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Synopsis: As more Down syndrome patients are living into adulthood, attention has been focused on health factors that affect the quality of the patient's life, and affect their ability to reach full potential. Down syndrome patients have several morphologic abnormalities that predispose them to problems with the ear, nose and throat, and appropriate treatment can have a significant impact on the quality of life of these patients. The Otolaryngologist will likely see many Down syndrome patients throughout their career. The purpose of this paper is to review the literature in order to provide information and recommendations regarding management of Down syndrome for the Otolaryngologist, as well as the pediatrician, so that together we may provide excellent care for these patients.

I. Down Syndrome: Introduction and Background Information

A "syndrome" is a collection of features which occur together and make up a characteristic clinical entity. John Landon Down described the syndrome including microgenia (round face), macroglossia, epicanthal folds, upslanting palpebral fissures, shorter limbs, a single transverse palmar crease, poor muscle tone, mental retardation, and learning disabilities in 1886. The condition was identified as a chromosome 21 trisomy by Jérôme Lejeune in 1959. Today, Down syndrome is the most common congenital chromosome anomaly, occurring 1/700 live births.¹ Recent advances in surgery for the treatment of congenital heart defects have greatly enhanced the survival of children with Down syndrome.² Although life expectancy among

persons with Down syndrome remain decreased relative to the general population, studies in developed countries document sizable gains in child survival, from 25 years in 1983³ to an estimated life expectancy of 50-60 years today.⁴ As more of these patients are living into adulthood, attention has been focused on health factors that affect the quality of the patient's life, and affect their ability to reach full potential. A survey of parents attending a Down syndrome association conference showed that 50% of Down syndrome children saw an Otolaryngologist regularly.⁵ It is likely that the practicing Otolaryngologist will encounter many Down syndrome children, and appropriate treatment can have a significant impact on the quality of life of these patients.

Down syndrome patients have several morphologic abnormalities that predispose them to problems with the ear, nose and throat. These include midface hypoplasia with malformation of the Eustachian tube,⁶ leading to increased number of ear infections and hearing loss, much of which is preventable with aggressive intervention. Patients also have a shortened palate⁷, relative macroglossia, narrowing of the oropharynx and nasopharynx⁸, and generalized hypotonia, which greatly increases the frequency and severity of obstructive sleep apnea in this population. Alterations in the paranasal sinuses,⁹ abnormalities of serum immunoglobulins¹⁰ and ciliary dyskinesia¹¹ contribute to the high incidence of chronic sinusitis. In addition, these patients have many comorbidities that must be considered by the surgeon and anesthesiologist. These include congenital heart disease, pulmonary hypertension, GERD, subglottic stenosis, and cervical instability. As care for patients with Down syndrome has been de-institutionalized in recent decades, and as more of these children are cared for by their parents, integration into schools and social acceptance of these patients has grown. Because of this, more resources have been made available to help these children integrate into society and lead fulfilled, productive, and independent lives. The role of the Otolaryngologist in these patient's lives can be a significant one. While most needed in childhood, the Otolaryngologist will play a role throughout the Down syndrome patient's life.

II. Prenatal

On rare occasion, the Otolaryngologist may be consulted due to lack of nasal bones as seen on prenatal ultrasound. A combined number of approximately 49,000 fetuses from several studies yields a prevalence of nasal bone absence of 65% in trisomy 21 and 1% to 3% in euploid fetuses.¹² If nasal bone evaluation is to be used in screening for Down syndrome, it is important to have sonographers who are formally trained to perform such evaluation. Differences in studies have ranged from a reported rate of 16.7% absent nasal bones in fetuses with trisomy 21 evaluated by sonographers without training or quality assurance,¹³ to 70% prevalence in studies where sonographers were appropriately trained. In the first trimester, the purpose of an ultrasound evaluation of the nasal bones is to recognize whether the nasal bones are present or absent.¹⁴ Ultrasound assessment of nasal bones, in addition to several other ultrasound markers can increase the performance of first trimester screening tests to greater than 90% for a fixed false positive rate of 5%.¹⁵ In the second trimester, the screening focuses on nasal bone length, with hypoplastic nasal bones, being the marker for Down syndrome. Hypoplastic nasal bones are defined as absent or shorter than 2.5 mm.¹⁶ It has been shown that using sonographic markers of prenasal thickness, nasal bone length, and nuchal skin fold, increased the detection of Down syndrome in the second trimester by 19-23% compared to serum markers alone.¹⁷ This rate of 93% detection for a fixed false positive rate of 5% is comparable to first trimester screening protocols.¹⁷ Although absent nasal bones are an important additional finding in prenatal screening, the significance of an isolated finding of absent nasal bones is less clear. One study showed that in 14 patients with absent nasal bones, only 6 had Down syndrome and 8 had a normal karyotype.¹⁸ In this study, 6/6 100% of fetuses with the isolated finding of absent nasal bones had normal karyotypes, however, 6/8 (75%) of the patients who had absent nasal bones in addition to other abnormal ultrasound findings, did have Down syndrome. Although there is no role for Otolaryngologic intervention at this time, it is helpful for the Otolaryngologist to be familiar with this screening tool, as one may be consulted for an opinion or assessment.

III. Ear

The ears of the Down syndrome patient will likely be the impetus for the first encounter with the Otolaryngologist. Down syndrome patients have a range of otologic problems including

stenotic ear canals, increased incidence of secretory otitis media, chronic ear disease and secondary hearing loss, as well as hearing loss caused by ossicular abnormalities and inner ear dysplasia. In early life, it has been estimated that 40-50% of newborns with Down syndrome have stenotic ear canals.¹⁹

These narrowed canals predispose the Down syndrome patient to cerumen impaction, and the cerumen combined with the stenotic canal make it difficult to adequately examine the ear. Further, it has been observed that patients with stenotic ear canals had a markedly increased incidence of associated middle ear effusions.¹⁹ These factors may make it difficult for the pediatrician to adequately examine the ear by otoscopic exam.

It is recommended that Down syndrome children establish care with an Otolaryngologist early in life, as the patient will frequently require microscopic exams and cerumen disimpaction of the canals under microscopy. It is also recommended that those with canal stenosis continue to follow up every 3 months with the Otolaryngologist for evaluation of the middle ear space, to ensure that there is no cerumen impaction, and to monitor for middle ear fluid and infection. Further research is needed on the natural progression of canal stenosis, however, the experience reported by Cincinnati Children's Hospital is that the majority of children with stenotic canals grow with age, and by years 2 or 3 this canal is no longer a obstacle to accurate examination.²⁰ Each patient should be followed regularly by the Otolaryngologist until it is clear that the patient is of appropriate age and size so that s/he is at low risk of serous otitis media and can be easily examined.

The high prevalence of serous otitis media in Down syndrome children has been well documented in academic literature.^{21, 22} There are several etiologic factors that explain this increased incidence of ear disease. Children with Down syndrome have an increased number of upper respiratory infections, possibly due to the reduction of both T and B lymphocyte function^{23, 24} impaired body response to specific pathogens, and defective neutrophil chemotaxis.²⁵ Down syndrome patients also have mid-face anatomy that predisposes them to chronic ear disease. The midface hypoplasia seen in many Down syndrome patients involves the nasopharynx and the eustachian tube openings. A study on the radiographic features of Down

syndrome patients showed that the bony confines of the nasopharynx were smaller in Down syndrome children, and therefore the normal sized soft tissue of the nasopharynx can only occupy this space at the expense of the airway.²⁶ This decrease in post nasal space may cause even small to medium sized adenoids to give rise to Eustachian tube dysfunction. It has also been demonstrated that the eustachian tube in these patients are extremely small, and collapsed in several portions.²⁷ A histopathologic study of Eustachian tubes in Down syndrome patients compared to controls showed that the cartilage cell density in Down syndrome individuals was decreased at all ages, predisposing the canal to collapse.²⁸ Further, it has been hypothesized that the generalized hypotonia of these patients can lead to decreased function of the tensor veli palatini muscle of the palate, which is responsible for opening the Eustachian tube¹⁹. All of these factors combine to cause collapse of the Eustachian tube. This collapse can cause negative pressure in the middle ear space and result in chronic otitis media and fluid accumulation. In addition to the Eustachian tube dysfunction, there may be factors within the middle ear itself that contribute to disease. In a study of otitis media, Ts65Dn mice, which share many phenotypic characteristics of human Down syndrome, were used as a model for human Down syndrome.²⁹ When examined, 11/15 of the Ts65Dn mice had middle ear effusions, as compared to only 2/11 of the wild type mice. On histopathologic exam, the Ts65Dn mice were found to have thickened mucosa and goblet cells were distributed with higher density in the epithelium of the middle ear cavity. Also, bacteria of pathogenic importance to humans was identified in these mice. If we assume these characteristics are also present in the Down syndrome child, it is no wonder these children fight recurring battles with ear infections. The etiologic conditions of secretory otitis media are many, and the impact on the hearing of a Down syndrome child can be profound.

