Original Article

Best Practices in Peri-Operative Management of Patients with Skeletal Dysplasias[1]

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ABSTRACT

Patients with skeletal dysplasia frequently require surgery. This patient population has an increased risk for peri-operative complications related to the anatomy of their upper airway, abnormalities of tracheal-bronchial morphology and function; deformity of their chest wall; abnormal mobility of their upper cervical spine; and associated issues with general health and body habitus. Utilizing evidence analysis and expert opinion, this study aims to describe best practices regarding the peri-operative management of patients with skeletal dysplasia.

A panel of 13 multidisciplinary international experts participated in a Delphi process that included a thorough literature review; a list of 22 possible care recommendations; two rounds of anonymous voting; and a face to face meeting. Those recommendations with more than 80% agreement were considered as consensual.

Consensus was reached to support 19 recommendations for best pre-operative management of patients with skeletal dysplasia. These recommendations include pre-operative pulmonary, polysomnography; cardiac, and neurological evaluations; imaging of the cervical spine; and anesthetic management of patients with a difficult airway for intubation and extubation.

The goals of this consensus based best practice guideline are to provide a minimum of standardized care, reduce perioperative complications, and improve clinical outcomes for patients with skeletal dysplasia.

Keywords: skeletal dysplasias, perioperative management

INTRODUCTION

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Skeletal dysplasias are a heterogeneous and collectively common group of inherited disorders of development, growth and maintenance of the human skeleton [Savarirayan et al., 2004]. Many patients with these conditions require a range of surgical procedures, most commonly orthopedic in nature, but also necessitated by concomitant medical complications that can affect almost every organ system [Savarirayan et al., 2004]. The potential for increased peri-operative morbidity and mortality in individuals with skeletal dysplasias is related to multiple factors including abnormal upper airway and/or tracheal-bronchial morphology and function, and abnormal mobility of the upper cervical spine. With over 400 described forms of skeletal dysplasia, there is extreme phenotypic variability affecting patients in this population [Bonafe et al., 2015]. These factors, combined with the rarity of each condition, make it extremely important that patients are assessed and managed in facilities that are aware of these potential complications, and have the skill and resources to anticipate and manage them. The aim of these expert guidelines is to make relevant health care physicians aware of these risks in patients with skeletal dysplasias, and to optimize surgical and patient outcomes through "best" peri-operative management practices.

METHODS

A RAND-UCLA modified Delphi method was used to create consensus-based guidelines for the perioperative practices in patients with skeletal dysplasia. Briefly, this methodology consists of a systematic literature review, a creation of a list of statements or indications, multiple rounds vetting those statements, and a face-to-face meeting where these indications are rated anonymously by a group of experts [Linstone et al., 1975; Fitch et al., 2001; Adler et al., 1996]. This methodology has been widely used in medical

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research to determine appropriate treatment and best practice guidelines [Stefanoides et al., 2015; Vitale et al., 2014; Wong et al., 2014; Vitale et al., 2013]. This methodology has been successfully used by this group previously [White et al., 2015].

The primary author (K.K.W) created a list of statements based on a systematic literature review. This initial list was evaluated by three others (M.J.G., R.S., and W.M.) who made modifications and suggestions to the list. The first electronic survey consisted of 22 statements and was distributed, along with the referenced literature search, to a panel of international experts in October 2015 (Round 1) (Table I). Respondents rated the statements using a 5-point Likert scale (Strongly Agree, Agree, Neutral, Disagree and Disagree Strongly). A month later, at a face-to-face meeting, the results of the survey and the literature review were presented. Participants focused the discussion on the areas of disagreement and were given the opportunity to modify the statements if desired. A series of modifications were suggested by the panel, and participants had the opportunity to rate the statements anonymously for a second time using an electronic survey (Round 2).

Consensus of 80% is considered the standard for most Delphi processes, and in this case, that percentage was agreed *a priori*. Statements with ≥80% of agreement between two categories (strongly agree and agree; or strongly disagree or disagree) were interpreted as appropriate or inappropriate and included in the guidelines. The panel consisted of 13 international experts on skeletal dysplasia. Other specialists were selected based on their clinical expertise and record of relevant research. A total of 6 pediatric orthopedic surgeons, 4 geneticists, 1 pediatric anesthesiologist, 1 pediatric pulmonologist and 1 pediatric radiologist participated in this effort.

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RESULTS

The mean years-in-practice for the panel of experts was 21.4 years (range, 9-44 years).The panel have an average of 16.6 years (range, 9-40) treating patients with skeletal dysplasia. During Round 1, 15 out of 22 statements reached consensus of ≥80% (Table I). The seven statements that did not reach consensus were related to the use of preoperative polysomnography, cardiology exam, cervical imaging and the use of epidural anesthesia and sedative premedication (Table II).

In the face-to face meeting, the list was modified into 20 statements. This list was rated in Round 2, where 19 statements reached ≥80% consensus (Table III) and only 1 statement did not (Table IV).

The Delphi process substantially increased consensus for both including and excluding indications and as a result, a list of 19 best practice guidelines was created (Table III). After review of the results, all participants agreed to support its publication.

DISCUSSION

Our group proposes the following rationale for acceptance or declination of the final Delphi statements. As of 2015, there were 436 identified forms of skeletal dysplasia with significant variation in phenotypic expression and medical needs. As such integration of these recommendations into clinical practice should include an appreciation of this diversity.

A. GENERAL CONSIDERATIONS

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Statement 1: The mortality and morbidity risk for a patient with skeletal dysplasia undergoing surgery are greater than the general population.

Statement 2: Because of the high risk of anesthesia complications in patients with skeletal dysplasia, such patients should undergo surgery at facilities that can anticipate and manage life-threatening complications.

The risks for general anesthesia are greater in many patients with skeletal dysplasia for the following reasons:

1) A disproportionate body habitus (e.g. short limb or short trunk) makes measurement of height, weight, BMI and surface area difficult to calculate, and such measures are often unreliable.
2) The disproportionate body may have a smaller chest and narrow airway.
3) Disproportionate craniofacial growth may lead to jaw malformations and limited mouth opening that can challenge airway intubation and maintenance.
4) Obesity is common in those with skeletal dysplasia.
5) Abundant subcutaneous fat and joint contractures makes intravenous access difficult.
6) While specific genetic mutations can result in characteristic skeletal deformities, non-skeletal organ systems may also be affected by the same mutation. Collagen II mutations, for example, can lead to tracheomalacia, laryngomalacia, and eye globe fragility, all of which increase the risks of anesthesia complications. Mucopolysaccharidoses thickens cardiac valves, adversely affecting cardiac function. Occult renal disease can occur in other skeletal dysplasias.

