued lung growth and development. Clinicians can group TIS patients based on their diagnoses but also the type of volume-depletion deformity (VDD) of their thorax. Medical and surgical treatment options are constantly evolving and will ultimately be informed by obtaining accurate and reproducible pulmonary function data in the future.

Key Concepts:

- Thoracic insufficiency syndrome is the inability of the thorax to support normal respiration or lung growth/development and occurs with disordered spine and chest growth.
- Surgical decision-making in EOS/TIS should be based on evolution of chest wall deformity as much as spinal deformity.
- Current surgical procedures have not normalized predicted pulmonary function values but have decreased infant and early childhood mortality.
- Future goals for EOS/TIS treatment will focus on improving thoracic volume while maintaining (or creating) chest wall compliance and diaphragmatic function.

Introduction

Syndromes and chest/spine deformities that give rise to what we now refer to as thoracic insufficiency syndrome (TIS) have historically been treated with a variety of medical and surgical means but with high levels of morbidity and early mortality. The term TIS was first published in 2003 by Campbell et al. with the defining feature being an “inability of the thorax to support normal respiration or lung growth.”¹ Quality of life scores in children with TIS have been shown to be lower than those found in children with various chronic conditions such as cardiac disease and even malignancy.² Primary and secondary TIS are both described. Primary TIS is a result of anatomic

differences of the spine or thorax that directly impair lung development and performance. Secondary TIS denotes inability of the spine and thorax to support lung function secondary to global neuromuscular differences causing weakness or contracture. Ultimately, restrictive lung disease is found with both primary and secondary TIS.

Normal growth and development of the spine, chest wall, and lungs are closely interrelated and often inhibited in TIS. Spinal growth is maximal in the first 5 years of life and then once again during the adolescent growth spurt with an average of 2 cm height increase per year.³ In the intervening years (5-10 years old) spinal growth is

slower and averages 1 cm height increase per year from T1 to S1.^{3,4} Early lung development happens concurrently with early spine growth in the first years of life. Alveoli and lung volumes increase exponentially in the first few years of life with more modest increases during late childhood and adolescence.⁵⁻⁷ Concurrent rapid growth in the spine, lungs, and chest wall place patients at risk for progression of deformity in the first few years of life. This is a particularly vulnerable time for children who may go on to develop TIS.

Presentation and Diagnosis of TIS

TIS can develop in a wide range of pediatric diagnoses. All early congenital or developmental spine deformities are at risk for TIS as is any chest wall abnormality such as fused, absent, or dysplastic ribs. There is no definitive diagnostic finding that typifies and demarcates a patient who has TIS as opposed to a patient who is at risk for developing TIS. In many ways, this makes early TIS an ambiguous phenomenon with possibilities for incredible variability in diagnosis and management. Even in the largest available registries of such patients, fewer than 5% have pulmonary function data available.⁸ For spine surgeons who use curve magnitude as an indicator for treatment, Cobb angle is a poor prognostic indicator for diagnosis or surveillance of TIS.⁹ Patients with mild congenital spine deformities may present without initial findings of TIS, but it is vital for the orthopaedist to ascertain the patient's activity level, sleep patterns, and any changes over time. A diagnosis of TIS can be made in patients who have bony or neuromuscular differences affecting pulmonary function that exhibit signs of occult respiratory insufficiency or worsening of their pulmonary status over time.

Evaluation of the Patient with Potential TIS

Physical Examination

Thoracic growth and height are primary concerns in the management of TIS and examination should start with upright height and weight. Patients with TIS will generally have greater caloric expenditure with respiration; thus, many children will already meet criteria for failure

to thrive upon presentation.⁸ As such, overall growth and tracking on the growth chart should be monitored with particular attention when patients have digression on their growth curves. Chest wall differences should be examined and recorded appropriately as well as any asymmetry in thoracic motion during the respiration cycle. Thoracic motion can be examined grossly with visualization, or the Thumb Excursion Test, as described by Campbell et al., can be employed.¹ In this examination maneuver, the bilateral thumbs are placed equidistant from the spine posteriorly on the chest wall with the hands loosely gripping the thorax. During inspiration, the amount of lateralization of the thumb(s) are noted and graded as a measure of overall or asymmetric chest wall expansion. Respiratory rate and oxygen saturation should be documented along with standard vital sign measurements. The patient's lips and fingertips should be examined for signs of cyanosis and clubbing which can be a sign of chronic hypoxemia.

