Tympanostomy Tube Placement for Otitis Media with Effusion in Children with Cleft Lip and Palate

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Additional information is available at the end of the chapter

Abstract

The condition of cleft lip/palate (CLP) in children is psychologically stressful for family members and debilitating for the patients themselves. These children must undergo a series of major invasive surgeries following birth, including cleft lip repair surgery, cleft palate repair surgery, bone grafting surgery, and dental implant surgery. Unfortunately, the clinical significance of otitis media with effusion (OME), a complication associated with CLP, is often overlooked, and very few studies have explored this condition in depth. This chapter reviews pathogenesis, clinical manifestations, consequences, examination, and diagnosis related to OME in children with CLP. Controversies surrounding the treatment of OME in CLP children are also discussed. We also provide a flowchart for management guidance in OME in children with CLP.

Keywords: otitis media, middle ear effusion, cleft lip and palate, conductive hearing loss, grommet tube, children

1. Introduction

Cleft lip/palate (CLP) is a congenital orofacial anomaly that is debilitating for patients and psychologically stressful for family members. Children with CLP are forced to undergo a series of major invasive surgeries, including surgery for cleft lip repair, bone grafting, and dental implants [1].

Otitis media with effusion (OME), also called serous/secretory otitis media or glue ear, is a collection of nonpurulent fluid within the middle ear space. OME is a common condition among infants and children between the ages of 1 and 3 years [2]. Compared to healthy children, children with CLP are more susceptible to OME [3]. Despite the fact that the vast majority of patients (about 80%) do not have OME at birth [4], statistics show that OME occurs

at least once before the first birthday in as many as 90% of the infants born with CLP [2]. In addition, as many as 97% of the infants born with CLP suffer concurrent OME within the first two years of life [5].

The clinical significance of OME is often overlooked, and very few studies have explored this condition in depth, despite it being a complication commonly associated with CLP. This chapter reviews pathogenesis, clinical manifestations, consequences, examination, and diagnosis related to OME in children with CLP. Controversies surrounding the treatment of OME in CLP children are also discussed. We also provide a flowchart for management guidance in OME in children with CLP. It is our hope that the results of this study will provide clinicians and patients/parents with a valuable reference.

2. Pathogenesis

Numerous factors have been cited in the development of OME in children suffering from CLP, including (1) immature development of the Eustachian tube, (2) abnormalities in the muscle associated with the Eustachian tube, and (3) craniofacial bone abnormalities [3].

2.1. Immature development of the Eustachian tube

The Eustachian tube of children is not yet fully developed and therefore shorter than that of adults. It is positioned at a more horizontal angle, and the opening to the nasopharynx is narrower. When upper respiratory tract infection causes swelling and inflammation of the respiratory mucosa, the narrow opening of the Eustachian tube can easily be clogged, leading to negative pressure in the middle ear. In addition, the position and length of the Eustachian tube allow viruses and bacteria from the upper respiratory tract to easily pass into the middle ear cavity, which can cause middle ear infection with effusion. Even after infection has been controlled, it is difficult to discharge fluid from the middle ear through the Eustachian tube to the throat, because the Eustachian tube is shorter and more horizontal with a narrow opening. The remaining fluid can lead to OME [6–9].

2.2. Abnormalities of Eustachian tube-associated muscle

Anatomical or structural defects associated with cleft palate can affect velopharyngeal function. In children with CLP, the abnormal reflux of food and fluid from the mouth into the nasal cavity due to velopharyngeal insufficiency can result in inflammation and edema of the Eustachian orifices and hypertrophy of adenoid pads, leading to tubal obstruction and secondary OME [6]. In addition, abnormal development of the tensor veli palatini (TVP) muscle and levator veli palatini muscle in children with CLP can cause maladjustment in the regular opening of the Eustachian tube [10, 11]. When the atmospheric pressure of the environment changes (e.g., during descent in an airplane) or the gas in the middle ear is absorbed by mucosa, the Eustachian tube is unable to open and thereby relieve pressure in the middle ear. The resulting negative pressure can cause the eardrum to retract, leading to the collection of fluid in the middle ear, which can again lead to OME [6].