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Comparative anesthesia mortality and morbidity data for patients with skeletal dysplasias as related to hospital size and volume are absent. Nonetheless, the number of specialists involved in clinical preparation and management of patients with skeletal dysplasia and the higher risk of anesthesia complications allows us to recommend that surgery be performed at facilities that can anticipate and manage such complications.

B. PRE-OPERATIVE ASSESSMENT

Spinal Issues

Statement 3: Patients with skeletal dysplasia should have a comprehensive neurological examination prior to general or regional anesthesia.

Statement 4: Patients with skeletal dysplasia should have evaluation of neuroaxial integrity and stability with appropriate imaging including cervical, thoracic, and lumbar spine prior to anesthesia.

Statement 5: Flexion/extension MRI is a useful and safe imaging adjunct for the pre-operative assessment of those patients with skeletal dysplasia in whom there is a concern for cervical spinal cord compromise.

Patients with skeletal dysplasia are at risk for neural compression at both the central and peripheral levels. Their abnormal skeletons can lead to significant spinal deformity as well as spinal cord compression, which can be multifocal, particularly in lysosomal storage disorders such as Morquio syndrome. These include foramen magnum stenosis, upper cervical instability, spinal stenosis, and thoracic and lumbar kyphosis. Among the most significant risks is cervical instability, which can lead to spinal cord injury and quadriplegia during even minor procedures if unrecognized [Mackenzie et al.,

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2013; Tomatsu et al., 2012]. Neurologic injury can also occur in non-spinal procedures from neural compression due to positioning where there is pre-existing deformity. For example, there are reports of paraplegia and quadriplegia after non-spinal procedures in skeletal dysplasia patients, [Drummond et al., 2015; Pruszczynski et al., 2015; Tong et al., 2012] as a result of spinal cord injury from preexisting spinal stenosis exacerbated by positioning and anesthesia.

There is some disagreement among our group as to what type of evaluation is necessary as some types of skeletal dysplasia are milder (such as hypochondroplasia and mild forms osteogenesis imperfecta) and thus are unlikely to have any spinal involvement that would cause anesthetic complication. All agreed that any skeletal dysplasia with significant spinal deformity such as achondroplasia, spondyloepiphyseal dysplasia, or the MPS disorders should have a clinical or imaging evaluation to lessen the risk of spinal cord injuries. Our group agreed that a global assessment of the patient's skeletal dysplasia phenotype as well as genotype, where possible, is appropriate as there is heterogeneity among even conserved mutations such as achondroplasia and osteogenesis imperfecta. A baseline neurologic examination can identify concerning findings such as sensory changes, asymmetric/abnormal reflexes, and clonus. A history of positional extremity numbness, paresthesias, and/or weakness should raise concern as should need for frequent squatting due to leg weakness/pain while walking (frequently seen in patients with achondroplasia and progressive lumbar stenosis), and any bowel/bladder incontinence [Tomatsu et al., 2012; White, 2011; Katz et al., 1987].

Appropriate imaging, ranging from static plain radiographs, dynamic lateral cervical spine radiographs, to MRI of the entire neuroaxis is appropriate for most patients

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with skeletal dysplasias. [Charrow et al., 2015; Hendriksz et al., 2015; Solanki et al., 2013; Tofield et al., 2003; Drummond et al., 2015; Tong et al., 2012.] Cervical spine abnormalities have been well described in patients with skeletal dysplasia, noted to affect over 20% of dysplasias [Lachman 1997]. Developmental anomalies include hypoplastic or poorly ossified vertebrae, odontoid hypoplasia, C1-C2 subluxation, abnormal development of posterior elements, cervical, thoracic or thoracolumbar kyphosis, and vertebral compression fractures in cases of poor bone mineralization such as osteogenesis imperfecta [Lachman 1997]. A combination of spinal stenosis and/or ligamentous laxity may contribute to spinal cord compression and subsequent myelopathy if left untreated [Solanki et al., 2013].

Plain radiographs, which often provide poor visualization of the craniocervical junction in this patient population, CT (computed tomography) and MRI (magnetic resonance imaging) can be employed to evaluate anatomy and potential abnormal motion. While CT has the advantage of decreased scan time (seconds), and therefore decreased exposure to a position that creates potential neural compromise, it is most optimal for evaluation of bones and offers limited evaluation of soft tissue structures. MRI provides much better visualization of neural elements and cartilage, while avoiding the ionizing radiation associated with CT.

Flexion extension cervical spine MRI has been well described in other clinical situations where potential cervical instability or neural compromise exist, including patients with cord compression [Bartlett et al., 2012], blunt trauma injury with suspected ligamentous injury [Sierink et al., 2013], rheumatoid arthritis patients with atlantoaxial

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subluxation and cord compression [Soderman et al., 2015], and dynamic cord compression with cervical spondylotic myelopathy [Hayishi et al., 2014].

Mukherjee et al. [2014] demonstrated cord compression and anterior CSF flow obliteration in the flexed position on MRI that was not evident in the neutral position. This comprised approximately 14% of surgical cases of symptomatic achondroplasia patients receiving foramen magnum decompression. All patients demonstrated clinical and imaging improvement after foramen magnum decompression. Also, Ruangchainikom et al. [2014] described increased spinal cord compression in patients with cervical kyphosis in extension relative to flexion.

While neutral position MRI of the cervical spine is generally considered to be a safe procedure for skeletal dysplasia patients (beyond the potential complications of anesthesia), the use of dynamic MRI of the cervical spine with flexion and extension can create some uncertainty on the part of the ordering clinician and managing radiologist. This concern often arises due to the longer time periods the patient is required to be in a fixed flexion or extension position required for this type of imaging (several minutes).

Little has been written about the safety of dynamic MRI imaging in patients with skeletal dysplasia. No prospective trials have been reported, to our knowledge. Mackenzie et al. [2013] performed a retrospective review of 31 children with skeletal dysplasia who underwent flexion-extension cervical spine MRI under sedation/anesthesia. Standardized flexion and extension positions were used, and if there was any concern from the anesthesiologist regarding compromise of the airway or from the radiologist regarding cord compression during the neutral position scout images, the

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study was terminated. In no cases was there significant change in the neurological status following the examination.