A detailed neurologic examination should be performed to rule out spinal dysraphism, particularly in patients with known congenital spine differences. The back and associated soft tissues should be carefully evaluated for hairy patches, lipomata, dimples, and abnormal pigmentation which can be markers for intraspinal pathology or global syndromes. A detailed lower extremity evaluation is mandatory with particular attention to asymmetry in size or motion, foot differences, and gait disturbance as these can also be warning signs for spinal dysraphism.

Imaging

Imaging in TIS takes on dual roles and each are important in defining pathology, classifying malformations, and making treatment plans. The first is imaging evaluation of the bony architecture that has led to TIS, and the second role is the assessment of the lungs and cardiopulmonary system. Plain radiographs are the first step in the imaging evaluation of TIS. Many patients will present to the clinic with some level of radiographic evaluation, often a chest x-ray or "babygram." We recommend upright/standing (may be supine if the patient cannot sit upright) posterior-anterior (PA) and lateral views of the

spine (including the ribs) for initial evaluation of bony architecture followed by monitoring of progression with EOS (EOS Imaging, Paris, France) if available. EOS has been shown to be reliable in adolescent idiopathic scoliosis (AIS) and limb length measurements, but its reliability has been questioned in TIS and congenital spine differences where many patterns of malformation are possible.^{10,11} The chief advantage of EOS is reduction in radiation exposure for young patients who will carry a high radiation burden into adulthood. The coronal plane spinal radiographs can reliably measure Cobb angles, thoracic height, and the space available for the lung (Figure 1). Lateral radiographs allow for investigation of kyphosis and lordosis, the latter of which has a deleterious effect on thoracic depth.¹

Computed Tomography (CT) scans offer a wealth of information regarding osseous anomalies and their relationships. Due to the radiation content of this imaging technique (even with pediatric dosing), every effort should be made to minimize unnecessary evaluation. In addition to fine detail of bony anatomy, CT scans can provide volumetric reconstruction of the thorax to provide measurements for lung volume.^{12,13} The measurements can be compared to normalized data for age and also followed for changes over time with reduction in lung volume resulting from progression of deformity. CT with three-dimension reconstruction (3D-CT) is also vital in surgical planning for complex spine and rib deformity. In the EOS population, Hedequist and Emans compared the findings in direct radiograph and 3D-CT of congenital scoliosis patients with the findings in surgery. In all patients, anterior and posterior anatomy correlated with the CT findings. It is clear that a three-dimensional analysis of abnormal vertebrae and ribs can demonstrate the relationship between anatomic structures and assist with planning osteotomy and anchor placement.¹⁴

Traditionally, magnetic resonance imaging (MRI) is performed on most TIS patients as an assessment for intraspinal abnormalities. As in congenital scoliosis without TIS, these patients have been shown to have rates of