2.3. Craniofacial bone abnormalities

Other abnormalities in the structure of the Eustachian tube in children with CLP have also been associated with the pathogenesis of OME. These abnormalities include increased nasopharyngeal space, alterations to the medial pterygoid plate and hamulus, a shorter tube, larger angle between the cartilage and TVP, higher cartilage cell density, a smaller ratio of lateral and medial lamina area in the cartilage, less curvature of the lumen, less elastin in the hinge portion of the cartilage, and a lower insertion ratio of TVP to the cartilage [12, 13]. Kemaloglu et al. evaluated clinical and cephalometric data of 37 Japanese children with unilateral complete CLP or isolated cleft palate and compared them to 40 non-cleft children. They found that differences in the mastoid-middle ear-Eustachian tube system are associated with a tendency toward OME in CLP children. This fact helps to elucidate the pathogenesis of OME in children with CLP [14].

3. Clinical manifestations

Aside from mild conductive hearing loss, OME does not cause any other symptoms of discomfort and is therefore easily overlooked. In infants, OME combined with hearing loss may continue for weeks or even months without being detected. A child with OME may also suffer poor sleep quality [15]. Parents of children with CLP should pay particular attention to how their children interact with others and how they react to sound. If any abnormality is observed, the child should undergo expert evaluation. More importantly, children should visit an otolaryngologist for a regular otologic examination to ascertain whether they are suffering from OME. Early diagnosis and treatment are invaluable in preventing or alleviating future hearing loss.

4. Consequences of OME in CLP

Children with CLP may suffer recurrent or continuous OME, causing atelectasis, ossicular fixation, and tympanosclerosis [2, 16, 17], which can result in conductive hearing loss of up to 30 decibels (dB). Researchers have previously shown that, regardless of whether they have undergone cleft palate repair surgery, as many as 90% of children with CLP suffer from OME or conductive hearing loss, while 50% suffer from recurrent otitis media [2, 5, 18–20]. In comparison, the prevalence of conductive hearing loss among children without CLP is 12.9%. Although the likelihood of developing OME is reduced after reaching adulthood, it is estimated that 50% of these children suffer from permanent conductive hearing loss [21, 22]. Additionally, 0.9–5.9% of patients with CLP develop primary acquired cholesteatoma, the probability of which is 100–200 times higher among those without CLP [23, 24].

In addition, sensorineural losses have been ascribed to pathologic changes in the inner ear resulting from inflammation in the middle ear and presumably mediated via the round or oval window [3]. Toxins produced by long-term inflammation can pass through the round window or the oval window into the inner ear, causing permanent sensorineural hearing loss [17, 25].

Many studies have indicated that although reconstructive surgery for CLP improves linguistic ability, language development depends on the extent to which hearing ability is maintained [23, 26]. If OME is not treated properly, long-term hearing loss can negatively influence the language development of children [27]. Hearing loss in children suffering from CLP can also affect their academic comprehension and learning performance [20, 27, 28]. Bess et al. indicated that even if children suffer hearing loss in only one ear, academic performance can still be seriously affected in up to 33% of patients and up to 40% of patients are unable to participate in regular activities or interactions due to hearing loss [29]. It has been found that children with cleft palate are prone to specific psychological problems [30, 31]. Children suffering from this condition may also display behavioral difficulties due to feelings of isolation [29].

5. Examination and diagnosis

Up to 90% of infants born with CLP suffer from OME before their first birthday [2]; therefore, it is recommended that otologic tests be conducted as soon as possible after birth to ascertain whether fluid has collected in the middle ear [21, 32]. The use of a pneumatic otoscope is the fastest and most direct method used for the inspection of the eardrum for color and contour and determining whether fluid has collected in the middle ear. It should be noted that the effectiveness of a pneumatic otoscope to test for OME depends on the experience and skill of the clinicians, the patient's full cooperation, and the anatomical structure of the ear canal [2].

Another method for inspecting the eardrum is videotelescopy. A telescope is placed against the eardrum through the external ear canal, and a charge-coupled device (CCD) camera captures images of the eardrum. The resulting magnified images can be presented on a monitor, thereby allowing clinicians to accurately diagnose middle ear effusion [33]. Guo and Shiao conducted a prospective study on the diagnostic efficacy of videotelescopy, pneumatic otoscopy, and tympanometry for the detection of pediatric OME. Their results demonstrate that the sensitivity, specificity, and accuracy of the videotelescopy were 97.8, 100, and 98.0%, respectively. These values significantly exceed the accuracy of conventional tests using pneumatic otoscope and tympanometry [33]. Videotelescopy provides clinicians with visual information with which to validate the accuracy of the pneumatic otoscopy.