The potential risks and benefits of dynamic cervical spine MRI should be carefully weighed along with a thorough clinical history and physical exam before performing these examinations. The importance of having an experienced team in place for the imaging management of these complex patients is underscored. The group recommends that all decisions over investigations and management of cervical spine instability should be made in conjunction with subspecialists (neurosurgeon, orthopedic spine surgeon) in the care of the cranio-cervical junction.

Statement 6: Because patients with skeletal dysplasia have a high risk for morphologic abnormalities of the upper cervical spine, patients undergoing surgery should have pre-operative lateral flexion/extension x-ray of their cervical spine.

The group did *not* reach consensus on this statement, and as such is being addressed separately. At a minimum, preoperative screening for patients at risk for cervical spine instability with a lateral neutral radiograph of the cervical spine is standard. Potential abnormal findings include widening of the atlantoaxial interval (greater than 5 mm), narrowing of the bony neural canal width (space for the cord) at C1 (< 14 mm), developmental anomalies of the odontoid process such as os odontoideum, or additional skull base or cervical spine fusion or segmentation anomalies [Lustrin et al., 2003; Solanki et al., 2013]. However, a neutral lateral view does not assess for underlying ligamentous abnormalities that are often present in the skeletal dysplasias. Pathologic

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occipitocervical or intervertebral subluxation may only be demonstrated with flexion or extension views, and the presence of such instability may require surgical intervention to avoid spinal cord compression or injury. At some institutions, flexion and extension radiographs are not obtained in the absence of positive screening factors on a lateral neutral view. The addition of flexion and extension views is left to the clinician's discretion. Some of our experts felt that without flexion and extension, the cervical spine was incompletely assessed, and felt it was absolutely necessary. Others however felt that there is often poor visualization of the cervicomedually junction, or that abnormal findings detected on screening lateral radiograph of the cervical spine are best assessed by CT scan or MRI in a neutral position along with flexion and extension views to better assesses anatomy and potential abnormal motion.

Airway Issues

Statement 7: Patients with skeletal dysplasia are more likely than the general population to have decreased mobility of the cervical spine, which will contribute to difficulty with securing the airway.

Statement 8: Patients with skeletal dysplasia are more likely than the general population to have abnormal upper airway morphology and function, which can contribute to increased morbidity and mortality.

Statement 9: Patients with skeletal dysplasia are more likely than the general population to have abnormal tracheal-bronchial morphology and function that contributes to increased mortality and morbidity.

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Statement 10: Patients with skeletal dysplasia with respiratory signs or symptoms or thoracic cage structural abnormalities should have pre-operative pulmonary evaluation.

Statement 11: Polysomnography should be considered in the pre operative assessment of patients with skeletal dysplasia.

Statement 12: Cardiac evaluation should be considered for patients with skeletal dysplasia prior to surgery particularly for adults.

An array of abnormalities affects the cervical spine and can make intubation and securing the airway difficult. Stiffening of ligaments and precocious arthritis can affect cervical mobility. A number of other dysplasias have segmentation and fusion defects that can also limit neck mobility.

The disproportionate facial growth (e.g. mid-face hypoplasia in achondroplasia) results in a smaller airway and an airway more likely to be obstructed even by non-pathologic average size tonsils and adenoids. Patients with type II collagenopathies have clefts or other abnormalities in their hard and soft palate, as well as tracheo- and laryngomalacia. Craniofacial abnormalities commonly include disproportioned jaw size, malocclusion and both supernumerary and deficient teeth.

Patients with skeletal dysplasia that result in a small thorax (such as Jeune syndrome), and patients with scoliosis and deformities of the sternum (such as Conradi-Hunermann and SEDC) can have secondary abnormalities, such as spinal intrusion on the tracheal-bronchial tree.

Both obstructive and restrictive lung disease are common in children with skeletal dysplasia. The presence of an intrinsically small chest, spinal deformity including scoliosis and kyphosis, and thoracic cage abnormalities (such as a pectus excavatum), can

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produce both restrictive and obstructive lung disease. In addition, abnormalities of the trachea and tracheal bronchial tree produce respiratory symptoms that may be mistaken for asthma. There is a high incidence of disturbed sleep patterns in children with skeletal dysplasias. Enlarged tonsils and adenoids lead to obstructive sleep apnea. Evaluation by a pulmonary specialist for consideration of pulmonary function studies or polysomnography is recommended prior to anesthesia and surgery.

The authors recommended to 'consider polysomnography' (PSG) given the spectrum of disease and the variable phenotypical presentations in regard to the severity of symptoms seen in skeletal dysplasias [Bonafe et al., 2015]. PSG is best utilized when performed in patients whose clinical symptoms are indicative of sleep disordered breathing [Aurora et al., 2011]. In skeletal dysplasia patients obstructive upper airway symptoms are the leading indication [Theroux et al., 2012]. Even among skeletal dysplasia patients who may not have history of 'snoring' or obstruction, central apnea and hypopnea with oxy-hemoglobin desaturation may occur. Some of these patients have reduced ventilation in the presence of low lung volumes with or without inherent muscle weakness, which leads to recurrent hypoxemia, arousals, and poor sleep quality. These patients can benefit from nighttime interventions such as non-invasive positive airway pressure during sleep.

Screening for sleep–related breathing disorders includes sleep history, a sleep log, physical exam (neurologically impaired respiratory muscles result in paradoxical respiration) and in some cases imaging studies. For example, infants with achondroplasia may have episodes of apnea due to foramen magnum stenosis, which will need to be

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differentiated from disordered breathing resulting from upper airway obstruction. Imaging studies (MRI) can greatly aid in differentiating between the two.

There may be a group of patients who do not display symptoms attributable to airway obstruction and yet are candidates for polysomnography. These are patients who may be older and yet unable to give adequate history. Often other evidence of airway obstruction may be evident in these patients including position of their head and neck (Morquio syndrome). Elevated end-tidal carbon dioxide during clinic visits and increased bicarbonate level in the metabolic panel are indicative of chronic carbon dioxide retention. A screening echocardiogram can also identify right ventricular hypertrophy and abnormal septal motion, resulting from pulmonary hypertension due to hypoxemia during sleep.

Skeletal dysplasia patients with a high prevalence of airway obstruction (e.g. achondroplasia, mucopolysacchridosis, diastrophic and camptomelic dysplasia) should undergo a PSG at an earlier age unless they have very mild disease.