It has been documented that hearing loss in children with Down syndrome is more frequent than in healthy children.³⁰ In studies which have conducted audio screening on randomly selected children with Down syndrome, results have shown that 50-90% of Down syndrome children have a hearing impairment.^{31, 32, 33, 34} In one study, 90% of children were found to have at least a mild-moderate hearing loss. Despite the high point prevalence of hearing loss found in this sample group, only a small percentage of parents (15.2%) reported a positive history of hearing loss.³⁴ Hearing impairment may be masked in patients with intellectual

impairment, as speech delays, and lack of response to verbal cues may be attributed to mental retardation. It is particularly important for the Otolaryngologist to monitor these patients as they are especially susceptible to otitis media and its resulting conductive hearing loss. Detection of this loss is critical, as it is agreed that the detrimental effects of hearing loss on language development are believed to be greater for those children with learning disabilities compared to children without mental retardation.^{35, 36}

It is recommended that all children with Down syndrome go for routine audiologic screening. The American Academy of Pediatrics Committee on Genetic and the Down Syndrome Interest Group Guideline recommend audiologic testing at birth, then every 6 months up to age 3 years, with annual testing after 3 years of age, or when ear specific pure tone audiometry may be obtained.^{37, 38} The initial audiologic evaluation is done by auditory brainstem response (ABR) or otoacoustic emissions (OAE). As the patient grows older, the preferred method of audiologic testing is debated. The evaluation of hearing by behavioral audiometry in young patients is frequently challenging, and is made more difficult in patients who are intellectually challenged. The subject with Down syndrome may have a limited voluntary response during testing, due to lack of attention and poor psychomotor skills. Further, this type of sound field testing does not differentiate between ears, as it evaluates both ears together, so a unilateral hearing loss can be missed. It was demonstrated in a Chinese study that combined objective testing using tympanometry and transitory evoked otoacoustic emission (TEOAE) is a feasible protocol for screening school aged children with Down syndrome.³⁴ The TEOAE is able to detect mild hearing loss, but may be inaccurate in the presence of middle ear fluid. The tympanometry and pneumatic otoscopy by the Otolaryngologist will compliment the exam to screen for hearing loss. However, the TEOAE is costly, limiting accessibility to some patients. Due to cost restrictions, most patients with Down syndrome will go for biannual testing using behavioral audiometry, which should be performed by an audiologist who is experienced in behavioral testing and familiar with Down syndrome patients.

The benefits of pressure equalization tubes in Down syndrome patients has been debated over the past decade. The clinical efficacy of tympanostomy tubes has been well established for

OME in the general population, with reports that tympanostomy tubes decrease the duration of middle ear effusion compared to no surgical intervention.³⁹ However, in the Down syndrome patient, results have been varied. One study examined the short term effects of PE tubes, measured by pure tone audiometry 6-9 weeks after tube placement.⁴⁰ This study found improved hearing in only 60% of Down syndrome patients, compared to 91% improvement in the control group. In this study, all patients were greater than 6 years old, (mean age 8.1), and none had had PE tubes placed in the past. In the Down syndrome population, who are particularly vulnerable to early onset and prolonged duration of SOM, this delay of treatment could be the cause of failure, rather than the treatment itself. A study in Japan also showed poor outcomes in Down syndrome children and a very high complication rate.⁴¹ This study found that very few (21.4%) children were cured of OME by age 7, after the initial set of PE tubes was placed, whereas nearly 88% of controls were cured in this same timeframe. When reviewing this study, there is again faults that do not necessarily indicate treatment failure. Again, the mean age of these children was 5.4 years old, which may be past the critical point in intervening in the Down syndrome population. Secondly, the important finding in this study was that most children with Down syndrome had recurrent OME after extrusion of tubes. In normal controls, the incidence of OME is reported to peak in infancy and decline rapidly after the age of 6, when the immune system and Eustachian tube have reached maturity.⁴² However, it has been demonstrated that OME persists for a longer period in children with Down syndrome,⁴³ and that the canal stenosis, and the highly viscous nature of the mucous expressed, often require further insertion of tympanostomy tubes.⁴⁴ The population studied by Iino would have perhaps had greater success had tubes been reinserted in all patients. Also in this study there was a very high rate of complications in the Down syndrome patients compared to controls. Sequelae of OME were found in 15/50 of the ears in the Down syndrome group including; 4 cholesteatomas, 9 permanent perforations, and 2 atelactatic tympanic membranes. This complication rate has not been reported in other studies, however, it is important to consider when deciding between conservative management and surgical intervention. It is clear from the above literature that the Down syndrome patient cannot be treated with the same timeline and same algorithms that are used for the non syndromic child.

If surgical management is the chosen path, results must be closely monitored, and the surgeon must be aggressive with re-intervention. This has been demonstrated by a study at the Cincinnati Children's Hospital.⁴⁵ In this study, children with Down syndrome were enrolled before the age of 2 years, and were followed by an Otolaryngologist every 3-6 months, depending on the degree of canal stenosis present. All children were treated for chronic ear infections and middle ear effusions by placement of PE tubes, and replacement tubes as needed. At the end of the study two years later, 93% of the patients had normal hearing. The Down syndrome children with the PE tubes in place had a 3.6 higher chance of having normal hearing compared to the audiograms of Down syndrome children who presented at a similar age as the children finishing the study, but had not had aggressive management of OME and did not have PE tubes in place. Also reinforcing this concept is a study done on receptive and expressive language in adolescents with Down syndrome.⁴⁶ In this study, adolescents who had tympanostomy tubes placed when they were children showed significantly higher language scores than did the group of patients who had >3 known infections as a child, but never had tubes placed. This study again suggests that the effects of temporary hearing loss associated with otitis media may play an important role in the language deficits so commonly seen in the individuals with Down syndrome and the effects of the hearing loss extend far beyond the time course of the disease itself.

Surgical intervention by placement of PE tubes can be an effective strategy in management of Down syndrome patients with OME refractory to medical therapy. The otolaryngologist, however, must counsel the parents of the patient of the possible increased risks in these patients, including cholesteatoma, persistent perforation, and atelectatic tympanic membranes. The study by Iino had a nearly 30% complication rate, which they attribute in part to the fact that the eardrums of children with Down syndrome are very thin, which can be seen while applying force to the drum with the pneumatic otoscope or while performing myringotomy.⁴¹ They state, a thin eardrum lacks a lamina propria which lack blood vessels and collagen fibers and are susceptible to permanent perforation. Also, parents must be prepared for the potential that the patient may have persistent otorrhea after tube placement.⁴¹ Also, parents must understand that the treatment of OME in the Down child may differ from the treatment they

may be familiar with or have experienced through other children. They should know that the PE tubes may be placed earlier in the child's life, and to expect that the child may need multiple sets of tubes throughout childhood, even into adulthood. They should be counseled that reinsertion of tubes is a continuation of treatment, rather than failure of the original attempt. Parents should be counseled on the importance of follow up with the audiologist and the Otolaryngologist, and the need for aggressive intervention and re-intervention in order for the procedure to be successful at preventing hearing loss.

In addition to middle ear effusions, a component of conductive loss may be caused by abnormalities of the mastoid, or abnormality of the ossicular chain. A study reviewed neuroimaging of 59 patients with Down syndrome and found nonaeration or underaeration of mastoids in the majority (74%) of cases.⁴⁷ This finding agrees with a previous study, showing 63% of the mastoids examined on lateral cervical spine films with sclerosis and poor aeration.⁴⁸ Whether this increase in density is caused by a mastoid infection that occurred during maximum growth years, or a congenital component is yet to be determined. A study examining 107 patients with Down syndrome found that only 60% of the conductive hearing loss could be explained by middle ear effusions or tympanic membrane perforations. This prompted them to examine the temporal bones of five Down syndrome cadavers, as well as document OR findings during middle ear surgery in these patients.

The findings were as follows; ossicular abnormalities attributed to chronic disease, including erosion of the long process of the incus, of the manubrium of the malleus, and of the superstructure of the stapes. Interestingly, they also had some findings that were attributed to congenital deformities, including malformation of the stapes and dehiscence of the facial nerve.⁴⁹ These findings should be considered in children who have a persistent conductive hearing loss despite maximal management of middle ear effusion.

The increased incidence of chronic ear disease in Down syndrome patient predisposes them to cholesteatoma and erosion of the ossicular chain. Although the 1979 study by Balkany found little improvement in conductive hearing loss in patient with Down syndrome who underwent reconstructive surgery for ossicular chain abnormalities⁴⁹, a more recent study by

O'Malley in 2007 gives more promising results. This is the largest study to date on ear surgery for chronic conditions, including 21 Down syndrome patients, amongst 22 other patients with congenital syndromes. The findings of this study showed that such patients, including those with Down syndrome can successfully eradicate disease with creation of a safe, dry ear, and that ossicular chain reconstruction techniques did significantly improve hearing in this population.⁵⁰

Parents should be counseled that resolution of disease may require several operations. In the above study, 64% of ears were managed with a single surgery, and 89% of ears were controlled with two surgeries or less. Similarly, parents should also be counseled that canal wall preservation techniques may not be appropriate for this population. In Down syndrome patients with cholesteotoma, 70% of patients required a canal wall down study in this study, and 89% of patients required a canal wall down procedure in a study of 9 patients with Down syndrome.⁵¹ These procedures have been successful in eradication of disease in this population, but parents should be counseled appropriately about the likelihood of reoperation and difficulty using canal wall sparing procedures.

In addition to the conductive hearing loss caused by otitis media and middle ear effusion, it is known that Down syndrome children also have higher rates of mixed hearing loss and sensorineural hearing loss compared to other children. It is difficult to determine what percentage of this is due to chronic middle ear disease, and osteoid deposition in the fundus of the internal auditory canal and the region of the spiral tract, through which nerve bundles cross from the inner ear to the internal auditory canal. The true incidence of sensorineural hearing loss in Down syndrome children will be determined as future studies evaluate hearing in children who have been aided by early and aggressive care of their middle ear disease. While the exact figure of SNHL is difficult to determine, studies evaluating hearing in Down syndrome patients have found it to be 4-9%.^{33, 31} Several studies have been done examining inner ear anomalies that may contribute to hearing loss. One study found them to have uniformly small inner ear structures compared to controls, including hypoplastic cochlea, critically smaller cochlear nerve canal, narrowed internal auditory canal, hypoplastic lateral semicircular canal with a small bony island, and hypoplastic vestibules.⁴⁷