Pneumatic otoscopy and even videotelescopy are difficult to administer on newborns and small infants with CLP. Thus, objective acoustic immittance testing plays an important role in the diagnosis of OME in CLP patients [34]. Tympanometry is the most commonly used acoustic immittance test to measure pressure changes in the middle ear and the compliance of the eardrum [27]. Chen et al. found that the specificity of tympanometry, when used to test for OME in infants with CLP, was relatively low (only 59.6%). When used to test infants within 9 months of age, specificity dropped to only 37.5% [28]. Furthermore, when infants are crying or unable to cooperate during testing, it can be difficult to maintain airtight conditions in the ear, thereby preventing successful completion of the examination.

Pure tone audiometry can also be used to facilitate the diagnosis of OME; the results may reveal conductive or mixed hearing loss. The cooperation of children is required for this

procedure, which means that it may be unsuitable for children under 3 years of age [35]. For patients in this age group, spectral gradient acoustic reflectometry (SGAR) may be an effective alternative to pure tone audiometry in the diagnosis of OME. SGAR transmits ultrasound waves to the eardrum, whereupon a microcomputer is used to filter, record, and analyze the ultrasound waves reflected back. SGAR is an efficient diagnostic tool for the detection of OME, requiring less than one second to complete the procedure. Although the sensitivity and specificity are somewhat low, SGAR is a noninvasive test that is unaffected by crying, cerumen, client cooperation, or the quality of the air seal in the ear, thereby making it useful for testing difficult infants [28, 36–38].

6. Watchful waiting for OME

Alt first identified the relationship between CLP and hearing impairment in 1878, and OME has since been the subject of investigation [39]. The severe complications caused by OME in CLP children can have far-reaching consequences; therefore, determining the optimal treatment strategy is a topic worthy of in-depth exploration.

Many researchers have recommended watchful waiting as a treatment of choice for OME among children with CLP, particularly when parents prefer to avoid or postpone surgery. Muntz reported that more than 50% of CLP children who develop OME naturally recover from OME and have no need to undergo ventilation tube surgery after 3 years of age [40]. Flynn et al. studied the longitudinal prevalence of OME in CLP children between 7 and 16 years of age and found that middle ear problems gradually dissipate between 7 and 13 years of age [41]. Rynnel-Dagoo et al. found that 82% of the CLP children with or without OME had a normal hearing at 3–4 years of age, indicating recovery from OME [42]. Smith et al. found that the Eustachian tube function of most children with CLP significantly improved by 6–7.5 years of age [43].

A number of researchers have reported that OME and Eustachian tube function improve as the patient grows older [41, 43, 44], recommending watchful waiting for CLP children with OME for a period of 3–6 months from the diagnosis of effusion [41, 43–45]. During the observation period, patients can wear hearing aids to attain the same hearing performance of children with ventilation tubes [45]; however, it should be noted that children may find hearing aids inconvenient or may worry about the social stigma associated with wearing such aids [27, 46].

7. Ventilation tube insertion (VTI) for OME

Previous studies have shown that 90% or more of the children who undergo palatoplasty for CLP still suffer recurrent OME [20], which is a reflection of persistent poor Eustachian tube function after repair surgery [47]. Thus, many doctors prefer to perform the repair of cleft palate and ventilation tube surgery simultaneously when the child is 1 year old [2, 17, 48–50]. This combined surgical approach is done in the hope of overcoming the problem of middle ear effusion and improving the hearing ability of children, thereby enhancing their long-term linguistic development.

This chapter summarizes previous studies that addressed the effectiveness of VTI for OME in CLP children aged 18 years or less. Each of the studies we summarize below measured outcomes using a variety of methods. We attempted to normalize those measurements. As for hearing outcomes, the natural effect measure refers to the difference in hearing ability. For studies using outcome measures on different scales, we summarized the findings as the percentage of ears presenting hearing loss or improvement. For the frequency of grommet insertion, measurements were summarized as the percentages of ears that underwent one or more grommet insertions and the number of times that insertion was performed. For complications or sequelae, the main summary measure was the occurrence of complications. For middle ear status, the effect measures included the rates of OME recurrence and resolution and the percentage of ears presenting various types of tympanogram.