Primary congenital heart defects are a feature of a few skeletal dysplasias (e.g. Ellis-van Creveld). The cardiac consequences of long standing obstructive and restrictive lung disease, chest-wall, spine and sternum deformities, obstructive sleep apnea, and obesity are well documented in average stature adults and include right sided heart failure, pulmonary hypertension, cor pulmonale, and peripheral vascular hypertension [Jaroszewski et al., 2011; Han et al., 2007; Mannino et al., 2003]. The predisposing pulmonary disease, skeletal deformities, and weight issues are more common in adults with skeletal dysplasia than the general population, and clinical experience suggests a higher risk for cardiac morbidity and impaired health status in those with dwarfism.

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Hoover-Fong and associates reported the prevalence of hypertension in a cohort of 325 short stature skeletal dysplasia subjects to be nearly double the general US population; and while meeting the hypertension criteria for treatment, only a fraction were treated [Hoover-Fong et al., 2015]. Lysosomal storage disorders thicken and stiffen heart valves, cause conduction abnormalities, and predispose to coronary artery disease and early mortality [Braunlin et al., 2011]; and skeletal dysplasia with ligament laxity may be at risk for mitral valve prolapse and aortic root dilatation, similar to what occurs in ligamentous laxity connective tissue disorders.

C. PREOPERATIVE SEDATION

Statement 13: Pre-operative sedation may be given safely to patients with skeletal dysplasia.

Statement 14: Pre-operative sedation is NOT indicated in patients with skeletal dysplasia to reduce risk of spinal cord damage if patient struggles during induction.

When patients are scheduled for surgical procedures, routine preoperative medication may be given without fear of respiratory compromise. This statement is supported by case reports [Masuda et al., 1990; Monedero et al., 1997; Mehta et al., 1988] and the opinion of the panel. Preoperative sedation given orally is commonly practiced in pediatric anesthesia. At our respective institutions we do not hesitate to give preoperative sedation to our patients with a skeletal dysplasia unless the patients refuse the medication due to bad taste, etc. Fear of airway obstruction is rarely a concern and patients are given the premedication in the preoperative holding area under observation of nursing and physician staff. The authors have never witnessed an airway obstruction

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related to the use of premedication in any of our skeletal dysplasia patients. The purpose of preoperative sedation is to relieve or mitigate anxiety in patients with skeletal dysplasia; with the potential need for multiple surgical procedures, they should not be deprived of it.

In older patients the practice is to start an intravenous line to 'titrate in' premedication 'as needed' based on an individual patient's anxiety level. The patient might not need any anxiolytic or analgesic and may verbalize their needs much more readily when they are of an appropriate age. In the event that severe airway abnormalities are suspected, sedation may be initiated in the operating room itself under full monitoring and control of the airway personnel (i.e. anesthesiology and otolaryngology when appropriate).

Statement 14 was proposed due to concerns raised at the institution of one of the authors that preinduction sedation would be beneficial in reducing the risk of spinal cord injury for this at-risk population. The authors are unaware of any evidence or literature suggesting a risk of spinal cord injury at the time of induction of anesthesia due to patient struggles. Therefore this concern remains purely theoretical.

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D. ANESTHESIOLOGIC PRACTICE DURING SURGERY

Airway Issues

Statement 15: Abnormal anatomy of the head and neck in patients with skeletal dysplasia may preclude emergency tracheostomy. Therefore, pre-operative assessment of the position of the cricothyroid membrane is essential.

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Statement 16: For patients with skeletal dysplasia, equipment for intubation of a difficult airway such as a video laryngoscope and fiber optic bronchoscope must be immediately available in the operating room.

Statement 17: Post-operative extubation of a skeletal dysplasia patient is preferably performed in the operating room by an anesthesiologist.

Statement 18: Because of the higher risk of life threatening airway complications following anesthesia in patients with skeletal dysplasia, if extubation is to be performed outside of the operating room, qualified personnel and equipment must be immediately available.

There is abundant literature describing difficulty with airway management in patients with skeletal dysplasia. Etiological reasons are many: short neck, unstable spine, lack of mobility of the head and neck, not allowing for adequate extension during airway management, a large tongue in relationship to the size of the oropharynx, deposits that obscure the upper and lower airway structures, and stenosis, deviation and malacia of the tracheobronchial tree. In cases of osteogenesis imperfecta, the patient's airway should be managed with the understanding that fragility of the mandible may lead to fracture, and the possibility of odonto-axial dislocation may occur with over-extension of the cervical spine [Oakley et al., 2010].

The cricothyroid membrane, if situated at or below the sternal notch will render placement of a tracheostomy, especially in an emergency situation, very difficult and often impossible [Pelley et al., 2007; Shinhar et al., 2004; Sim et al., 2007]. The cricoid cartilage (see Figure 1) therefore needs to be palpable in the neck in order to perform this procedure. When the cricoid cartilage is situated at or below the sternal notch, the

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placement of tracheostomy will require splitting of the sternum (Figure 2). Patients, especially when known to have a particularly difficult airway prior to anesthesia, should be evaluated for this aberrant variation in anatomy, and should be made aware of the risks involved, including whether a tracheostomy is possible should an emergency tracheostomy become necessary.

Currently the most commonly used tool to intubate patients with a difficult airway is a video laryngoscope such as Glidescope (GlideScope, Verathon, Bothell, WA) or Storz video laryngoscope. The fiberoptic bronchoscope, another time-tested tool to intubate the difficult airway, should be readily available as well [Theroux et al., 2012; Okutani et al., 2014]. Not all patients may be intubated with one technique. However, video laryngoscopes, in general have the optimal ability to displace redundant oropharyngeal tissue commonly encountered in patients with skeletal dysplasia. Video laryngoscope may be considered a primary tool to intubate the trachea in patients with skeletal dysplasia [Aziz et al., 2011]. This statement, however, is a generalization and there are patients who may require a different technique such as use of flexible fiberoptic bronchoscope used with or without a facilitating conduit such as laryngeal mask airway [Stallmer et al., 2008; Appleby et al., 1996; Walker et al., 1997].

A difficult airway that requires the skill and expertise of an anesthesiologist for intubation and intraoperative monitoring is best managed by a similar team of anesthesiology personnel when it is time for extubation of the trachea. Should there be a need to reintubate, the best possible outcome would mandate that the anesthesiology personnel with same tools be readily available [Diaz et al., 1993; Tofield et al., 2003]. Most such situations are optimally dealt with in the same location where the intubation

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took place and hence the recommendation that extubation may be best performed in the operating room [Mashour et al., 2008; Mather, 1966].