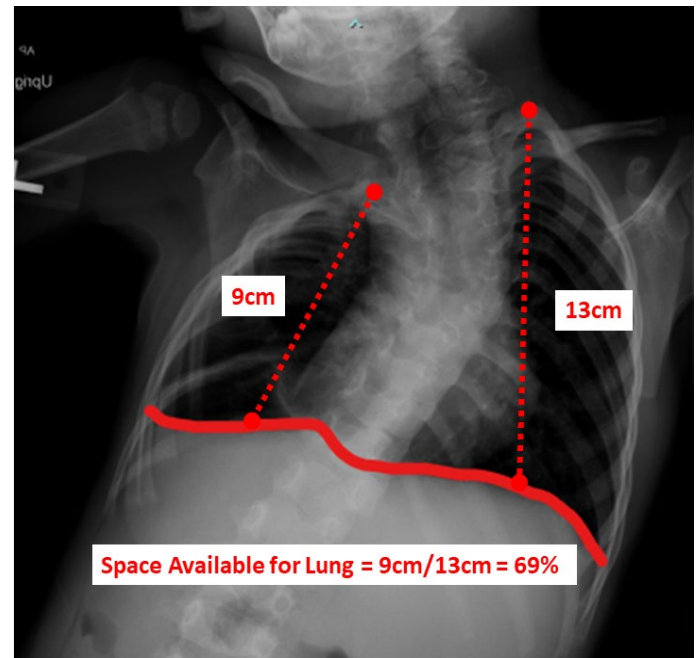


Figure 1. Space available for the lung is measured from the middle of the most cephalad rib to the center of each hemidiaphragm. It is reported as a percentage of one hemithorax to the other and can be tracked in evaluation of TIS progression.

intraspinal pathology up to 38%.^{15–17} Recent studies with dynamic MRI (dMRI) have displayed the ability to show lung volumes across the respiration cycle as well as diaphragmatic excursion.^{18,19} In the future, this may be a viable option for serially assessing thoracic function in patients who are unable to complete traditional pulmonary function testing.

Pulmonary Assessment

Care of the TIS patient is a multidisciplinary endeavor and the importance of the pulmonary team cannot be overstated. Ultimately, the work of the orthopaedist is in support of maintaining functional respiratory physiology. Because many young patients cannot perform standard pulmonary function testing (PFT), there is a reliance on indirect measures in these patients. As mentioned above, CT scan and dMRI can show lung volumes and anatomic evolution over time.^{12,13,18,19} As patients come of age and are capable of fully participating in PFTs, this information can be assessed longitudinally for progression of TIS. PFT data should be normalized based on the patient's arm span as a surrogate for height

which can be reduced secondary to spinal curvatures. If that is not a possibility, secondary to contracture or other congenital differences than single bone measurements of tibial and/or ulnar length can also be used for normalization of respiratory parameters.^{20,21} For patients who require respiratory support at the time of presentation, the extent of TIS can be evaluated by *assisted ventilator ratings* (AVR) (Table 1).²²

Table 1. Assisted Ventilation Rating (AVR)²²

+0	No assistance/room air
+1	Supplemental oxygen required
+2	Night only ventilator/cPAP* support
+3	Part-time ventilator/cPAP* support
+4	Full-time ventilator support
cPAP = continuous positive airway pressure support	

Patients who have progression of AVR (requiring enhancement of respiratory support measures) should be considered for surgical intervention of their TIS and spinal differences.

Associated Differences

Patients with TIS or impending TIS secondary to congenital rib and spinal differences should be evaluated for associated differences in a manner similar to congenital scoliosis patients. The exception is a patient with neuromuscular and/or syndromic causes for TIS who will have an individualized evaluation based on their diagnoses. Tsirikos and McMaster found that 19.2% of patients with congenital scoliosis presented with concurrent rib anomalies.²³ A study by Xue et al. found rib differences in 50.3% of operatively treated congenital scoliosis patients, and that the rate of intraspinal anomalies was significantly higher in the patients with rib deformity.²⁴ MRI screening has been

shown to identify intraspinal pathology in 28-38% of patients with congenital scoliosis.¹⁵⁻¹⁷

Differences within the renal system are present in 18-40% of patients with congenital spine differences and the most common of these anomalies has been shown to be unilateral renal agenesis.²⁵ Duplication of the kidneys and ureteral obstruction are also commonly found.^{26,27}

Cardiac differences have been reported in 10-54% of patients with congenital spine and rib differences.²⁵ The most common abnormalities are atrial and ventricular septal defects, although, more complex malformations are seen as well.^{28,29}