Early reports on other options to enhance Down syndrome patient's hearing are promising. The bone anchored hearing aid (BAHA) has been successfully used in Down syndrome patients who failed conventional hearing aides and ventilation tubes. A review of BAHA centers in Ireland and the UK showed that 18/81 BAHA centers are performing surgery on Down syndrome patients.⁵² Of the 43 patients with Down syndrome who were implanted, all but one wore the BAHA on a daily basis, which indicates a high level of patient satisfaction. A survey on perceived patient and parent/caregiver satisfaction was completed by the centers, and showed 27/28 were very pleased or pleased with the results. Similarly, a study surveying 15 patients with BAHA found all 15 using the BAHA regularly, with audiologic benefit.⁵³ To evaluate the overall benefit of the BAHA, the Glasgow Children's Benefit Inventory was used, which evaluates emotion, physical health, learning and vitality. The results of this study showed a significant benefit in all categories in Down syndrome children. Complications in the first study were 50%, which is significantly higher than previously reported 9-16% in non-syndromic children and 32% in adults. The complication rate in the second study was 20%. In both, the most common complications were soft tissue problems, including excessive healing of the graft site with hypertrophy of soft tissues, graft infection, and skin reaction. All were resolved within a relatively short time, usually within 2 months. The increase in soft tissue complications in patients with Down syndrome may be attributed to the fact that patients with learning difficulties have a tendency to interfere with the area, leading to disturbances of the dressing, sutures and possible graft failure. A solution to this was proposed, where following BAHA abutment a perforated thermoplastic cage is formed over the surgical site and sutured into place. The empirical evidence within this practice has shown this to be effective.⁵⁴

Cochlear implants were originally not recommended to patients with additional disabilities beyond hearing loss. However, with a growing body of knowledge and good results, inclusion criteria are expanding and there are now increasing numbers of such candidates, including patients with Down syndrome. A study published in 2010 reported that at least four patients with Down syndrome had received cochlear implants in the UK and Ireland.⁵⁵ In all cases the deafness was congenital, and all four of the patients had middle ear disease pre operatively, with two patients requiring PE tubes. However, all of the patients were treated pre

operatively and none of the cases had any complications associated with otitis media. Despite the previous discussion of mastoid underaeration and opacification, inner ear dysplasia, shortened cochlear lengths, and dehiscent facial nerve, none of the patients implanted had any of these findings and none had intraoperative difficulties. The outcomes of these four implanted patients have been modest gains in auditory performance, with the eldest child, who has had the implant the longest, showing the most improvement. As more patients with Down syndrome become candidates for cochlear implants, patients and families must be counseled about expectations. There are abnormalities in the temporal bone of a child with Down syndrome that may increase the risk of complications. Even in technically successful implantation, the outcomes may not be as good as children without additional disabilities, as learning and communication difficulties may prolong the rehabilitation. Still, these patients do show improvement, and future Down syndrome patients with profound SNHL may be referred for assessment at cochlear implant programs.

In addition to surgical options, initial studies using sound-field amplification and speech/language intervention have shown excellent results. A pilot study tested an aggressive multi-disciplinary model, consisting of amplification technology and speech/language intervention that emphasizes auditory-verbal therapy, as well as aggressive medical and surgical management of ear pathology.⁵⁶ This program was initiated in children with Down syndrome less than one year old. The findings in these six children enrolled in the program were that the children in the intervention group had developed age appropriate early language skills, with no apparent gap between their receptive and oral expressive language abilities. A group of Down syndrome children of the same age who did not have the intervention were used as comparison, and the no intervention group exhibited generalized language delays with a noticeable gap between receptive understanding and oral expressive language. Another study examined the benefits of sound field amplification in 4 children with Down syndrome in the classroom setting.⁵⁷ The study found that that participant's speech perception significantly improved when the FM sound field amplification was being used. The sound field amplifier is recommended over a traditional hearing aid in this population, as the sound field amplifier selectively amplifies the teacher's voice, which improves the signal-to-noise ratio, whereas the hearing aid increases

all sounds equally, including background noise that can be distracting. In the patients with Down syndrome, who are prone to fluctuating conductive hearing loss, the effects of poor classroom acoustics are significant. As more of these Down syndrome children are mainstreamed and placed in public schools, additional support is needed to achieve full potential. More outcomes research is needed, but sound field amplifiers have the potential to improve classroom performance.

IV. Obstructive Sleep Apnea and Sleep Disordered Breathing

Although obstructive sleep apnea syndrome (OSAS) is seen in only 0.7% to 2.0% of the general pediatric population^{58, 59}, the prevalence in pediatric Down syndrome patients has been estimated at 77-80%.^{60, 61}

Children with Down syndrome have many predisposing factors of OSAS. These include midfacial and mandibular hypoplasia⁶² glossoptosis, an abnormally small upper airway with superficially positioned tonsils and relative tonsillar and adenoidal encroachment,⁸ increased secretions, and increased incidence of lower respiratory tract anomalies, obesity and generalized hypotonia with resultant collapse of the airway during inspiration. It has had been shown that children with OSAS have a worsened trend in word reading speed, visual attention, and verbal fluency.⁶³ Further, OSAS has been shown to result in neurodevelopmental problems such as daytime somnolence, behavioral disturbances, school failure, and developmental delay.⁶⁴ Obstructive sleep apnea can cause pulmonary hypertension resulting in cor pulmonale and congestive heart failure secondary to the chronic, intermittent hypoxemia and respiratory acidosis during sleep.⁶⁵ Although we know of no published studies specifically examining these effects of neurodevelopment and learning on children with Down syndrome, it is logical to expect that this population, who is already predisposed to learning delay and difficulty in school, would be significantly impaired by the effects of sleep apnea. Similarly, children with Down syndrome are predisposed to congenital cardiac anomalies, and are more likely to have pulmonary hypertension than are non syndromic children with the same cardiac anomalies.⁶⁶ Again, this may be exacerbated or worsened by OSAS.

The diagnosis of OSAS should come from an overnight polysomnography whenever possible. A study examining 53 patients with Down syndrome for OSAS by nap study, and of those, 16 patient had both a nap polysomnography and an overnight polysomnography.⁶⁰ Of those 16 patients, all 16 (100%) had abnormal overnight polysomnograms, but the nap study was less sensitive in detecting OSAS, with only 12 (75%) of these patients having abnormal nap studies. The degrees of hypoventilation and desaturations were significantly higher in the overnight studies, and thus the nap studies under estimated abnormalities.

The diagnosis of sleep apnea is not limited to the Down syndrome children who snore, although those that do snore have a very high likelihood of having a positive sleep study. In a retrospective review of Down syndrome patients who were referred for polysomnography due to snoring, 97% of these snoring patients did have a positive sleep study.⁶⁷

The Down syndrome child who is not reported to snore is still at significant risk for sleep apnea. It may be difficult for a parent to tell if a child is suffering from sleep apnea, as the most severe apneic events often happen during REM sleep, very late at night, when the parents are also asleep. In the Down syndrome child, the parent may assume that their child's irregular breathing at night is normal for a child with Down syndrome, a frequently expressed comment.⁶¹ It has been concluded that parental reports are not reliable in ruling out sleep apnea. A study showed that 11/35 (31%) of Down syndrome parents reports that their child had sleep problems, but these parents were correct about a sleep abnormality in only about 4/11 (36%) of cases. The other 7/11 (64%) had normal PSG. Of the 24/35 (69%) of parents who reported no sleep problems, 13/24 (54%) of the children had abnormal PSG, and did indeed have obstructive sleep apnea.⁶¹ In the another study, 19/49 children (39%) had histories suggestive of OSAS. Polysomnograms were abnormal in all 19 (100%) of the patients with a positive history. However, 18/30 (60%) of the children with negative histories also had abnormal polysomnograms. Down syndrome children who snore are very likely to have sleep apnea, but those that do not snore are still at high risk for OSAS and should be evaluated.

Because of the unreliability of parental reporting, the high prevalence of OSAS in this population, and the negative effects of sleep apnea, it is recommended that all children with

Down syndrome between the ages of 3 and 4 years, go for objective testing using full overnight polysomnography for a baseline study.⁶¹

Because of the possibility of health problems associated with OSAS in a population already at higher health risk, it is important to learn as much as possible about the etiology of the disease. One established risk factor for OSA in adults and children in the general population is high BMI, and weight reduction is often effective at decreasing the effects of sleep apnea.⁶⁸ The correlation between BMI and OSAS in the Down syndrome patient is not so clear, however. A study surveyed consecutively encountered, non selected Down syndrome patients. He found 79% of them to have OSAS, and higher BMI was significantly associated with a higher apnea index and lower SaO₂ level.⁶⁹ A study in 2010 compared age matched Down syndrome children with OSA and without OSA based on PSG results.⁷⁰ The results of this were that mean BMI z-score was statistically significantly different between OSA and non-OSA groups, with the OSAS group having a BMI z-score of 2.09 and the non sleep apnea with a BMI z-score of 1.4. The BMI z-score, also called BMI standard deviation score, are measures of relative weight adjusted for child age and sex.⁷¹ However, there were some patients in this review who had an extremely high BMI who had a normal sleep study, and several patients with a low BMI did have OSAS. Similarly, in the study by Fitzgerald et al in 2007, 91% of his study subjects were not obese, yet 97% had OSA and 50% of those had severe OSA.⁶⁷ Based on these results, OSAS is likely a multi-factorial disease with several contributing factors in these patients. Still, BMI is a modifiable risk factor, and the results of the above studies suggest that weight reduction may show some benefit in the management of OSA in Down syndrome children.