That being said, extubation outside of the operating room is often necessary, especially when the patient requires positive pressure ventilation, and therefore remains intubated in the intensive care unit during the immediate post operative period. The same precautions utilizing the above mentioned difficult airway tools should be available to the airway management team, similar to extubation occurring in the operating room [Tomatsu et al., 2012].

Spinal Issues

Statement 19: Anecdotal reports suggest that epidural anesthesia be used with caution in children with skeletal dysplasia due to risk of neurological injury.

Statement 20: In patients with skeletal dysplasia and evidence of spinal cord compromise or "spine at risk" findings, neuromonitoring is recommended for all surgical procedures.

There are several reports of patients with skeletal dysplasia developing paralysis after lower extremity orthopedic procedures [Pruszczynski et al., 2015; Drummond et al., 2015]. One common factor in these reports is the use of an epidural anesthetic; however, it remains unclear whether there is a causal relationship between the use of an epidural and the development of paralysis. Several factors have been identified as contributing to the risk for spinal cord injury during non-spine surgery. These include a preexisting kyphotic deformity at spinal cord level, the development of low blood pressure during surgery, an extended duration of surgery, inappropriate positioning of the patient while on the operating table, and underappreciated vascular disease. The addition of localized

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pressure on the thecal sac by an infusion of anesthetic medication could also represent a theoretical contribution to the development of spinal cord injury in these patients.

The issue of epidural use contributing to spinal cord risk during surgery in this population was explored by Drummond et al. [2015] who stated "We doubt that epidural anesthesia per se is directly injurious to the spinal cord of patients with Morquio A-related spinal stenosis, and two of us….have employed epidurals to good effect in these patients. Nonetheless, because of the apparent vulnerability of Morquio A patients to spinal cord ischemia, [the authors] view epidural anesthesia as relatively contraindicated for a number of reasons. First, epidural anesthesia has the potential to make the necessary blood pressure support more difficult. More importantly, it has the potential to delay diagnosis and/or confuse a diagnostic evaluation" [Drummond et al., 2015]. Given this group's level of concern over the development of a spinal cord injury during non-spine surgery in patients with skeletal dysplasias, neuromonitoring has been recommended in a select subset (see recommendation #19). For these patients, neuromonitoring is not feasible with the use of an epidural anesthetic. So for practical reasons as well as the theoretical, an epidural anesthetic is not generally considered an appropriate option in patients with skeletal dysplasia.

In as much as prompt recognition of intraoperative spinal cord monitoring signal loss allows for corrective action to minimize the potential for sustained spinal cord injury, this study group feels that the risk of a "never event" such as a permanent spinal cord injury warrants the use of this technology, in at least a subset of patients with skeletal dysplasia undergoing non-spine surgeries. Because children with skeletal dysplasia and other significant spinal deformities may be at increased risk for spinal cord injury during non-

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spine surgery, the concept of a "Spine at Risk" (SAR) population has been proposed [O'Donnell et al., manuscript in preparation].

The SAR program consists of a protocol to identify patients preemptively, through the electronic medical record, which might be at risk for intraoperative spinal cord injury but not otherwise identified as such by providers not as familiar with these conditions. The SAR program mandates preoperative assessment and identification of special precautions to avoid intraoperative spinal cord injury for patients with at-risk diagnoses. This group of patients includes any patient with a known skeletal dysplasia. In this program a consensus is reached among experienced pediatric orthopedic and neurosurgeons for conditions that have a high-risk spinal deformity, instability or stenosis. Once a patient is identified as SAR, a chart and imaging evaluation by a member of the orthopedic surgery or neurosurgical team must be completed before that patient can be scheduled for any surgical procedure or imaging study requiring general anesthesia. When appropriate the patient may be scheduled for a formal consultation with orthopedics or neurosurgery. Imaging studies (radiographs, computed tomography (CT), or magnetic resonance imaging (MRI) of the spine could be ordered according to the consultant's discretion. Recommendations, including the need for intraoperative spinal cord monitoring are then made.

In this study spinal cord monitoring was recommended for 83/315 (26%) patients in procedures expected to last more than 45 minutes. To date the benefits of such a program are yet to be seen, however preliminary cost analysis suggests that programs such as this are appropriate for this high-risk population [O'Donnell et al.].

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SUMMARY

Patients with skeletal dysplasia present unique risks when undergoing general anesthesia. Due to the relative rarity of these conditions, many centers have little or no experience with the pitfalls that may exist when caring for this group. This report intends to outline the best practices in anesthetic care for patients with skeletal dysplasia. In general, a thorough preoperative assessment of cardiac, pulmonary and neurological status is required. Imaging of the spinal column and assessment of airway elements are necessary to avoid catastrophic consequences. Perioperative care should be performed by appropriately experienced personnel who have access to difficult airway equipment.

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UpToDate.com – Royalties

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The other authors have indicated they have no financial relationships or conflict of interests relevant to this article to disclose.

Contributors Statement:

Klane K White and Ravi Savarirayan: Drs. White and Savarirayan conceptualized and designed the study, participated in the Delphi process, drafted the initial manuscript, and approved the final manuscript as submitted.

Viviana Bompadre: Dr Bompadre led the Delphi process, carried the out the initial analyses, drafted, and revised the manuscript, and approved the final manuscript as submitted.

Drs. Michael J Goldberg, Michael B Bober, William Mackenzie, Gregory J Redding, Tae-Joon Cho, Julie Hoover-Fong, Shawn E Kamps, Cathleen Raggio, Mary C Theroux, Samantha A Spencer and Melita Irving participated in the Delphi process, drafted, reviewed and approved the manuscript as submitted.

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All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Figures

Figure 1 - Relationship of thyroid and Cricoid cartilage and Cricothyroid membrane. In an airway emergency Cricothyroid membrane is used to insert a small tracheal tube and thus ventilate the patient (emergency tracheostomy). Therefore, being able to palpate the Cricothyroid membrane is essential in order to consider an emergency surgical airway

Figure 2 - Lateral cervical spine radiograph of a 21 year old patient with metatropic dysplasia. Note the stiff/ankylosed vertebral bodies with a stenotic canal posteriorly. The sternal heads of the clavicles are the most prominently felt structures in the sternal notch. The cricoid is not palpable in this patient as it is located below the sternal notch.