Concurrent musculoskeletal pathology can also be present in patients with TIS and congenital spinal differences. Anomalies such as Klippel-Feil syndrome, Sprengel's deformity, and various lower extremity differences should trigger an evaluation for intraspinal pathology.³⁰

Classification System for Volume-Depletion Deformities of the Thorax

Campbell and Smith created the term Volume-Depletion Deformities (VDD) of the thorax and then created a classification system of the anatomic variants causing TIS (Table 2).³¹ This classification system attempts to guide surgical management and give prognostic insights.

During their 2 decades of treating TIS together, Campbell and Smith created their "Core" procedures for surgery with the original Vertical Expandable Prosthetic Titanium Rib (VEPTR) system, but many have since evolved into hybrid constructs using a variety of implants.^{32,33} The goal of each of the core procedures is expansion of the thorax or affected hemithorax to allow for lung expansion while adding support to the chest wall architecture. An overarching theme for the classification system is that VDD Types I and II are asymmetric and will generally have a scoliosis deformity in the affected region, whereas Types IIIa and IIIb have global chest wall differences with or without a coronal plane spinal deformity. Type IIIa was originally described as Jarcho-

Table 2. Thoracic Volume-Depletion Deformities (modified from Campbell and Smith *JBJS* 2007)³¹

Type of VDD	Thoracic Deficit	Mechanism of Lung-Volume Loss	Examples
Type I (Absent ribs and scoliosis)	Unilateral thoracic hypoplasia	Flail chest physiology with loss of lung volume	VACTERL*, absent ribs (congenital or iatrogenic), Poland syndrome, and congenital scoliosis
Type II (Fused ribs and scoliosis)		Constriction of lung from fused ribs and shortening of the hemithorax	VACTERL*, fused ribs and congenital scoliosis, thoracogenic scoliosis from prior thoracotomy, severe lateral thoracic flexion contracture
Type IIIa (Longitudinally deficient thorax)	Global Thoracic hypoplasia	Bilateral longitudinal constriction of lungs from loss of thoracic height	Jarcho-Levin syndromes (spondylocostal dysplasia and spondylocostal dysostosis), congenital spine difference without rib fusion
Type IIIb (Transversely constricted thorax)		Lateral constriction of lung from rib deformity and/or hypoplasia	Jeune syndrome, hypotonic neuromuscular scoliosis, scoliosis with windswept deformity of the thorax

*VACTERL = vertebral defects, anal atresia, cardiac defects, tracheo-esophageal fistula, renal anomalies, and limb abnormalities

Levin syndrome, but it is now recognized that the eponym likely covers a broad range of different clinical and genetic diagnoses which have in common a vertical shortening and stiffening of the thorax leading to TIS.³⁴ Historically, Jeune syndrome was most associated with the Type IIIb, but similarly to the IIIa differences, there are many diagnoses that will fit into the VDD Type IIIb grouping. These include infantile scoliosis and many hypotonic neuromuscular scoliosis as well. The commonality of Type IIIb TIS is a global reduction in chest wall circumference resulting in transverse plan constriction. Although not specifically described in the original publication of VDD, neuromuscular patients with TIS are the most numerous and can present with a mixture of the VDD pathologies.⁸

VDD Type I

Absent ribs and unilateral flail-chest physiology are the hallmark of the Type I VDD (Figure 2). This can be

secondary to a congenital absence or from rib/chest wall resections for other pathologic processes. With these chest wall deficiencies, the lung will prolapse into the chest with resultant loss of lung volume on the affected hemithorax. The goal of surgery in this setting is stabilization and lengthening of the hemithorax while maintaining ability for continued growth. Support of the chest wall theoretically allows for creation of appropriate negative pressure during diaphragmatic motion and an increase in available space for lung expansion, but no surgical strategy has consistently improved testable lung function in TIS patients.⁸

VDD Type II

The Type II VDD exhibits rib fusion and scoliosis. This can be a fully congenital thoracospinal difference but can also be iatrogenic from prior thoracotomy with subsequent rib fusions (Figures 3 and 4). This is a common cause for TIS in patients with VACTERL syndrome.