Before entertaining tonsil and adenoid surgery in the Down syndrome population, it is now recommended that a pre-operative polysomnography is obtained.⁷² For those children who are diagnosed with OSAS after a sleep study, the initial surgical treatment for OSAS in children is tonsillectomy and adenoidectomy,⁷³ including children with Down syndrome. The efficacy of tonsillectomy and adenoidectomy in curing sleep apnea in Down syndrome patients is generally accepted to be lower, with 30-50% of Down syndrome patients requiring continuous positive pressure airway support (CPAP), further surgery, or tracheostomy at a later date.^{8, 74} A recently

published paper confirms this, giving exact data on pre operative and post operative polysomnograms in both Down syndrome, and non syndromic children who served as age and BMI matched controls.⁷⁵ In the Down syndrome group, the AHI showed improvement after surgery, but was not as significant as the improvement in the control group. The REM-AHI and lowest SaO2 did not show significant change in the Down syndrome children, whereas all respiratory parameters improved in the control children. None of the non syndromic children required CPAP or further surgery after T&A, despite having elevated BMI (average 27.6). 73% of the Down syndrome children went on to require CPAP, BiPAP, supplemental oxygen for persistent OSA after T&A. This cure rate is lower than the rate previously cited, where 48% of Down syndrome patients had a persistently elevated AHI after T&A.⁷⁶ The variability between these two outcomes is likely due to patient co morbidities, as it has been shown that patients with multiple co morbidities have poorer outcomes in curing OSA.⁷⁷ Although the success rates of T&A in curing sleep apnea in Down syndrome children is not what we see in non-syndromic children, the procedure may still be recommended if the parents are given appropriate information about expectations and can give informed consent. It is very important to ensure that parental expectations of T&A in the Down syndrome patient is not for complete cure, but for improvement in symptoms. In the study above, all patients showed some improvement in AHI after T&A. Although we know of no exact data, this improvement in AHI and partial relief of obstruction, may decrease the need for CPAP or oxygen. Although the patient may still require supplemental breathing support at night, the setting on the CPAP may be decreased, resulting in greater patient comfort. It is known that CPAP compliance is low in normal adults⁷⁸, and it is even more difficult for children with a developmental disability, who do not understand the disease or the treatment, to be fully compliant. Therefore, a likelihood of reducing dependence on CPAP, and/or a 25-50% chance of being weaned completely from a nighttime breathing apparatus, may make the surgery a good option for many Down syndrome patients. In addition to managing parental expectations about the success of tonsillectomy and adenoidectomy, parents also need to be counseled on the risks.

A questionnaire survey of 74 parents of children with Down syndrome was conducted and found that 2/74 Down syndrome patients developed transient velopharyngeal insufficiency,

and 2/74 other patients reported permanent hypernasal speech after adenotonsillectomy.⁷⁹ Although it is difficult to extrapolate from this to determine the exact frequency with which VPI and hypernasality occur in Down syndrome patients after T&A, we can assume it is significantly higher than the 1:2000- 1:3000 rate of complication seen in the general population.^{80, 81} When given complete evaluation, these patients who reported complications were found to have both structural and functional causes of hypernasality. Structural causes of hypernasality included a high arched, and short soft palate. The functional component included hypotonia, slowed motor learning, and oral-motor developmental delay. From this information, we can assume that all patients with Down syndrome are at higher risk of developing VPI or hypernasality post operatively, as the above listed characteristics are common to Down syndrome patients. Further, a different study reviewed post operative complications in Down syndrome children compared to controls, and found a higher incidence of complications in the Down syndrome group after adenotonsillectomy, including increased hospital stay, fivefold increase in respiratory complications requiring intervention, and increased duration until adequate PO intake.⁸² Parents are best counseled on the risks pre-operatively, and special precautions and preparations should be made on a case by case basis, based on the child's condition and co-morbidities.

Most patients who have persistent OSAS after tonsillectomy can be treated with CPAP. In an ideal world CPAP is a very effective therapy. Realistically, the therapeutic benefit of CPAP is limited by poor patient compliance, especially in the pediatric population. For this reason, patients often prefer a surgical option if one is available. The next step in surgical treatment, after T&A, is more complex. Patients with Down syndrome have anatomy that predisposes them to multi level airway collapse, and preoperative planning must identify the level responsible for collapse as well as the severity. Standard work up has included history and physical examination, including flexible nasopharyngoscopy to the level of the larynx. "Sleep nasoendoscopy" has been used in the past to determine sites of airway obstruction. In this procedure, the child is put under light sedation with spontaneous respirations in a supine position. Flexible endoscopy is performed and the airways can be evaluated and recorded.⁸³ However this technique is flawed, as one cannot see the entire airway at the same time, so one cannot evaluate the effects of sequential obstruction; ie, how one level of obstruction affects a

second level. Recently, cine MRI has been used with good results to assist in planning additional surgical intervention.^{84, 85} Cine MRI was originally used by neurosurgeons to evaluate CSF flow in real time. Now it is being used in some institutions to assess sleep apnea patients. In this case, the patient is placed supine on the table, sleep is induced by sleep deprivation, spontaneous sleep or sedation. The evaluation is most accurate if imaging takes place when the patient is snoring or having apneic events during spontaneous respirations. The cine MRI obtains multiple sagittal and axial images in real time, creating a dynamic, three dimensional video of the airway collapse. This view can appreciate multiple levels of collapse, and it has also been noted that adenoid enlargement and nasopharyngeal obstruction are more prominent on cine MRI.⁸⁴

Although many patients may go on to need further surgery for OSAS, there is not data to support more aggressive surgery initially. A study examined patients with Down syndrome who underwent T&A, and Down syndrome patients who underwent T&A plus lateral pharyngoplasty as initial therapy for OSAS. They found no significant difference between the groups, with 48% in the T&A only group to have persistently abnormal AHI post operatively, and 63% in the T&A plus lateral pharyngoplasty group to have abnormal AHI after surgery.⁷⁴ Therefore, it is recommended that tonsillectomy and adenoidectomy alone be the initial surgical treatment, and the patient may return for subsequent treatment if this procedure is not curative. Recently data was published on combined genioglossus advancement and radiofrequency ablation of the tongue base in pediatric patients with OSAS refractory to T&A. In this study, 61% of the patients had Down syndrome.⁸⁶ Successful outcome was achieved in 12/19 patients with Down syndrome, resulting in AHI of <5, maintaining an oxygen saturation of >90% throughout the night, and end tidal CO₂ above 50 mmHg less than 10% of the total sleep time. The findings of this study support treatment of refractory OSA with GGA and RFA in the Down syndrome population. Although this report is promising, further research is needed supporting and validating other methods of treating refractory OSA with multi level obstruction.

V. Rhinitis and Sinusitis

The Down syndrome patient is predisposed to chronic nasal drainage, nasal obstruction, and sinusitis due to the narrowing of the nose and nasal sinuses. One study of Down syndrome patients found that 17.6% of Down syndrome children were reported to have a continual runny nose.³⁹ The narrowing of their nasopharynx leads normal growth of adenoid tissue to obstruct the airway, predisposing patients to nasal congestion and subsequent infection. Additionally, several studies have shown abnormalities in the immunoglobulin (Ig) levels in Down syndrome^{23, 87} with IgG4 subclass deficiency the most common finding in patients with recurrent infection.⁸⁸ A review of immunological features of Down syndrome describes that while the primary immune defect seems to be greatest in the cellular compartment, even the humoral immunity in Down syndrome subjects undergoes a precocious aging.⁸⁹ The combination of an anatomically small and obstructed nasopharynx, combined with decreased immunity, predisposes the Down syndrome patient to chronic rhinorrhea and sinusitis. Treatment of this nasal drainage is similar to the general population, with nasal irrigation, nasal steroids, antihistamines, decongestants and antibiotics as needed. One study treated 25 Down syndrome children empirically with low dose ampicillin daily, from the onset of symptoms until May. This treatment gave an excellent response, as reported by parents.⁸ In patients whose sinusitis and rhinitis are not aided by medical management surgical intervention may be warranted. Flexible nasopharyngoscopy should be preformed to look for adenoid hypertrophy, which may be obstructing the choanae. This should be done even if the patient has already had an adenoidectomy, as regrowth of adenoid tissue is more common in the Down syndrome patient compared to the general population.⁸⁴ If the patient does have obstructing adenoid tissue, it is important to know that adenoidectomy is less effective in treating nasal and middle ear syndromes in children with Down syndrome compared to controls. One study examined adenoidectomy in Down syndrome children compared to controls, and the efficacy in treatment of nasal obstruction, snoring, mouth breathing and middle ear disease. The findings were that while a moderate portion of the Down syndrome patients improved, the percentage of patients who were symptom free after adenoidectomy was significantly lower than the control group with nearly every symptom. Again, parents should be counseled pre operatively, and given

expectations for improvement, but not necessarily a cure. The physical exam and nasal endoscopy should assess septal deviation, as well as turbinate hypertrophy that may be amenable to surgical correction. If patient continues to have persistent sinusitis despite maximal medical therapy, then a CT scan of the sinuses is recommend. Based on the results, functional endoscopic sinus surgery may be warranted.

A new method of treating nasal obstruction is currently being explored; rapid maxillary expansion has been used to augment nasal volume and reduce ear, nose and throat infections. Rapid maxillary expansion is an orthodontic procedure used to correct a narrow transverse maxillary diameter. The two maxillary bones are separated at the mid-palatal structure using and intraoral screw mechanism. This leads to a widening of the perimeter of the arch. Although the major effect is noticed clinically in the area of dentition, the transverse enlargement of the apical bone also affects nasal width. Usually, these changes result in altered nasal airway flow, with consequently improved nasal ventilation.⁹⁰ In this study 13 patients with Down syndrome used the intraoral maxillary expansion device and 10 patients with Down syndrome did not. The results showed a significant increase in the total nasal volume, which persisted five months after removal of the device.⁹¹ The study further reported a significantly improved incidence of acute otitis media, adenoiditis, and tonsillitis in the RME group, as well as improved severity of snoring, mouth breathing, restlessness, word articulation, tongue protrusion and facial aesthetics. Although the small sample sized used in this study is not sufficient to create general guidelines, it is hopeful that the promising results of this study will prompt further investigation into this area.

VI. Airway Abnormalities

sleep apnea, patients with Down syndrome have anomalies of the upper and lower airway that, combined with comorbidities such as GERD, hypotonia, and obesity, may create complex and chronic large airway obstruction. A review of all patients referred to a tertiary care center in New Mexico over a 2 ½ year period for upper airway obstruction showed the most common reason for referral was laryngomalacia (43%), with the majority of these patients being under one month of age.⁹² Laryngomalacia is more common in children with neurologic disorders,

particularly hypotonia. Down syndrome patients have generalized hypotonia, leading to flaccidity of the supraglottis, anatomical changes in the epiglottis, arytenoids, and aryepiglottic folds and a high prevalence of GERD. Severe laryngomalacia can usually be surgically corrected by aryepiglottoplasty, which is safe and effective in children without significant comorbidities.⁹³ We know of no published data on the outcomes of aryepiglottoplasty in Down syndrome patients; however, the generalized hypotonia, the high incidence of GERD, and the likelihood of multiple intubations for further surgical procedures, makes this a more complicated procedure in the Down syndrome patient. It is therefore recommended that patients be referred to tertiary care centers that are familiar with taking care of these patients.