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Table I First Round -Statements with ≥ 80% of agreement

	Agree Strongly	Agree	Neutral	Disagree	Disagree Strongly
1. The mortality/morbidity rates for patients with skeletal dysplasias undergoing elective (non-urgent) surgery are greater than the matched general population.	3 (23%)	10 (73%)	0	0	0
2.Abnormal upper airway morphology and function contributes to increased morbidity/mortality in patients with skeletal dysplasias.	6 (46%)	7 (54%)	0	0	0
3.Patients with skeletal dysplasias develop abnormalities of airway shape and position.	2 (15%)	9 (69%)	1 (8%)	1 (8%)	0
4.Fused cervical spine, surgically or spontaneously will contribute to difficulty with securing the airway.	5 (38%)	8 (62%)	0	0	0
5.All patients with skeletal dysplasias that require surgery and general anesthesia pose significantly grater risk and should be managed in a tertiary level hospital with appropriate ICU facilities.	8 (62%)	4 (31%)	0	1 (8%)	0
6. All patients with generalized skeletal dysplasias that require surgery and general anesthesia should have a thorough neurologic clinical examination prior to surgery.	6 (46%)	5 (38%)	1 (8%)	1 (8%)	0
7.All patients with a skeletal dysplasia that affects thoracic cage development/size should have pulmonary consult and age appropriate pulmonary function studies.	3 (23%)	8 (62%)	2 (15%)	0	0
8.Polysomnography should be obtained if patients have symptoms of obstruction of their upper airway.	8 (62%)	4 (31%)	1 (8%)	0	0
9. In patients who have a known difficult airway, assessment of the position of the crico-thyroid membrane should be made during pre-operative evaluation to assess the feasibility of placing an emergency tracheostomy in the event of failure to secure airway in a conventional manner.	1 (8%)	10 (80%)	2 (15%)	0	0
10.All skeletal dysplasia patients should be cared for at a tertiary center and be cared for by experienced anesthesiologists who are familiar with skeletal dysplasias.	2 (15%)	9 (69%)	1 (8%)	1 (8%)	0
11.Difficult airway equipment, such as a video laryngoscope and fiber optic bronchoscope should be available in the operating rooms.	8 (62%)	4 (31%)	0	1 (8%)	0
12.Extubation of the trachea should be preferably performed in the operating room by an anesthesiologist.	1 (8%)	9 (75%)	1 (8%)	1 (8%)	0
13.If extubation is postponed to be done in the intensive care unit, an anesthesiologist should be present in the event of airway difficulty with equipment, such as a video laryngoscope and fiber optic bronchoscope available in the operating rooms.	3 (25%)	8 (67%)	1 (8%)	0	0
14..Most recent MRI of the cervical, thoracic and lumbar spine should be evaluated for “spine-at-risk” findings*.	6 (46%)	7 (54%)	0	0	0
15. Spinal cord monitoring is recommended for all surgical procedures where there is evidence of significant spinal cord compromise or spine at risk findings* for procedures exceeding 45 minutes.	4 (30%)	7 (54%)	1 (8%)	1 (8%)	0

*“Spine-at-risk” findings include: spinal cord impingement from FMS, atlantoaxial instability, cervical stenosis, cervical kyphosis, cervicothoracic kyphosis, thoracic level spinal stenosis, cord level thoracolumbar kyphosis, syrinx, cord signal change on T_2 MRI

Table II First Round - Statements that did not reach 80% of agreement

	Agree Strongly	Agree	Neutral	Disagree	Disagree Strongly
1.A large number of patients with skeletal dysplasia have an abnormal trachea leading to progressive obstruction.	0	6 (46%)	4 (31%)	3 (23%)	0
2. All patents with skeletal dysplasias affecting the cervical spine should have pre-operative polysomnography.	2 (15%)	3 (23%)	4 (31%)	4 (31%)	0
3. Patients with skeletal dysplasia should have imaging studies to evaluate neuraxial integrity and stability prior to surgery and anesthesia, including the cervical, thoracic and lumbar spine.	3 (23%)	6 (46%)	1 (8%)	1 (8%)	2 (15%)
4. Pre-operative imaging of the cervical spine should include flexion/extension radiographs and flexion extension MRI.	0	5 (38%)	4 (31%)	3 (23%)	1 (8%)
5.All patients with a skeletal dysplasia should have a preoperative cardiology evaluation.	1 (8%)	2 (15%)	3 (23%)	6 (46%)	1 (8%)
6.Pre-operative sedative premedication is indicated in patients with skeletal dysplasia to reduce risk of potential spinal cord damage if patient struggles during induction.	0	0	8 (62%)	4 (31%)	1 (8%)
7. Epidural anesthesia should not be used in patients with skeletal dysplasias affecting the spine.	2 (15%)	3 (23%)	6 (46%)	1 (8%)	1 (8%)

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Table III Second Round -Statements with ≥ 80% of agreement – Recommended guidelines