7.1. Comparative effectiveness for hearing outcome

7.1.1. CLP children versus age-matched non-CLP children

Two studies compared CLP children with age-matched healthy children with regard to hearing outcomes after VTI for OME [51, 52]. One prospective study with an excellent study design reported similar hearing outcomes between children with and without palate conditions (CLP group 10.5 dB versus control group 10.9 dB, p > 0.05, follow-up 5–7 years) over the short term [51]. The other retrospective study of moderate study design reported a significantly higher percentage of ears with hearing loss (CLP group 24% versus control group 0%, follow-up 3–5 years) [52]. However, 64% of children in the CLP group underwent VTI, while only 6% in the non-CLP group underwent VTI (p < 0.0005).

7.1.2. Pre-VTI versus post-VTI hearing outcomes

Hearing outcomes were evaluated in several case-series studies [16, 23, 43, 53–57]. Over the long term, between 50 and 94% of CLP children recovered normal hearing after being administered VTI in conjunction with palatoplasty (follow-up 5.5–15.4 years) [16, 43, 54–57]. Furthermore, children requiring a higher number of VTIs were at increased significant risk for long-standing hearing loss [16, 23].

7.1.3. VTI versus non-VTI

Zheng et al. conducted a randomized controlled trial to determine the effectiveness of grommets on hearing recovery among CLP children with OME [58]. The authors reported hearing improvement in only 22 of 39 CLP children with VTI; however, no hearing results were obtained from those that did not undergo VTI. Furthermore, the authors reported hearing outcomes over the short term (6 months of observation); however, little emphasis was placed on the long-term outcomes, which makes it difficult to interpret their results.

Several prospective [51, 59, 60] and retrospective [20, 44, 46, 52, 61–68] cohort studies evaluated hearing outcomes. Among these cohort studies, several studies compared VTI with non-VTI (i.e., myringotomy alone, hearing aids, watchful waiting) [44, 60, 62, 64–68]. It has been reported that the improvements in hearing afforded by VTI over the short term (within 18 months after VTI)

are more pronounced than those of myringotomy, watchful waiting, or HA [64–66]. Potsic et al. found that, compared with CLP children without VTI for OME, those with VTI had a lower percentage of ears presenting hearing loss over the short term (less than 5 years) [68]. As for long-term hearing outcomes, Hubbard et al. reported that early VTI (3 month of age) could have a greater effect on hearing than that achieved when adopting a conservative approach to treatment [60].

Despite the fact that most studies on hearing outcomes have advocated VTI for CLP children, a number of researchers have expressed reservations, based on conflicting results. Some cohort studies observed that CLP children that had undergone VTI for OME presented worse hearing outcomes over the short term (less than 5 years) [44] or a higher percentage of ears with hearing loss after surgery over the long term (9–21 years), compared to children that did not undergo the procedure [62, 67].

7.1.4. Summary of evidence on hearing outcome

More than half (50–94%) of CLP children recovered normal hearing 5–15 years after VTI [16, 43, 54–57]. Moreover, compared with conservative management, most studies have shown that VTI is beneficial to hearing recovery over the short as well as long term [60, 64–66, 68]. There remains a belief that early VTI at the time of palatoplasty is beneficial; however [69], there is little evidence indicating the optimal timing for grommet insertion.

7.2. Comparative effectiveness for speech and language outcomes

7.2.1. CLP children versus age- and sex-matched non-CLP control

One article compared CLP children with age- and sex-matched non-CLP controls with regard to post-VTI speech and language outcomes [69]. Normal or near-normal speech intelligibility ratings were similar in CLP (90%) and non-CLP children (96%).

7.2.2. VTI versus non-VTI

Several studies have assessed speech and language outcomes in CLP patients with OME, including prospective [60] and retrospective cohort studies [44, 69–72]. Five articles compared children that were or were not administered VTI for OME [44, 60, 70–72]. No differences in speech or language development were observed in short-term (0–5 years) [44, 72] or long-term (8–10 years) [70, 71] follow-ups. With one exception, all investigators used the same number of CLP children matched for cleft type, age, sex, socioeconomic status, and birth order. After a 9-year follow-up, consonant articulation was found to be better after early VTI (p = 0.03) [60]. However, the authors performed myringotomy on the control group (when deemed necessary), which prevented the clear elucidation of differences in functional outcome between children that did or did not undergo VTI for OME.

7.2.3. Summary of evidence on speech and language outcomes

No differences in speech or language development were observed between CLP children that underwent conservative observation and those that underwent aggressive VTI, over the short

term (0–5 years) [44, 72] or long term (8–10 years) [70, 71]. Further, assessments of speech by Merrick et al. revealed a similar percentage of children with normal or near-normal speech intelligibility ratings in the CLP and non-CLP groups [69]. These findings appear to indicate that speech and language skills do not depend on the VTI approach to OME treatment, but rather on the timing of palatoplasty.