A review of all Down syndrome patients with upper airway obstruction over 5 years at Egleston Children's Hospital shows the complexity of these patients, the multifactorial nature of their disease, and illustrates the treatment challenges.⁹⁴ In this study, 71/518 patients seen with Down syndrome were diagnosed with airway obstruction. Of these 71, the 39 that had the most severe symptoms underwent operative endoscopy including flexible fiberoptic endoscopy, rigid laryngoscopy and bronchoscopy. Multiple sites of obstruction were seen in 38% of cases. Tracheomalacia was found in 23/39 (59%), laryngomalacia in 28%, macroglossia (26%), subglottic stenosis (23%), and congenital tracheal stenosis (5%). In this study, children with severe symptoms were more likely to be younger, have more than one site of airway obstruction. Nearly ¼ of the patients in this study had residual symptoms after surgical correction, likely due to the severe baseline degree of obstruction, multiple anatomical sites of obstruction, and craniofacial structural problems. Again, it is important that these cases be managed by a tertiary care center that is familiar with treating the Down syndrome patient and is practiced at comprehensive airway evaluations and a systemic approach to surgery in the Down syndrome child. Even at centers with high volume of Down syndrome patients, parents should be counseled pre-operatively about the possibility of residual symptoms in children with severe obstruction.

Subglottic stenosis is also believed to be more prevalent in the Down syndrome population, although the exact prevalence and etiology is difficult to determine. A study

reviewing laryngotracheal reconstruction (LTR) showed that 4% of LTRs done at that hospital were on Down syndrome patients.⁹⁵ Given the prevalence of Down syndrome as 0.1%-0.15% of live births, they concluded that SGS may be more common in Down syndrome patients. The higher prevalence is likely due to higher incidence of congenital narrowing of the subglottis as well as acquired deformities. A retrospective review of 15 Down syndrome patients who underwent laryngotracheoplasty for subglottic stenosis found the risk factor for SGS in Down syndrome children to be the same in the Down syndrome group as for the general population; trauma to the subglottis.⁹⁶ The Down syndrome child has a higher rate of major surgery (i.e. cardiac anomalies) and intubation, as well as severe respiratory infections requiring intubation.⁸⁷ In Down syndrome patients this usually occurs at a young age, which predisposes them to subglottic injury and subsequently, subglottic stenosis. Therefore, SGS is more commonly seen in the Down syndrome population.²⁴ One study of 99 patients with Down syndrome who underwent surgery for cardiovascular surgery found 24 (24.2%) of the patients had post extubation stridor, and subglottic stenosis was found in 6 (6.1%).⁹⁷ In the 6 that were found to have subglottic stenosis, all 6 were less than the 10th percentile for weight, and an endotracheal tube of larger diameter than expected for age was used in 4 patients.

A key factor in preventing subglottic injury, is choosing an appropriate sized endotracheal tube, as age-appropriate endotracheal tubes are too large for the Down syndrome patient. One retrospective study reviewed 100 patients with Down syndrome undergoing endotracheal intubation.⁹⁸ Of these 100 Down syndrome patients, 20 required ET tubes smaller than their expected age, leading to the conclusion that the airway in the Down syndrome patient is inherently smaller. A prospective study evaluated 74 children, 42 with Down syndrome, 32 healthy controls, none of whom had wheezing, stridor, or previous intubation before surgery.⁹⁹ The Down syndrome children required an ETT 2-3 sizes smaller than age matched controls. Further, MRI showed that tracheal diameter was smaller in Down syndrome compared to controls, demonstrating that the overall smaller airway size is not limited to the subglottis, but includes a smaller trachea. In any surgery, the appropriate sized endotracheal tube should be used. In Down syndrome children, it is important to be cognizant of the fact that age appropriate ETT may be too large, and one should always check for an appropriate air leak around the

endotracheal tube. The recommendations based on this prospective study are that endotracheal tubes at least two sizes smaller should be initially used for intubation in children with Down syndrome.⁹⁸ To ensure proper sized tube placement, it is critical to confirm the fit of the tube after it is placed by checking for an audible air leak at an inspiratory pressure between 10-30 cm H₂O.

VIII. Anesthesia Considerations and Co-morbidities

In addition to the special needs for intubation and endotracheal tube selection, Down syndrome children are at higher risk for other complications of anesthesia. One consideration the Otolaryngologist must take into account is atlanto-axial instability (AAI). Although AAI is one of the most well known and feared problems associated with Down syndrome, reports of complications associated with AAI are few, and current guidelines and recommendations of airway management and positioning during surgery for the patients are vague. Studies have shown that the incidence of AAI seen on radiography is 14-20%^{100, 101} However, the incidence of symptomatic AAI is much less with only a few case reports throughout the literature. In the study of 404 patients with Down syndrome that found 14.6% to have radiographic evidence of AAI, only 1.5% of the patients had symptoms.⁹⁹ Atlanto axial instability, also called atlantoaxial subluxation, is the result of increased mobility at the articulation of the first and second cervical vertebrae. A review reports that craniocervical instability, most commonly atlantoaxial instability is the result of generalized ligamentous laxity, involving any of the three ligaments of the C1C2 joint. It can be acquired or precipitated by upper respiratory infections. Rotation of the head may result in C1C2 subluxation.¹⁰² The radiographic definition of AAI is made by measuring the distance between the anterior surface of the dens to the posterior surface of the tubercle of C1. An anterior atlantodental interval of greater than 4.5 indicates abnormal instability. Asymptomatic AAI is that which is diagnosed by radiography, but the patient has no neurologic symptoms. The patient who is symptomatic may experience easy fatigability, abnormal gait and difficulty walking, neck pain, limited neck mobility, torticollis, clumsiness, lack of coordination, sensory deficits, spasticity, hyperreflexia, clonus, incontinence, and extensor-plantar reflex.

The issue of atlanto axial instability came into wide recognition after the Special Olympics introduced a requirement in 1983 that all individuals with Down syndrome have a lateral neck radiograph before participating, and that those with evidence of instability be banned from certain activities. This was further supported by a statement by the American Academy of Pediatrics in 1984.¹⁰³ Since these statements were issued more research has been done on the subject, bringing evidence that radiographic screening is not the best method to prevent injury from AAI. One report prospectively studied 135 children with Down syndrome in an attempt to find clinical predictors of symptomatic AAI, and found that abnormal gait was the only significant clinical predictor of adverse outcome, and that radiographs of the neck to be unreliable at identifying atlantoaxial subluxation.¹⁰⁴ A review of case reports of individuals who have experienced catastrophic injury to the spinal cord by the AAP determined that trauma rarely causes the initial symptoms or progression of symptoms, and that nearly all the individuals who have experienced catastrophic injury to the spinal cord have had weeks to years of preceding, less severe, neurologic abnormalities.^{99, 101, 105, 106} In a 1995 statement, the AAP retired their previous statement, and revised their recommendations to state that evaluation and physical exam by a physician who has cared for the patient longitudinally, is a greater priority than obtaining radiographs when determining a Down syndrome patient's eligibility for participation in sports.¹⁰⁷ It is now recommended that the pediatrician perform a careful history and physical examination with attention to myelopathic signs and symptoms at every well-child visit, or when symptoms possibly attributable to spinal cord impingement are reported.³⁸

The 1980s focus on atlanto axial instability by the Special Olympics and AAP, has raised concerns by Otolaryngologists, who frequently perform surgery in non neutral neck positions. At least one case of quadriplegia attributed to atlantoaxial subluxation during ear surgery has been reported.¹⁰⁸ Recently, investigation into using somatosensory evoked potentials (SEP) to prevent spinal cord injury has been performed. The SEP measures the speed and efficiency of afferent neural transmission and processing. A delay in SEP latency suggests spinal cord compression. In one study, 17 patients with Down syndrome, who were undergoing elective Otolaryngologic surgery, with no evidence of C-spine problem by neurologic exam and had an atlantodens interval of less than 5mm by radiography, had SEP monitoring during surgery. In

each patient the head was rotated 60 degrees right and 60 degrees left. In all cases the patients maintained normal SEPs. The conclusion of this study is that patients with Down syndrome who are neurologically intact and who have normal lateral neck radiographs, with more than 99.99% certainty, do not appear at great risk with neck rotation, as would be performed in ear surgery. As the use of SEP continues to be studied and developed, it may become routine for use in cases involving patients with Down syndrome. As of now, there is not enough evidence to include SEP in guidelines. Because the poor ability of radiographs to detect clinical neurological compromise, it is imperative that every patient have a thorough neurologic exam pre operatively, preferably by a physician who knows the patient well. While gentle rotation of the head for ear surgery is likely safe, it is still recommended that the patient's head be supported throughout the procedure, and that extremes of neck positioning be avoided. When performing tonsillectomy, the patient should remain in a relatively neutral position..

Another comorbidity found with high prevalence in the Down syndrome population that is of particular interest to the Otolaryngologist is gastro-esophageal reflux disease (GERD). A study reviewing all patients with Down syndrome referred to a tertiary care center found systemic comorbidities in 93% of patients, with GERD being the most common, diagnosed in 59%.¹⁰⁹ It is known that ear, nose and throat disease is exacerbated by GERD.¹¹⁰ In a study of laryngotracheoplasty in Down syndrome, it was noted that in addition to having a high incidence of subglottic stenosis, there was also a higher rate of post glottic stenosis within Down syndrome patients compared to the overall series.⁹⁵ Of the patients who were tested for GERD, 9/9 were found positive. The authors of this study believe that GERD is a contributing factor in forming SGS, and in the face of previous mucosal injury, acid reflux may encourage scar formation in the posterior glottis. Additionally, failure to control reflux can interfere with graft healing.⁹⁵ It is imperative that the Otolaryngologist diagnose and aggressively manage GERD in the Down syndrome patient.