	Agree Strongly	Agree	Neutral	Disagree	Disagree Strongly
1.The mortality and morbidity risks for patients with skeletal dysplasia undergoing surgery are greater than the general population	9 (75%)	3 (25%)	0	0	0
2. Because of the higher risk of anesthesia complications in patients with skeletal dysplasia, such patients should undergo surgery at facilities that can anticipate and manage life-threatening complications.	10 (83%)	2 (17%)	0	0	0
3. Patients with skeletal dysplasias should have a comprehensive neurological examination prior to general or regional anesthesia.	11 (90%)	1 (10%)	0	0	0
4. Patients with skeletal dysplasia should have evaluation of neuroaxial integrity and stability with appropriate imaging including cervical, thoracic, and lumbar spine prior to anesthesia.	4 (33%)	7 (59%)	0	1 (8%)	0
5. Flexion/extension MRI is a useful and safe imaging adjunct for the pre-operative assessment of those patients with skeletal dysplasia in whom there is a concern for cervical spinal cord compromise.	5 (42%)	6 (50%)	1 (8%)	0	0
7. Patients with skeletal dysplasia are more likely than the general population to have decreased mobility of cervical spine which will contribute to difficulty with securing the airway.	4 (33%)	7 (59%)	1 (8%)	0	0
8. Patients with skeletal dysplasias are more likely than the general population to have abnormal upper airway morphology and function, which can contribute to increased morbidity/mortality.	7(58%)	5 (42%)	0	0	0
9. Patients with skeletal dysplasia are more likely than the general population to have abnormal tracheal bronchial morphology and function that contributes to increased mortality and morbidity.	3 (25%)	9 (75%)	0	0	0
10. Patients with skeletal dysplasia with respiratory signs or symptoms or thoracic cage structural abnormalities should have a pre-operative pulmonary evaluation.	6 (50%)	6 (50%)	0	0	0
11. Polysomnography should be considered in the pre-operative assessment of patients with skeletal dysplasia.	2 (17%)	10 (83%)	0	0	0
12. Cardiac evaluation should be considered for patients with skeletal dysplasia prior to surgery, particularly for adults.	3 (25%)	8 (67%)	0	1 (8%)	0
13. Pre-operative sedation can be given safely to patients with skeletal dysplasia.	5 (42%)	7 (58%)	0	0	0
14. Pre-operative sedation is NOT indicated in patients with skeletal dysplasia to reduce risk of spinal cord damage if patient struggles during induction.	6 (50%)	5 (42%)	1 (8%)	0	0
15. Abnormal anatomy of the head and neck in patients with skeletal dysplasia may preclude emergency tracheostomy. Therefore, pre-operative assessment of the position of the cricothyroid membrane is essential.	8 (67%)	4 (33%)	0	0	0
16. For patients with skeletal dysplasia, equipment for intubation of a difficult airway such as a video laryngoscope and fiber optic bronchoscope must be immediately available in the operating room.	11 (92%)	1 (8%)	0	0	0
17. Post-operative extubation of a skeletal dysplasia patient is preferably performed in the operating room by an anesthesiologist.	7 (58%)	5 (42%)	0	0	0
18. Because of the higher risk of life threatening airway complications following anesthesia in patients with skeletal dysplasia, if extubation is to be performed outside of the operating room, qualified personnel and equipment must be immediately available.	11 (92%)	0	0	1 (8%)	0
19. Anecdotal reports suggest that epidural anesthesia be used with caution in children with skeletal dysplasia due to risk of neurological injury.	6 (50%)	6 (50%)	0	0	0
20. In patients with skeletal dysplasia and evidence of spinal cord compromise or “spine at risk”* findings, neuromonitoring is recommended for all surgical procedures.	7 (58%)	5 (42%)	0	0	0

Table IV Second Round - Statement that did not reach 80% of agreement

	Agree Strongly	Agree	Neutral	Disagree	Disagree Strongly
6. Because patients with skeletal dysplasia have a high risk for morphologic abnormalities of the upper cervical spine, patients undergoing surgery should have pre-operative lateral flexion/extension x-ray of their cervical spine.	4 (33%)	5 (42%)	2 (17%)	1 (8%)	0

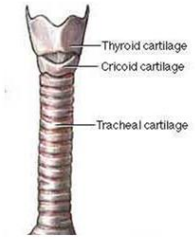

Figure 1

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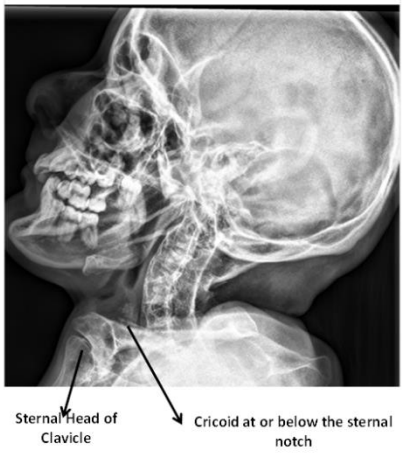

Figure 2

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	Agree Strongly	Agree	Neutral	Disagree	Disagree Strongly
1. The mortality/morbidity rates for patients with skeletal dysplasias undergoing elective (non-urgent) surgery are greater than the matched general population.	3 (23%)	10 (73%)	0	0	0
2.Abnormal upper airway morphology and function contributes to increased morbidity/mortality in patients with skeletal dysplasias.	6 (46%)	7 (54%)	0	0	0
3.Patients with skeletal dysplasias develop abnormalities of airway shape and position.	2 (15%)	9 (69%)	1 (8%)	1 (8%)	0
4.Fused cervical spine, surgically or spontaneously will contribute to difficulty with securing the airway.	5 (38%)	8 (62%)	0	0	0
5.All patients with skeletal dysplasias that require surgery and general anesthesia pose significantly grater risk and should be managed in a tertiary level hospital with appropriate ICU facilities.	8 (62%)	4 (31%)	0	1 (8%)	0
6. All patients with generalized skeletal dysplasias that require surgery and general anesthesia should have a thorough neurologic clinical examination prior to surgery.	6 (46%)	5 (38%)	1 (8%)	1 (8%)	0
7.All patients with a skeletal dysplasia that affects thoracic cage development/size should have pulmonary consult and age appropriate pulmonary function studies.	3 (23%)	8 (62%)	2 (15%)	0	0
8.Polysomnography should be obtained if patients have symptoms of obstruction of their upper airway.	8 (62%)	4 (31%)	1 (8%)	0	0
9. In patients who have a known difficult airway, assessment of the position of the crico-thyroid membrane should be made during pre-operative evaluation to assess the feasibility of placing an emergency tracheostomy in the event of failure to secure airway in a conventional manner.	1 (8%)	10 (80%)	2 (15%)	0	0
10.All skeletal dysplasia patients should be cared for at a tertiary center and be cared for by experienced anesthesiologists who are familiar with skeletal dysplasias.	2 (15%)	9 (69%)	1 (8%)	1 (8%)	0
11.Difficult airway equipment, such as a video laryngoscope and fiber optic bronchoscope should be available in the operating rooms.	8 (62%)	4 (31%)	0	1 (8%)	0
12.Extubation of the trachea should be preferably performed in the operating room by an anesthesiologist.	1 (8%)	9 (75%)	1 (8%)	1 (8%)	0
13.If extubation is postponed to be done in the intensive care unit, an anesthesiologist should be present in the event of airway difficulty with equipment, such as a video laryngoscope and fiber optic bronchoscope available in the operating rooms.	3 (25%)	8 (67%)	1 (8%)	0	0
14..Most recent MRI of the cervical, thoracic and lumbar spine should be evaluated for “spine-at-risk” findings*.	6 (46%)	7 (54%)	0	0	0
15. Spinal cord monitoring is recommended for all surgical procedures where there is evidence of significant spinal cord compromise or spine at risk findings* for procedures exceeding 45 minutes.	4 (30%)	7 (54%)	1 (8%)	1 (8%)	0