7.3. Complications of VTI for OME

7.3.1. CLP children versus age-matched healthy children

Two studies compared age-matched healthy control children with regard to VTI complications [51, 52]. One study showed that the prognosis of children with CLP that undergo early VTI is comparable to that of children without CLP [51]; however, the other study reported contradictory results with higher rates of complications among CLP children [52].

7.3.2. VTI versus non-VTI

Several retrospective cohort studies compared children with and without VTI (i.e., hearing aids or watchful waiting) with regard to post-VTI complications [44, 46, 61, 62, 66, 67, 72]. Those studies reported higher complication rates among children with VTI than among those without, over the short term (<5 years of follow-up) [44, 46, 61, 66, 72] as well as long term (9–21 years of observation) [62, 67]. All results were statistically significant; however, differences were not calculated in two of the studies [62, 72].

Among the various types of complications, tympanosclerosis and otorrhea generally present transient but common sequelae following VTI [73, 74], with other studies reported permanent perforations and cholesteatoma [73, 75, 76]. As for the occlusion of grommets, infection, and the presence of granulation tissue, the evidence was too limited and blurred to determine the direction of effects between VTI and adverse events in CLP children with OME.

7.3.3. Tympanosclerosis

Tympanosclerosis has little influence on hearing [16, 72, 77]; however, this is the most common VTI-related complication, the rates of which were in the range of 0–52% [4, 20, 44, 46, 52–54, 57, 58, 61, 65, 67, 72, 78]. Tympanosclerosis can, albeit rarely, cause conductive hearing loss if it extensively involves the ossicle chain [72].

7.3.4. Otorrhea

Otorrhea is a complication of the tympanostomy tubes in children who are otherwise healthy [79]. However, otorrhea has not been systematically studied in CLP children after VTI. Some studies have reported a low probability (4–11.5%) of post-VTI otorrhea in CLP children [44, 50, 66, 79], whereas others reported inconsistent results (55–68%) [31, 57, 78]. The evidence is inconclusive due to conflicting results among these studies. Otorrhea appeared to be more common in ears that underwent VTI than in those that did not [66]. However, the evidence is insufficient to reveal an association between the long-term use of grommets and otorrhea. Only one study on post-VTI otorrhea reported the management of otorrhea [72]. Freeland et al.

found that although 68% of infants developed otorrhea following the use of grommets over a mean duration of 3.9 months, the otorrhea usually responded promptly to antibiotic-corticosteroid drops or systemic antibiotic treatment in more resistant cases.

7.3.5. Eardrum perforation

In CPL children, eardrum perforation occurred in 0–19% of VT-treated ears in follow-ups of 1–15 years [4, 16, 20, 43, 44, 46, 50–54, 56–58, 60, 61, 66, 67, 70, 72, 78]. In a study by Shapiro, the rate of eardrum perforation was found to be as high as 50% after VTI [80]; however, the number of children with VTI (only six children) was too small to be of reference value (low-quality study design). In contrast, eardrum perforation was observed in only 0–7% of non-VT-treated ears (i.e., observation or hearing aids) during follow-ups of 1–4 years [61, 66, 72]. In non-CLP children with OME, only one study reported a 3% incidence of post-VTI eardrum perforation within a 5-year follow-up [51].

7.3.6. Cholesteatoma

Grommet insertion has been reported to be an iatrogenic cause of secondary acquired cholesteatoma [81–86]. The development of the disease is quite uncommon, with a reported rate of approximately 1% in non-CLP children with VTI [73, 87]. However, evidence has shown that the CLP children were at increased risk of developing cholesteatoma [66, 73], with a higher rate of 0–6.9% within 12 years after VTI [16, 23, 58, 62, 66, 67, 73, 80, 88].

It should be noted that Hornigold et al. reported an incidence of 29% for CLP children 21 years after VTI for OME [62], Similarly, Spilsbury et al. conducted a retrospective cohort study on the relationship between CLP and secondary cholesteatoma following VTI in children [73]. They examined the complete hospital in-patient history of a large unselected population (869 CLP children versus 56080 non-CLP children) over a 29-year period. The authors reported that children with CLP developed cholesteatoma 7.5 (95% confidence interval, 3.8–18.2) times faster after the first VTI, compared to children without CLP.