Other anesthetic considerations of Down syndrome patients include cardiac lesions and conductive disturbances, pulmonary hypertension, polycythemia in neonates, hypothyroidism, sensitivity to atropine, and decreased catecholamine release, resulting in deeper levels of

anesthesia. A full discussion of these comorbidities is beyond the scope of this paper. It is important for the surgeon to obtain all past medical and surgical history and to ensure all members of the surgical team are familiar with the patient's history and proper precautions are taken. Communication between the anesthesiologist, surgeon, and operating room team is key to successful outcomes.

IX. Conclusions

Down syndrome children live longer, and become integrated into mainstream society, more emphasis is being placed on quality of life and utilizing healthcare to help these children maximize their potential. It is likely that the majority of children with Down syndrome will be seen by an Otolaryngologist at some point. For stenotic ear canals and cerumen impaction, pediatricians should not hesitate to refer the child to an Otolaryngologist for cerumen removal and microscopic exam. The Down syndrome child should undergo behavioral audiologic testing every 6 months, or every 3 months if the patient has very stenotic ear canals. This behavioral audiologic testing should continue until the child is able to cooperate with ear specific testing. Treatment of recurrent otitis media and otitis media with effusion should be aggressive and post operative results should be closely followed with serial physical exams and audiometry. Parents should be prepared for multiple sets of pressure equalization tubes throughout the child's life. Patients with Down syndrome have a higher prevalence of obstructive sleep apnea than non syndromic children. The consequence of untreated obstructive sleep apnea is hypoxemia and hypoventilation, and this can lead to development of pulmonary hypertension and congestive heart failure. Because it has been shown that parents are not reliable predictors of sleep apnea, it is recommended that all children with Down syndrome get polysomnography between the ages of 3-4 years. Primary treatment of OSAS is tonsillectomy and adenoidectomy, but parents should be prepared that this is curative in only 25% of children, and that their child may require further surgery to alleviate obstruction. Treatment of chronic rhinitis and sinusitis should be aggressive and include saline nasal spray, antihistamines, decongestants, nasal steroids, and antibiotics if needed. Airway anomalies are more common in the Down syndrome population, with subglottic stenosis being more prevalent than the general population. Prevention of subglottic stenosis can be achieved in part by using an endotracheal tube two sizes smaller than

predicted for patient's age, and ensuring and audible air leak is present around the tube. In cases of complex airway trauma requiring surgical repair, these are better managed at a tertiary care center with experience in syndromic children, due to the high rate of complications in these patients. Due to the high prevalence of GERD in this population and the effect it can have on Otolaryngologic disease, all Down syndrome patients should be evaluated for GERD and aggressively treated if it is found to be present. During surgery in Down syndrome patients, the surgeon should always be aware of the possibility of atlanto axial instability, and no dramatic head movement should be made. In tonsillectomy, the patient's head should remain in neutral position, and during otologic surgery the patient's head may be turned, but should be supported at all times. Post operatively, Down syndrome patients tend to have a higher rate of complications including stridor, desaturations, poor oral intake, and behavioral problems. Because of this, it is recommended that children with DOWN SYNDROME be admitted for observation when intubation is required, even for short procedures such as tonsillectomy and adenoidectomy. Although these children have disease that is more complex and difficult to treat than the non syndromic pediatric patient, the general Otolaryngologist can have a profound impact on the Down syndrome patient. Proper management of ear, nose, and throat disorders by the Otolaryngologist can support the Down syndrome child's physical, emotional, and educational development.

Comments by Dr. Harold Pine and guest faculty on Dr. Regina Rodman's discussion of ENT problems encountered in Down syndrome children

Dr. Pine: Dr. Rodman, that was a really great review of the ENT problems encountered in the care of Down syndrome children, and we're fortunate to have with us **today two noted pediatric otolaryngologists, Dr. Austin Rose (Assoc. Prof. UNC Chapel Hill, N.C.) and Dr. Soham Roy (Assoc. Prof. UTHSC Houston, TX)**

Dr. Rose: In cases with cholesteatoma and chronic ear disease, probably the hardest I've ever dealt with have been the cases with Down syndrome. you know, we all deal with contracted mastoids in routine cholesteatoma, but these are really the toughest. Also, usually when these cases come up I bounce them off our otology colleagues as well.

Dr. Pine: I want to ask our visitors whether you routinely get flexion and extension X-Rays on Downs children for T&A. We don't here but I agree with Dr. Rodman that we should just take the usual precautions that we do anyway. In my own personal practice I have gone away from routinely getting films but that is with the assumption that they do not have neurological symptoms, much like not getting coagulation studies based on the fact that they have a negative history. You must have a good history or the notes from the pediatrician, because if something does go bad, the responsibility typically falls on the surgeon.

Dr. Roy: I would agree with that. You know, we used to get routine neck flexion and extension films all the time in these children and now what I do is , if you flex or extend them in the operating room something may happen, so why don't we do that in the office when they are awake. I have them look up at the ceiling and down at the floor and I see if they have any neurologic changes or if the parents have noticed any neurologic changes. If not, then I no longer get routine neck films. If they do, however, I absolutely get flexion and extension films preop.

Dr. Roy: Dr. Rodman, that was an excellent presentation. Can you make any comments on what you saw of some of the more modern procedures for obstructive sleep apnea in kids who have not improved, because as you mentioned a large population of children with Down syndrome are not going to improve after tonsillectomy and adenoidectomy? For example, central midline glossotomy has become a big operation for the population of Down syndrome with tongue base problems.

Dr. Rodman: I haven't done any real research on the other procedures and there is really not that much published at this point. I hope some of the high end places doing this stuff will publish their data. Perhaps Dr. Pine knows of some of the cool stuff going on out there.

Dr. Pine: (continuing) At the Academy meeting Peter Koltai from Stanford got up and presented some of his data showing that in the Down kid especially they get sort of an exuberant lingual tonsillectomy growth after you take out the tonsils and adenoids and he presented sort of an elegant way using the Jennings mouth gag and a zero or even a 30 degree Hopkins rod to get down to that area and then with just using the coblator to get rid of the lingual tonsils and I had previously not done that only because I couldn't think of a good way to get to there but I'm now anxious to try that in a Downs kid that still has obstructive sleep apnea after T&A. The other thing he also recommended was doing asleep nasal endoscopy which is gaining some renewed favor in trying to figure out where are the levels of obstruction and can you do something relatively simply to relieve that obstruction.

Dr. McCammon - UTMB: I was just going to add as far as getting down there that sleep apnea surgery may become the next frontier for robotic surgery. As you know we now have the robot system here at UTMB.

Dr. Pine, Dr. Roy, and Dr. Rose conclude with a discussion of the difficulty in cleaning the typically small external ear canals of a Down child, and they agree on the appropriateness of using general anesthesia to obtain access to the ear drum to treat middle ear effusions by myringotomy, suction, and insertion of ventilation tubes when possible.

SOURCES CITED

- ¹ Down syndrome prevalence at birth: United States, 1983-1990. *MMWR*. 1994;43:617-622.
- ² Yang Q, Rasmussen S, Friedman J. Mortality associated with Down's syndrome in the USA from 1983 to 1997: a population based study. *Lancet*. 2002; 359:1019-1025.
- ³ Roizen NJ, Patterson D, Down's Syndrome. *Lancet*. 2003;361:1281-9.
- ⁴ Bittles AH, Bower C, Hussain R, Glasson EJ. The four ages of Down Syndrome. *Eur J Public Health*. 2007;17(2):221-225.
- ⁵ Hans PS, Belloso A, Sheehan PZ. Parental Satisfaction with health services provided to children with Down Syndrome in north-west England:an ENT perspective. *The Journal of Laryngology and Otology*. 2006; 121,382-386.
- ⁶ Shibahara Y, Sando I. Congenital anomalies of the Eustachian tube in children with Down Syndrome. *Ann Otol Rhinol Laryngol*. 1989;98:543-547.
- ⁷ Austin J, Preger I, Siris E, taybi H. Short hard palate in newborn: roentgen sign of mongolism. *Radiology*. 1969;92:775-556.
- ⁸ Strome M. Obstructive Sleep Apnea in Down's Syndrome: a surgical approach. *Laryngoscope*. 1986;96:1340-1342.
- ⁹ Miller J, Capusten B, Lampard R. Changes at the base of the skull and cervical spine in Down Syndrome. *J Can Assoc Radiol* . 1986;37:85-89.
- ¹⁰ Gershwin ME, Crinella FM, Castles JJ, Trent JKT. Immunologic Characteristics of Down's Syndrome. *J Ment Defic*. 1977;21:237
- ¹¹ Kovesi T, Sinclair B, MacCormick J, Matsinger M, Carpenter B. Primary ciliary dyskinesia associated with Down Syndrome. *Chest*. 2000;117:1207-1209.
- ¹² Sonek J, Cicero S, Neiger R, Nicolaidis K. Nasal bone assessment in prenatal screening for trisomy 21. *American Journal of Obstetrics and Gynecology*. 2006; 195:1219-30
- ¹³ Prefumo F, Sairam S, Bhide A, Thilaganthan B. First trimester nuchal translucency, nasal bones, and trisomy 21 in selected and unselected populations. *American Journal Obstetrics and Gynecology*. 2006;194:828-833.
- ¹⁴ Sonek J, Nicolaidis K. Additional First-Trimester Ultrasound Markers. *Clinical Laboratory Medicine*. 2010;30:573-592.
- ¹⁵ Nicolaidis KH. Screening for fetal aneuploidies at 11-13 weeks. *Prenatal Diagnosis*. 2011;31(1):7-15.
- ¹⁶ Cicero S, Sonek JD, McKenna DS, Croom CS, Johnson L, Nicolaidis KH. Nasal bone hypoplasia in trisomy 21 at 15-22 weeks gestation. *Ultrasound Obstet Gynecol*. 2003; 21(1):15-18.