Table I First Round -Statements with ≥ 80% of agreement

*“Spine-at-risk” findings include: spinal cord impingement from FMS, atlantoaxial instability, cervical stenosis, cervical kyphosis, cervicothoracic kyphosis, thoracic level spinal stenosis, cord level thoracolumbar kyphosis, syrinx, cord signal change on T_2 MRI

Table II First Round - Statements that did not reach 80% of agreement

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	Agree Strongly	Agree	Neutral	Disagree	Disagree Strongly
1.A large number of patients with skeletal dysplasia have an abnormal trachea leading to progressive obstruction.	0	6 (46%)	4 (31%)	3 (23%)	0
2. All patents with skeletal dysplasias affecting the cervical spine should have pre-operative polysomnography.	2 (15%)	3 (23%)	4 (31%)	4 (31%)	0
3. Patients with skeletal dysplasia should have imaging studies to evaluate neuraxial integrity and stability prior to surgery and anesthesia, including the cervical, thoracic and lumbar spine.	3 (23%)	6 (46%)	1 (8%)	1 (8%)	2 (15%)
4. Pre-operative imaging of the cervical spine should include flexion/extension radiographs and flexion extension MRI.	0	5 (38%)	4 (31%)	3 (23%)	1 (8%)
5.All patients with a skeletal dysplasia should have a preoperative cardiology evaluation.	1 (8%)	2 (15%)	3 (23%)	6 (46%)	1 (8%)
6.Pre-operative sedative premedication is indicated in patients with skeletal dysplasia to reduce risk of potential spinal cord damage if patient struggles during induction.	0	0	8 (62%)	4 (31%)	1 (8%)
7. Epidural anesthesia should not be used in patients with skeletal dysplasias affecting the spine.	2 (15%)	3 (23%)	6 (46%)	1 (8%)	1 (8%)

Table III Second Round -Statements with ≥ 80% of agreement – Recommended guidelines

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	Agree Strongly	Agree	Neutral	Disagree	Disagree Strongly
1.The mortality and morbidity risks for patients with skeletal dysplasia undergoing surgery are greater than the general population	9 (75%)	3 (25%)	0	0	0
2. Because of the higher risk of anesthesia complications in patients with skeletal dysplasia, such patients should undergo surgery at facilities that can anticipate and manage life-threatening complications.	10 (83%)	2 (17%)	0	0	0
3. Patients with skeletal dysplasias should have a comprehensive neurological examination prior to general or regional anesthesia.	11 (90%)	1 (10%)	0	0	0
4. Patients with skeletal dysplasia should have evaluation of neuroaxial integrity and stability with appropriate imaging including cervical, thoracic, and lumbar spine prior to anesthesia.	4 (33%)	7 (59%)	0	1 (8%)	0
5. Flexion/extension MRI is a useful and safe imaging adjunct for the pre-operative assessment of those patients with skeletal dysplasia in whom there is a concern for cervical spinal cord compromise.	5 (42%)	6 (50%)	1 (8%)	0	0
7. Patients with skeletal dysplasia are more likely than the general population to have decreased mobility of cervical spine which will contribute to difficulty with securing the airway.	4 (33%)	7 (59%)	1 (8%)	0	0
8. Patients with skeletal dysplasias are more likely than the general population to have abnormal upper airway morphology and function, which can contribute to increased morbidity/mortality.	7(58%)	5 (42%)	0	0	0
9. Patients with skeletal dysplasia are more likely than the general population to have abnormal tracheal bronchial morphology and function that contributes to increased mortality and morbidity.	3 (25%)	9 (75%)	0	0	0
10. Patients with skeletal dysplasia with respiratory signs or symptoms or thoracic cage structural abnormalities should have a pre-operative pulmonary evaluation.	6 (50%)	6 (50%)	0	0	0
11. Polysomnography should be considered in the pre-operative assessment of patients with skeletal dysplasia.	2 (17%)	10 (83%)	0	0	0
12. Cardiac evaluation should be considered for patients with skeletal dysplasia prior to surgery, particularly for adults.	3 (25%)	8 (67%)	0	1 (8%)	0
13. Pre-operative sedation can be given safely to patients with skeletal dysplasia.	5 (42%)	7 (58%)	0	0	0
14. Pre-operative sedation is NOT indicated in patients with skeletal dysplasia to reduce risk of spinal cord damage if patient struggles during induction.	6 (50%)	5 (42%)	1 (8%)	0	0
15. Abnormal anatomy of the head and neck in patients with skeletal dysplasia may preclude emergency tracheostomy. Therefore, pre-operative assessment of the position of the cricothyroid membrane is essential.	8 (67%)	4 (33%)	0	0	0
16. For patients with skeletal dysplasia, equipment for intubation of a difficult airway such as a video laryngoscope and fiber optic bronchoscope must be immediately available in the operating room.	11 (92%)	1 (8%)	0	0	0
17. Post-operative extubation of a skeletal dysplasia patient is preferably performed in the operating room by an anesthesiologist.	7 (58%)	5 (42%)	0	0	0
18. Because of the higher risk of life threatening airway complications following anesthesia in patients with skeletal dysplasia, if extubation is to be performed outside of the operating room, qualified personnel and equipment must be immediately available.	11 (92%)	0	0	1 (8%)	0
19. Anecdotal reports suggest that epidural anesthesia be used with caution in children with skeletal dysplasia due to risk of neurological injury.	6 (50%)	6 (50%)	0	0	0
20. In patients with skeletal dysplasia and evidence of spinal cord compromise or “spine at risk”* findings, neuromonitoring is recommended for all surgical procedures.	7 (58%)	5 (42%)	0	0	0

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*"Spine-at-risk" findings include: spinal cord impingement from FMS, atlantoaxial instability, cervical stenosis, cervical kyphosis, cervicothoracic kyphosis, thoracic level spinal stenosis, cord level thoracolumbar kyphosis, syrinx, cord signal change on T_2 MRI

Table IV Second Round - Statement that did not reach 80% of agreement

	Agree Strongly	Agree	Neutral	Disagree	Disagree Strongly
6. Because patients with skeletal dysplasia have a high risk for morphologic abnormalities of the upper cervical spine, patients undergoing surgery should have pre-operative lateral flexion/extension x-ray of their cervical spine.	4 (33%)	5 (42%)	2 (17%)	1 (8%)	0

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