7.3.7. Summary of evidence on VTI complications

CLP children with VTI generally have a higher risk of complications than do those without, over the short-term (less than 5 years) [44, 46, 61, 66, 72] as well as long-term (9–21 years) follow-up [62, 67]. However, compared to non-CLP children with OME, there is insufficient evidence to draw any conclusions due to conflicting results among these studies on CLP and non-CLP children [51, 52].

7.4. Comparative effectiveness for middle ear status

Previous studies have compared the effect of VTI on middle ear by using outcome measurements including the rates of OME resolution, persistent OME, and OME recurrence. The rates of OME resolution were reported in three high-quality studies, including a randomized control trial, a prospective cohort study, and a retrospective cohort study [50, 51, 58]. The rates of OME resolution ranged from 48.7 to 86% within the first 6.5 years. These results were

supported by Goudy et al., who reported a median resolution time of conductive hearing loss of approximately 5 years [23]. Kuscu et al. observed that normal otoscopic examination findings were higher in CLP children without VTI than in those with VTI [89].

Persistent OME was observed in 29–52% of CLP children 4–7 years after VTI [20, 44, 68, 72]. Gordon et al. [67] found that only 5% of CLP children had persistent OME 9 years or more after palatoplasty with VTI, concluding that Eustachian tube function may be adequate by age of 9 years. These results are supported by Smith et al. [43], who found that Eustachian tube function eventually returned to normal in most CLP children and that the age of Eustachian tube normalization was approximately 8 years (1.5–17.3). As for OME recurrence, a number of studies have reported that 17–45% of CLP children had OME recurrence 3–6 years after VTI, at a mean age of approximately 7 years [20, 56, 57, 61].

7.4.1. CLP children versus non-CLP control

Four articles reported in post-VTI middle ear function in CLP and non-CLP children [51, 52, 59, 69], three of which included an age-matched non-CLP control group [51, 52, 69]. The results in studies by Ovesen and Blegvad-Andersen [52] and Broen et al. [59] were not considered for further interpretation because only 6 and 31% of the non-CLP children with OME underwent VTI, respectively. Merrick et al. reported comparable rates of persistent OME in children with and without cleft palate (24% versus 14%, p = 0.31) [69]. Valtonen et al. reported similar OME resolution rates in CLP and non-CLP children (64.1% versus 60.6%) [51]. In summary, the prognosis for middle ear recovery among CLP children with early VTI is comparable to that of children without CLP.

7.4.2. VTI versus non-VTI

Zheng et al. performed a randomized controlled trial comparing OME resolution rates between CLP children with and without VTI [58]. They reported a significantly higher OME resolution rate (48.7%) in children undergoing palatoplasty and VTI than in those undergoing palatoplasty alone (24.5%, p < 0.01). Children with VTI had a shorter observation period (6 months versus 20 months); however, the authors expected that the OME resolution rate would have been higher if the children had been followed up for the same period as those without VTI, such that the difference in resolution rate between the groups would become increasingly pronounced. In another study by Potsic et al., [68] the authors found that CLP children that did not undergo VTI had a significantly higher rate of persistent OME at the age of 5 years than did those with VTI. Freeland et al. [72] obtained the same result for CLP children at the age of 4 years. However, two other studies reported conflicting results, i.e., a higher rate of persistent OME in CLP children with VTI [44, 67].

7.4.3. Summary of evidence on middle ear status

Three high-quality studies reported that more than half (48.7–86%) of the CLP children that underwent VTI presented OME resolution within the first 6.5 years [50, 51, 58]. The median resolution time of conductive hearing loss was found to be approximately 5 years [23]. The high OME resolution rates were supported by four other studies, in which persistent OME

was observed in less than half (29–52%) of the CLP children in the first 4–7 years after VTI [20, 44, 68, 72]. Eustachian tube function began to normalize by 7–9 years of age [20, 43, 44, 50, 51, 58, 67, 68, 72]. In addition, fewer than half of the CLP children (17–45%) presented OME recurrence within the first 3–6 years of follow-up [20, 56, 57, 61]. Importantly, the prognosis for CLP children that undergo early VTI was comparable to that of the children without CLP.