- 17 Miguelez J, Moskovitch M, Cuckle H, Zugaib M, et al. Model-Predicted performance of second-trimester Down syndrome screening with sonographic prenatal thickness. *Journal of Ultrasound Medicine*. 2010;29:1791-1747.
- 18 Ting YH, Lao T, Lau TK, Chung MK, Leung TY. Isolated anset of hypoplastic nasal bone in the second trimester fetus: is amniocentesis necessary? *The Journal of Maternal-Fetal and Neonatal Medicine*.
- 19 Strome M. Down's Syndrome-A modern otorhinolaryngological perspective. *Laryngoscope* 1981. 42:1581-1594.
- 20 Shott SR. Down Syndrome: Common Otolaryngologic manifestations. *Am J Med Genet Part C Semin Med Genet* 2006. 142C:131-140.
- 21 Cunningham C, McArthur K. Hearing Loss and treatment in young Downs syndrome children. *Child:Care, Health and Development*. 1982;7:357-374.
- 22 Selikowitz M. Health problems and health checks in school aged children with Down syndrome. *Journal of Pediatrics and Child Health* 1992;28:383-386.
- 23 Gershwin ME, Crinella FM, Castels JJ, Trent JK. Immunological characteristics of Down's syndrome. *J of Ment Defic Res*. 1977;21:237-248.
- 24 Chaushu S, Yefenof E, Becker A, Shapira J et al. A link between parotid salivary Ig level and recurrent respiratory infections in young Down's syndrome patients. *Oral Microbiol Immunol* 2002;17:172-176.
- 25 Nespoli L, Burgio GR, Ugazio AG, Maccario R. Immunological feature of Down's syndrome: a review. *J Intellect Disabil Res*. 1993;37:543-551.
- 26 Brown PM, Lewis GT, Parker AJ, Maw A. The skull base and nasopharynx in relation in Down's syndrome in relation to hearing impairment. *Clinical Otolaryngology*. 1989;14:241-246.
- 27 Shibahara Y, Sando I. Congenital anomalies of the Eustachian tube in Down syndrome. Histopathologic case report. *Ann Otol Rhinol Laryngol*. 1989;Jul;98(7):543-7.
- 28 Yamaguchi N, Sando I, Hashida Y, Takahashi H, Matsune S, Histologic study of Eustachian tube cartilage with and without congenital anomalies: A preliminary study. *Ann Otol Rhinol Laryngol* 99:984-987.
- 29 Han F, Yu H, Zhang J, Tian C, Schmidt C, et al. Otitis media in a mouse model for Down syndrome. *International Journal of Experimental Pathology*. 2009;90:480-488.
- 30 Krecicki T, Zalesska-Krecicka M, ubiak K, Gawron W. Brain auditory potentials in children with Down syndrome. *Int J Pediatr Otorhinolaryngology*. 2005;69(5):615-620.
- 31 Hess C, Rosanowski F, Eysholdt U, Schuster M. Hearing impairment in children and adolescents with Down syndrome. *HNO*. 2006;54(3):227-32.

- ³² Harigai S. Longitudinal studies in hearing-impaired children with Down syndrome. *Nippon Jibiinkoka Gakkai Kaiho*. 1994;97(12):2208-18.
- ³³ Cunningham C. Hearing loss and treatment in young Down syndrome children. *Child care, health and development*. 1981;7(6):357-74.
- ³⁴ McPherson B, Lai S, Leung K, Ng I. Hearing Loss in Chinese school children with Down syndrome. *Int J Pediatric Otorhinolaryngology*. 2007;71:1905-1915.
- ³⁵ Balkany TJ, Dows MP, Jafek BW, Krajicek MJ. Hearing loss in Downs syndrome: a treatable handicap more common than generally recognized. *Clinical Pediatrics*. 1979;18:116-118.
- ³⁶ Downs MP. The hearing of Downs individuals. *Seminars in Speech, Language and Hearing*. 1980;1:25-37.
- ³⁷ Cohen WI. Health care guidelines for individuals with Down syndrome. *Down syndrome Q* 4:1-16.
- ³⁸ Bull M, AAP Committee on Genetics. AAP Clinical Report: Health Supervision for children with Down syndrome. *Pediatrics* 128(2):393-406.
- ³⁹ Maw R, Bawden R. Spontaneous resolution of severe chronic glue ear in children and the effect of adenoideotomy, tonsillectomy and insertion of ventilation tubes (grommets). *British Medical Journal*. 1993;306:756-60.
- ⁴⁰ Selikowitz M. Short term efficacy of tympanostomy tubes for secretory otitis media in children with Down syndrome. *Developmental Medicine and Child Neurology*. 1993;35:511-515
- ⁴¹ Iino Y, Imamura Y, Harigai S, Tanaka Y. Efficacy of tympanostomy tube insertion for otitis media with effusion in children with Down Syndrome. *Int J of Pediatric OtoRhinoLaryngology*. 1999;49:143-149.
- ⁴² CD Bluestone, JO Kein. Otitis media in infants and children, 2nd ed. Saunders, Philadelphia, PA 1995.
- ⁴³ Iino Y, Imamura Y, Haigai S, Tanka Y, Nagai K. Clinical course of otitis media with effusion in child with Down syndrome, :Recent advances in otitis media, Decker Inc, Hamilton, Ontario, 1996 pp52-53.
- ⁴⁴ Davies B, Land D, Stratford B. Hearing problems in Down Syndrome Current Approaches to Down syndrome. London: Cassell pp 85-102.
- ⁴⁵ Shott SR, Joseph A, Heithaus D. Hearing loss in children with Down syndrome. *Int J Pediatr Otorhinolaryngology*. 2001;61:199-205.
- ⁴⁶ Whiteman B, Simpson G, Compton W. Relationship of otitis media and language impairment in adolescents with Down syndrome. *Mental Retardation*. 1986;24(6):353-356.

- 47 Blaser S, Propst E, Martin D, Feigenbaum A, et al. Inner ear dysplasia is common in children with Down syndrome (trisomy 21). *The Laryngoscope* 2006;116:2113-2119.
- 48 Glass RB, Yousefzadeh DK, Roizen NJ. Mastoid abnormalities in Down syndrome. *Pediatric Radiology*. 1989;19:311-312.
- 49 Balkany T, Mischke R, Downs M, Jafek B. Ossicular abnormalities in Downs syndrome. *Otolaryngology Head and Neck Surgery*. 1979;87:372-384.
- 50 O'Malley M, Kaylie D, Himbergen D, Bennett M, Jackson G. Chronic ear surgery in patients with syndromes and multiple congenital malformations. *The Laryngoscope* 2007;117:1993-1998.
- 51 Bacciu A, Pasanisi E, Vincenti V, et al. Surgical treatment of middle ear cholesteotoma in children with Down syndrome. *Otol Nerotol* 2005;26:1007-1010.
- 52 Sheehan P, Hans P. UK and Ireland experience of bone anchored hearing aids (BAHA) in individuals with Down syndrome. *International Journal of Pediatric Otorhinolaryngology*. 2006;70:981-986.
- 53 McDremott A, Williams J, Kuo M, Peid A, Proops D. The role of bone anchored hearing aides in children with Down syndrome. *International Journal of Pediatric Otorhinolaryngology* 2008;72:751-757.
- 54 Watson GJ, Sheehan PZ. A Protective cage for the post operative care of the skin graft and wound of the BAHA site in patients with Down syndrome and other learning disabilities. *Clinics Otolaryngology* 2008;33(1):73-4
- 55 Hans PS, England R, Prowse S, Young E, Sheehan PZ. UK and Ireland experience of cochlear implants in children with Down syndrome. *International Journal of Pediatric Otorhinolaryngology*. 2010;74:260-264.
- 56 Pappas D, Flexer C, Shackelford L. Otolological and Habilitative Management of Children with Down Syndrome. *The Laryngoscope*. 1994;104(9) 1065-70
- 57 Bennetts L, Flynn M. Improving the classroom listening skills of children with Down syndrome by using sound field amplification. *Down Syndrome Research and Practice* 2002;8(1):19-24.
- 58 Ali NJ, Pitson DJ, Strandling JR. Snoring, sleep disturbance, and behavior in 4-5 year olds. *Arch Dis Child* 1993;68:360-366.
- 59 Gislason T, Benediktsdottir B. Snoring, apneic episodes, and nocturnal hypoxemia among children 6 months to 6 years old. *Chest*. 1995; 107:963-966.
- 60 Marcus C, Keens T, Bautista D, Pechmann W, Davidson S. Obstructive Sleep Apnea in Children with Down Syndrome. *Pediatrics*. 1991;88(1):132-139