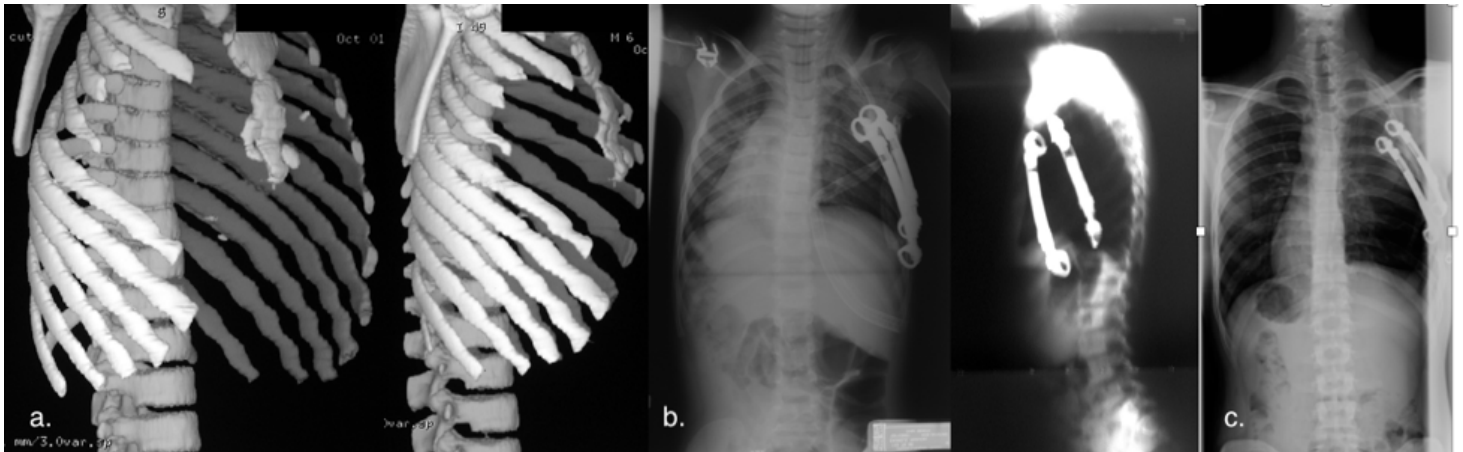


Figure 2. 3-year-old male with congenital absence of ribs secondary to Poland syndrome. Preoperative CT shows absence of ribs consistent with VDD Type I (a). Postoperative images at 3 years old shows reconstruction of chest wall with VEPTR Device (b). Final follow-up at 19 years old shows excellent space available for the lung (c), and the patient is active in sports without any respiratory assistance.

The confluence of scoliosis with a concave rib tether has the ability to create large deformities during growth at very early ages. As a result, the concave lung is constricted and cannot appropriately contribute to total lung volume. In this scenario, the natural history is that the deformity and lung differences will worsen over time. These patients have been indicated for an expansion thoracoplasty originally described by Campbell and Smith.³⁵ This procedure is often done in TIS patient who also have been diagnosed with congenital scoliosis. Improvement of associated scoliosis is best if the expansion thoracostomy(ies) extends posteriorly to the rib heads (complete thoracostomy) and corresponds to an open disc space(s).