7.5. Frequency of grommet insertion

A significant proportion (53.2–98%) of CLP children with OME required VTI [4, 51, 54, 61, 78] with an average of between 0.55 and 2.2 VTIs per patient in the first 7 years of observation [20, 44, 59, 66]. Cleft defects play an important role in OME formation; therefore, it would be reasonable to assume a higher need for grommets in children with more overt palatal malformations. This assumption is supported by several studies [67, 71, 88], in which a relationship was established between the degree of clefting and the frequency of VTI, with severe or complete clefts more likely to involve grommet insertion. Children with cleft palate had a significantly higher frequency of VTIs than those without [51, 59]. However, this issue requires further investigation. Lithovius et al. reported that the severity of the cleft was not a significant factor related to the number of ventilation tubes required [90]. Surgical techniques used to repair the cleft palate are not significantly associated with the number of VTI required [90]; however, palatoplasty may indeed decrease the rate of ventilation tube reinsertion in children with cleft palate, as evidenced by a recent population-based study [91].

7.6. Summary of evidence pertaining to effectiveness of VTI for OME

Compared with a conservative approach, early VTI was shown to improve hearing, and this improvement was maintained in more than half of the CLP children 5–15 years after surgery. Nonetheless, VTI does not necessarily lead to improvements in speech or language development in CLP children, and the CLP children with VTI had a higher risk of complications than did those without. It appears that VTI is beneficial for the recovery from OME in CLP patients. There is insufficient evidence to suggest the optimal timing of VTI (e.g., at the time of repair of lip/palate); however, it may be convenient for surgeons to combine these procedures.

7.7. Limitations of previous studies

Despite considerable research into subgroups of CLP children with regard to the effectiveness of grommets for OME, heterogeneity in the design of studies has proven a formidable barrier to the synthesis of evidence [92, 93]. Most previous studies failed to clearly describe their criteria in the definition of OME. Previous studies included subjects of different ages with different types of cleft who had undergone different procedures and employed different criteria for VTI. Grommet insertion (unilateral or bilateral) was treated as a single procedure in some studies or as two procedures in other studies. The measures used in the studies were nonuniform; different time points were used for the determination of outcomes, and baseline measures were not always provided. Studies also varied in the length of observation periods.

Most studies in this review were retrospective studies. Only otologic findings during a particular month, or interpolation from examinations in adjoining months, were used in arriving at the monthly status of each ear. Thus, patient history was of limited value because it was difficult to determine when grommets had been extruded and if ear drainage was occurring. Due to mixed results, statistical differences could not be calculated for each complication, such that it is unclear whether the differences reached statistical significance. Finally, the issue of missing data was not taken into account.

8. Debate concerning selection of treatment strategy

A review of previous studies shows that there is currently no consensus as to the optimal method of treating OME, and many researchers are at odds regarding their views on the subject [46]. Most previous studies are based on retrospective analysis and vary widely in their design; therefore, it is difficult to make an informative comparison. Even in prospective studies on OME in CLP children [51, 58, 59], there remains a lack of high-quality, adequately powered randomized controlled trials. One reason may be that most parents require recommendations pertaining to treatment, rather than allowing their child to be randomly included in an experimental or control group, particularly children who have undergone or will undergo a series of major invasive surgeries. Thus, it is currently impossible to conduct a meta-analysis of previous research, which could be used to summarize treatment methods and/or provide guidance with regard to treatment choices [2, 45].

9. Clinical guidelines

9.1. NICE clinical guideline

The UK National Institute for Health and Clinical Excellence has published clinical guidelines for the surgical treatment of OME in children with or without CLP [45]. Those guidelines indicate that there is currently insufficient evidence to prove that simultaneous cleft palate repair surgery and ventilation tube surgery are effective approaches to the alleviation of OME. Thus, the simultaneous insertion of a ventilation tube during the surgical repair of a cleft palate is not recommended unless careful otological and audiological assessments have been performed. The guidelines recommend that treatment be based on the needs and desires of children and their parents and that ventilation tube surgery be viewed as an alternative to hearing aids in CLP children with persistent bilateral OME and hearing loss.

9.2. Clinical guidelines of AAO-HNSF, AAP, and AAFP

Updated clinical guidelines have recently been published for OME. These guidelines were codeveloped by the American Academy of Otolaryngology-Head and Neck Surgery Foundation (AAO-HNSF), the American Academy of Pediatrics (AAP), and the American Academy of Family Physicians (AAFP) [94]. The guideline update group claims that it may

be appropriate to offer tympanostomy tubes on an individualized basis for cleft palate infants with OME that persists after failing hearing tests. They claim that resolving the issue of middle ear effusion could facilitate the assessment of hearing status.