- ⁶¹ Shott S, Amin R, Chini B, Heubi C, Hotze S, Akers R. Obstructive sleep apnea: should all children with Down syndrome be tested? *Arch Otolaryngol Head Neck Surg* 2006;132:432-436.
- ⁶² Fink GB, Madaus WK, Walker GF. A quantitative study of the face in Downs syndrome. *Am Journal Orthod.* 1975;67:540-553.
- ⁶³ Beebe DW, Wells CT, Jeffries J et al. Neuropsychological effects of pediatric obstructive sleep apnea. *J Int Neuropsychol.* 2004;10:962-975.
- ⁶⁴ Brouillette RT, Fernbach SK, Hunt CE. Obstructive sleep apnea in infants and children. *J Pediatric.* 1982;100:31-40.
- ⁶⁵ Perkin RM, Anas NG. Pulmonary hypertension in pediatric patients. *J Pediatrics.* 1984;105:511-522
- ⁶⁶ Hals J, hagemo PS, Thaulow E, Sorland SJ. Pulmonary vascular resistance in complete atrioventricular septal defect: a comparison between children with and without Downs syndrome. *Acta Paediatrica.* 1993;82:595-598.
- ⁶⁷ Fitzgerald D, Paul A, Richmond C. Severity of obstructive sleep apnoea in children with Down syndrome who snore. *Arch Dis Child* 2007;92:423-425.
- ⁶⁸ Sutherland K, Lee RW, Phillips CL, Dungan G, et al. Effect of weight loss on upper airway size in facial fat in men with obstructive sleep apnoea. *Thorax.* 2011
- ⁶⁹ Dyken M, Lin Dykin D, Poulton M, Simmerman M. Prospective polysomnographic analysis of obstruction sleep apnea in Down syndrome. *Arch Pediatric Adolesc Med.* 2003;157:655-660.
- ⁷⁰ Shires C, Anold S, Schoumacher R, Dehoff G et al. Body mass index as an indicator of obstructive sleep apnea in pediatric Down syndrome. *Int Journal of Pediatric Otorhinolaryngology.* 2010;74:768-772.
- ⁷¹ Must A, Anderson SE. Body mass index in children and adolescents: considerations for population-based applications. *International Journal of Obesity.* 2006;30:590-594.
- ⁷² Roland P, Rosenfield R, Brooks L, Friedman N et al. Polysomnography for sleep disordered breathing prior to tonsillectomy in children. *Otolaryngology- Head and Neck Surgery.* 2011;145:(1):S1-S15.
- ⁷³ Mitchell RB. Adenotonsillectomy for obstructive sleep apnea in children: outcome evaluated by pre-and postoperative polysomnography. *Laryngoscope.* 2007;117(10);1844-1854.
- ⁷⁴ Donnelly L, Shott S, LaRose C, Chini B, Amin R. Causes of persistent obstructive sleep apnea despite previous tonsillectomy and adenoidectomy in children with Down syndrome as depicted on static and dynamic cine MRI. *Am Journal Roentgenology* 1994;183:175-181.

- ⁷⁵ Shete M, Stocks R, Sebelik M, Schoumacher R. Effects of adeno-tonsillectomy on polysomnography patterns in Down syndrome children with obstructive sleep apnea: A comparative study with children without Down syndrome. *Int Journal of Pediatric Otorhinolaryngology*. 2010; 74:241-244.
- ⁷⁶ Merrell J, Shott S. OSAS in Down syndrome:T&A versus T&A plus lateral pharyngoplasty. *International Pediatric Otorhinolaryngology*. 2007;71:1197-1203.
- ⁷⁷ Freidman M, Wilson M, Lin LC, Chang HW. Updated systemic review of tonsillectomy and adenoidectomy for treatment of pediatric obstructive sleep apnea/hypopnea syndrome. *Otolaryngology Head and Neck Surgery*. Otolaryngology. 2009;140:800-808.
- ⁷⁸ Wolkove N, Blatzan M, Kamel H, Dabrusin R, Palayew M. Long term compliance with continuous positive pressure airway pressure in parents with obstructive sleep apnea. *Can Respir Journal*; 2008;15(7):365-369.
- ⁷⁹ Kavanagh K, Kahane J, Kordan B. Risks and benefits of adenotonsillectomy for children with Down syndrome. *American Journal of Mental Deficiency* 1986;91(1)22-29
- ⁸⁰ Gelder LV. Open nasal speech following adenoidectomy and tonsillectomy. *Journal of Communications Disorders*, 1974;4:263-267
- ⁸¹ Gibb AG. Hypernasality (rhinolalia aperta) following tonsil and adenoid removal. *Journal of Laryngology and Otology* 1958;72:433-451
- ⁸² Goldstein N, Armfield D, Kingsley L, Borland L, Alen G, Post C. Postoperative complications after tonsillectomy and adenoidectomy in children with Down syndrome. *Arch Otolaryngol Head Neck Surg* 1998;124:171-176.
- ⁸³ Caulfield H. Investigations in pediatric obstructive sleep apnea: do we need them? *Int Journal of Pediatric Otorhinolaryngology* 2003;67S1:S107-S110.
- ⁸⁴ Shott S, Donnelly L. Cine magnetic resonance imaging: Evaluation of persistent airway obstruction after tonsil and adenoidectomy in children with Down syndrome. *The Laryngoscope* 2004;114:1724-1729.
- ⁸⁵ Donnelly L, Shott S, LaRose C, Chini B, Amin R. Causes of persistent obstructive sleep apnea despite previous tonsillectomy and adenoidectomy in children with Down syndrome as depicted on static and dynamic cine MRI. *Am Journal of Roentgenology*. 2004;183:175-181.
- ⁸⁶ Wootten C, Shott S. Evolving therapies to treat retroglossal and base of tongue obstruction in pediatric obstructive sleep apnea. *Arch Otolaryngology Head and Neck Surgery* 2010;136(10) 983-987.
- ⁸⁷ Chaushu S, Chaushu G, Zigmund M, Yefenof E et al. Age-dependency in saliva and salivary secretion in Downs syndrome. *Arch Oral Biol* 2007;52(11);1088:1096.

- ⁸⁸ Chaushu S, Yefe Nof E, Becker A, Shapira J, Chaushu G. Parotid salivary immunoglobulins, recurrent respiratory tract infections and gingival health in institutionalized and non-institutionalized subjects with Down's syndrome. *J Intellect Disabil Res* 2003;47:101-107..
- ⁸⁹ Nespoli L, Burgio R, Ugazio AG, Maccario R. Immunological features of Down's syndrome: a review. *Journal of Intellectual disability research*. 1993;37:543-551.
- ⁹⁰ Moura CP, Andrade D, Cunha LM, Tavares MJ et al. Down syndrome: otolaryngological effects of rapid maxillary expansion. *Journal of laryngology and Otology*. 2008;122: 1318-1324.
- ⁹¹ Moura CP, Andrade D, Cunha LM, Tavares MJ et al. Rapid maxillary expansion and nasal patency in children with down syndrome. *Rhinology*. 2005;43:138-142.
- ⁹² Mitchell R, Call E, Kelly J. Diagnosis and therapy for airway obstruction in children with Down syndrome. *Arch otolaryngol Head and Neck Surg* 2003;129:642-645.
- ⁹³ Roger G, Denoyelle F, Triglia J, et al. Severe laryngomalacia: surgical indications and results in 115 patients. *Laryngoscope*. 1995;105:1111-1117.
- ⁹⁴ Jacobs I, Gray R, Todd W. Upper airway obstruction in children with Down syndrome. *Arch Otolaryngol Head Neck Surgery*. 1996;22:945-950.
- ⁹⁵ Miller R, Gray S, Cotton R, Myer C, Netterville J. Subglottic stenosis and Down syndrome. *Pediatric Otolaryngology, Am J Otolaryngology*. 1990;11:274-277.
- ⁹⁶ Boseley M, Link D, Shott S, Fitton C, Myer C, Cotton R. Laryngotracheoplasty for subglottic stenosis in Down Syndrome children: the Cincinnati experience. *International Journal of Pediatric Otorhinolaryngology*. 2001;57: 11-15.
- ⁹⁷ De Long AL, Sulek M, Nihill M et al. Tenous Airway in children with trisomy 21. *Laryngoscope* 1997;107:345-349.
- ⁹⁸ Kobel M, Creighton RE, Steward DJ. Anaesthetic considerations in Downs syndrome: with 100 patients and a review of the literature. *Canada Anaesthesia Society Journal* 1982;29:393-398.
- ⁹⁹ Shott SR. Down Syndrome: analysis of airway size and guide for appropriate intubation. *Laryngoscope* 2000;110:585-592.
- ¹⁰⁰ Pueschel S, Scola F. Atlantoaxial instability in individuals with Down syndrome: epidemiologic, radiographic, and clinical studies. *Pediatrics*. 1987; 80(4):555-560.
- ¹⁰¹ Miller J, Bapusten B, Lampard R. Changes at the base of skull and cervical spine in Down syndrome. *Journal of the Canadian Association of Radiologists*. 1986;37:85-89.
- ¹⁰² Bhattarai B, Kulkarni H, Kalingarayar S, Upadya MP. Anesthetic management of a child with Down's syndrome having atlanto-axial instability. *J Nepal Med Assoc*. 2009;48(173):66-69.

- ¹⁰³ American Academy of Pediatrics, Committee on Sports Medicine. Atlantoaxial instability in Down Syndrome. *Pediatrics*. 1984;74:152-154.
- ¹⁰⁴ Selby K, Newton R Gupta S, Hunt L. Clinical predictors and radiological reliability in atlantoaxial sublaxation in Downs syndrome. *Archives of Disease in Childhood* 1991; 66: 876-878.
- ¹⁰⁵ Riaz S, Drake J, Hedden D. Images in Spine Surgery: Atlantoaxial Instability in Down syndrome. *Journal of the Pakistan Medical Association*. 2007;57(4):213-214.
- ¹⁰⁶ Hreidarsson S, Magram G, Singer H. Symptomatic atlantoaxial dislocation in Down syndrome. *Pediatrics*. 1982;69(5):568-571.
- ¹⁰⁷ American Academy of Pediatrics, Committee on Sports Medicine and Fitness. Atlantoaxial instability in Down syndrome: Subject Review. *Pediatrics* 1995;96:151-154.
- ¹⁰⁸ Litman RS, Perkins FM. Atlantoaxial sublaxation after tympanomastoidectomy in a child with trisomy 21. *Otolaryngology Head and Neck Surg* 1994;110:584-586.
- ¹⁰⁹ Mitchell R, Call E, Kelly J. Ear, nose and throat disorders in children with Down syndrome. *The Laryngoscope*. 2003;113:259-263.
- ¹¹⁰ Suskind D, Zeringue G, Kluka E, Udall J, Liu D. Gastroesophageal reflux and pediatric otolaryngologic disease:the role of anti reflux surgery. *Arch Otolaryngol Head Neck Surg*. 2001;127:511-514.
-