VDD Type IIIa

The original description of the Type IIIa VDD identified Jarcho-Levin syndrome as the primary diagnosis. In the intervening years, it has become evident that the eponymous syndrome is actually a number of different diagnoses (spondylocostal dysplasia [SCD], spondylothoracic dysplasia [STD], congenital scoliosis without rib fusion) which have in common the propensity for creating a longitudinal hypoplasia of the thorax.³⁶ Cornier et al. proposed an algorithm to differentiate Types of IIIa VDD on the basis of absence of rib anomalies, symmetric rib fusion, or asymmetric rib fusion (Figure 5).³⁶



Figure 3. 33-month-old male with congenital scoliosis, left-sided rib fusions, severe bronchomalacia, tracheostomy, and ventilator dependency. Preoperative image (a) and postoperative image after thoracostomy and expansion with VEPTR device (b), 19 year old with VEPTR device in place after expansions (c), and postoperative image after final fusion (d). Patient works manual labor and does not require respiratory assistance devices.

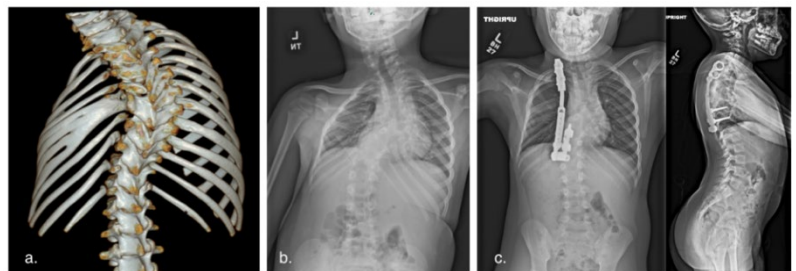


Figure 4. 7-year-old male with fused ribs and scoliosis. Preoperative 3D-CT shows rib fusions as well as an open disc space within the congenital vertebral anomalies (a), preoperative PA x-ray (b), postoperative PA and lateral x-ray after expansion thoracostomy (placed to correspond to the open disc space) and placement of hybrid VEPTR construct (c).

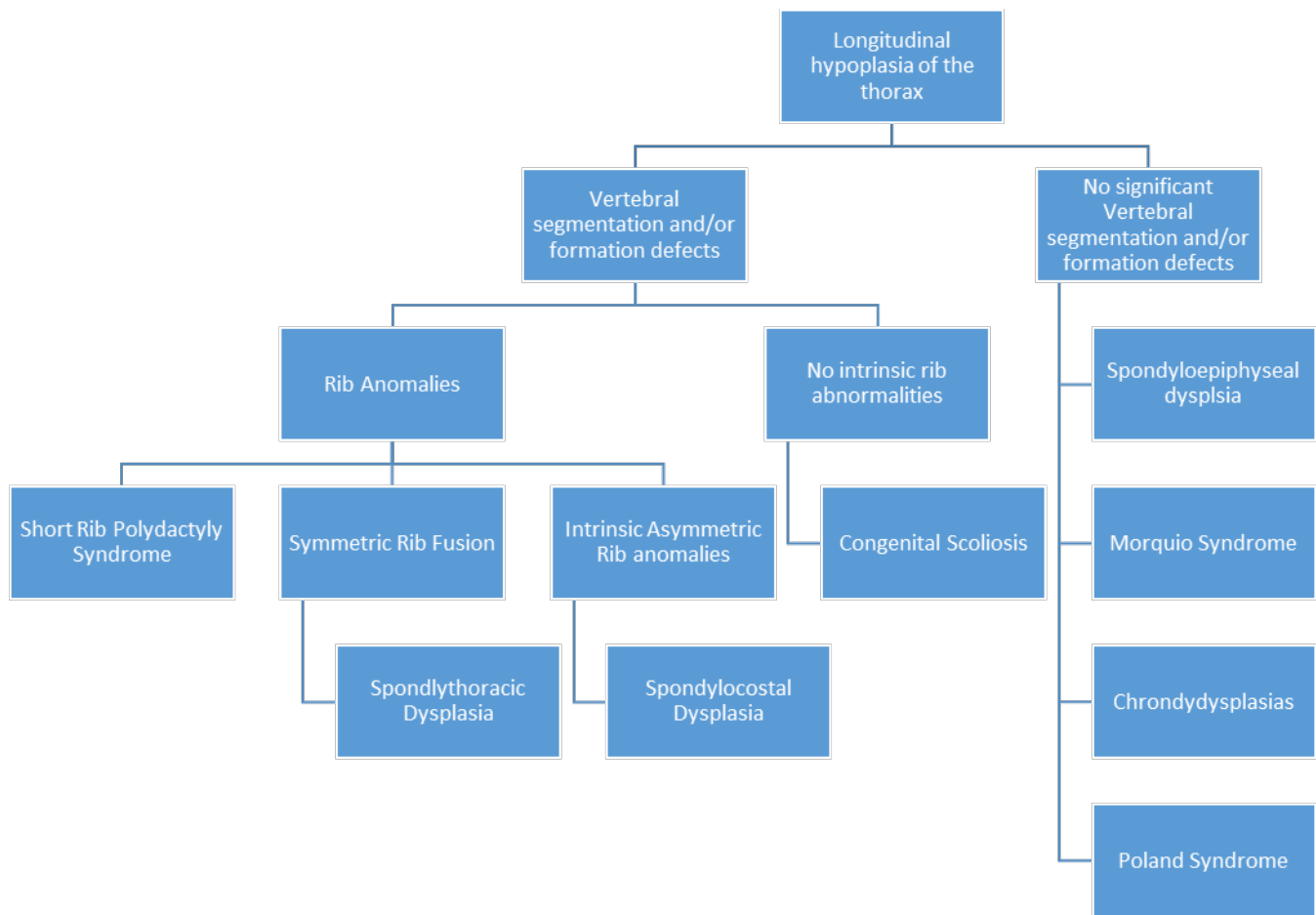


Figure 5. Radiographic Algorithm Differentiating VDD Type IIIa. (Modified from Cornier et al. *Current Opinion in Pediatrics* 2003)³⁶

The differentiation between SCD and STD are of prognostic value when choosing appropriate interventions. The natural history of untreated STD patients who live past the first 6 months of life (44% mortality at 6 months) leads to adults with symmetrically hypoplastic thorax but “normal intelligence, achieving their intellectual goals with a good independent quality of life.”³⁷ Bilateral opening-wedge thoracostomies with placement of a VEPTR device (Figure 6) has been the mainstay of treatment for VDD Type IIIa, but it has been noted that rib expansion without commensurate spinal growth can have deleterious effects.^{31,38} Hybrid constructs which support rib and spine expansion have become more common and can be performed with or without the VEPTR device (Figure 7). In addition, these hybrid constructs may have a lower overall complication rate.³³

VDD Type IIIb

Jeune syndrome, or asphyxiating thoracic dystrophy, is an autosomal recessive skeletal dysplasia first described in 1955.³⁹ Jeune syndrome is the most common descriptive pathology used when discussing Type IIIb VDD (Figure 8), but this grouping can be applied to any TIS caused by narrowing of the thorax creating a transverse restriction of respiration and lung development. Within Type IIIb VDD, Jeune syndrome carries 60-80% mortality in childhood, but Type IIIb VDD from other causes can be more insidious in onset and present after infancy such as spinal muscular atrophy (SMA), muscular dystrophies, and congenital myopathies.⁴⁰⁻⁴³

Multiple surgical techniques have been described for the various presentations of the Type IIIb VDD. O’Brien et al. published their experience using the 70 mm radius

VEPTR for thoracic expansion in their Jeune syndrome population and were able to show a reduction in mortality with a tendency towards improvement or stabilization of AVR.⁴⁴ Multiple methods of acute and gradual transverse plane expansion have been described, but it is still unclear as to the final efficacy of these procedures.^{45,46 47} Patients with hypotonic neuromuscular disease will often manifest TIS with a collapsing chest wall and resultant “parasol” deformity. Livingston et al. compared VEPTR and traditional growing rods (TGR) in this population and found both treatments lead to a maintenance of AVR, but the TGR cohort had overall fewer complications and neither corrected the parasol deformity.⁴³

Summary

Thoracic insufficiency syndrome exhibits often debilitating and life-threatening pathology in the growing chest and spine. There are a wide range of diagnoses that can contribute to TIS and each of these differences will require patient-specific planning with a multidisciplinary approach. To date, we do not have a surgical procedure that approximates predicted values of lung function in these patients, but it is evident there have been positive effects on infant and early childhood mortality rates secondary to these efforts.⁴⁴ With use of past strategies, we have been able to change very small, stiff chest walls into larger, stiff chest walls. The next stage of orthopaedic involvement in TIS is the development of spine and thoracic interventions that will allow for continued growth while not contributing to the already present restrictive pathology. The involvement of pediatric orthopaedists will continue to be of importance in the treatment of these patients, particularly in patients who have yet to exhibit the pulmonary symptoms of TIS. Our charges for the future are to gather pulmonary data before and after treatment in the most reproducible way possible, work closely with our medical and surgical colleagues for this multisystem issue, and continue to create thoughtful solutions to these difficult problems.

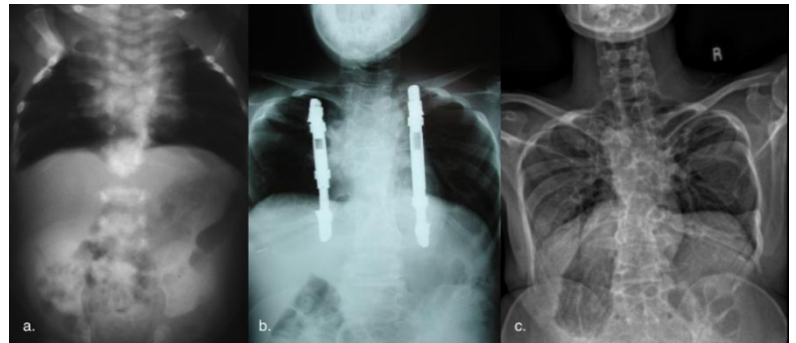


Figure 6. Infant with congenital scoliosis/bilateral fused ribs and segmental spinal dysgenesis (a) who had anterior and posterior decompression and fusion at level of lumbar dysgenesis. At age 3, patient underwent bilateral expansion thoracostomy with VEPTR placement (b). Final follow-up at age 27 after removal of VEPTRs for localized pain (c). Patient has shortness of breath with symptoms of adult respiratory insufficiency but ambulates and is able to enjoy hiking.

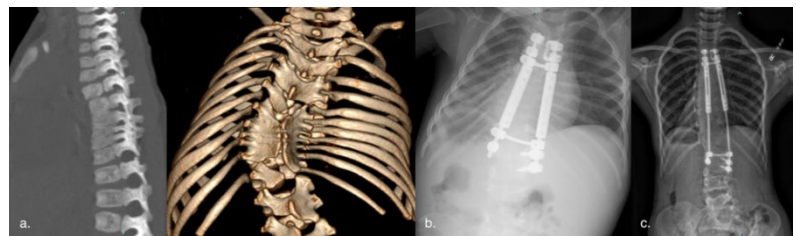


Figure 7. CT and 3D-CT of a 20-month-old female with extensive congenital thoracic fusions and early TIS without rib fusions (a). Postoperative x-ray after complete excision of the congenital posterior laminar fusion including pedicles to the level of the synchondrosis and placement of growing rod construct (b). Patient is currently 11 years old and leads an active and happy life without respiratory support. Lengthenings are maintained at 6-month intervals and previous lengthening x-ray is pictured above (c).



Figure 8. Preop CT (a) and x-ray (b) of a 2-year-old female with Jeune syndrome. Postoperative CT (c) and x-ray (d) after bilateral anterior and posterior osteotomies with placement of short-radius VEPTR device. Patient follow-up x-ray at 11 years old (e) after continued lengthenings.

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