It is also recommended that clinicians evaluate children with cleft palate for OME and hearing loss at the time at which cleft palate is first diagnosed. Monitoring for OME and hearing loss should continue throughout childhood, including after palate repair. Specifically, the guideline update group recommends that middle ear status be assessed at 12–18 months of age, considering that this is a critical period in the development of language skills, speech, balance, and coordination. By 18 months of age, delays in language and speech development are easily identified.

In these guidelines, it is recommended that VTI be considered when type B tympanogram or OME persists for 3 months or longer. These recommendations are based on the assumption that the likelihood of spontaneous resolution is low. For children who do not receive tympanostomy tubes, the follow-up schedule to monitor OME and hearing loss until OME resolves should be more frequent than the 3- to 6-month intervals recommended for children without cleft palate.

9.3. PRISMA-compliant systematic review

Many clinical guidelines fail to provide clear recommendations with regard to treatment approaches, due to a lack of conclusive studies [27, 95]. Despite the fact that a number of reviews have been published on treatment choices for the management of OME in CLP children, a number of these are narrative reviews [3, 6, 96–98], whereas others are systematic reviews pertaining mainly to otherwise healthy children [27, 45, 77, 95, 99–105]. The lack of research on the CLP subgroup of children means that there is currently no evidence-based information for clinicians or parents with regard to the effectiveness of grommets for OME in CLP children.

Ponduri et al. performed a systematic review on the routine early insertion of grommets for OME in CLP children [2]. The authors concluded that there is currently insufficient evidence on which to base recommendations pertaining to clinical practice in this area. However, they did not perform data synthesis with regard to patient-centered outcomes, nor did they provide a detailed, well-described protocol, such as The Cochrane [106] and PRISMA [107]. A systematic review based on predefined eligibility criteria conducted in accordance with a predefined methodological approach could facilitate the appraisal of review methods and reveal modifications to methods and selective reporting in completed reviews [108].

A recent systematic review by Kuo et al. published in *Pediatrics* addressed the effects of VTI in children with cleft palate and OME with regard to patient-centered outcomes [109]. The review followed the protocol outlined in Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) to enable full and transparent assessment of the existing literature, in order to provide evidence-based information pertaining to the management of OME in children with cleft palate.

That review indicated that 38–53% of CLP children underwent VTI for OME and that more severe cases were more likely to undergo grommet insertion. Compared with a conservative approach, it appears that VTI may improve hearing outcomes in CLP children and that these improvements could remain for at least 1–9 years after surgery. In addition, children who have undergone VTI face a higher risk of complications than do those who have not received this form of treatment. The most common post-VTI complications include eardrum retraction and tympanosclerosis, with incidence rates of 11–37%. Of particular importance is the need to perform grommet insertion within a highly specified time frame. The authors concluded that existing evidence is insufficient to support any assertions with regard to the use of grommets, either therapeutically or prophylactically, at the time of palatoplasty or afterward.

9.4. Future research needs

In the future, there may be a need to develop rigorous methodologies for the examination of functional outcomes in CLP children after VTI. Further multi-institute prospective studies or well-designed randomized controlled trials are needed to develop a comprehensive base of evidence sufficient to clarify the effectiveness of VTI for OME in CLP children.

10. Recommendations for management

Strategies related to the treatment of OME in CLP children are still under debate, and there is insufficient evidence with which to establish absolute guidelines. We believe that the lack of consensus regarding the optimal treatment for OME in CLP children should prompt a relatively conservative approach. Patients and parents should also be given a range of treatment options based on their individual needs and desires.

Figure 1 presents a flowchart of recommended OME management in CLP children. From the time of birth, children with CLP should undergo continual and regular otologic examinations and audiological monitoring for the assessment of OME. Children with delayed speech and/or language development should be suspected of having OME, such that otolaryngology referral is indicated. Once OME is confirmed, the coexisting sensorineural component of hearing loss should be further investigated. It is recommended that children suffering from middle ear effusion without significant hearing loss (hearing threshold ≤30 dB) remain under observation [45]. Children with hearing loss exceeding 30 dB can be managed through active observation for 3 months or alternatively referred for surgery, in accordance with the child's developmental, social, and educational status. If a patient suffers OME in only one ear, the observation period may be extended to 6 months [49]. During the observation period, hearing aids could be considered [110]. Patients suffering from recurrent OME following surgery may undergo repeated ventilation tube surgery, and those in whom the disease persists after an observation period of 3–6 months may be referred for surgery.
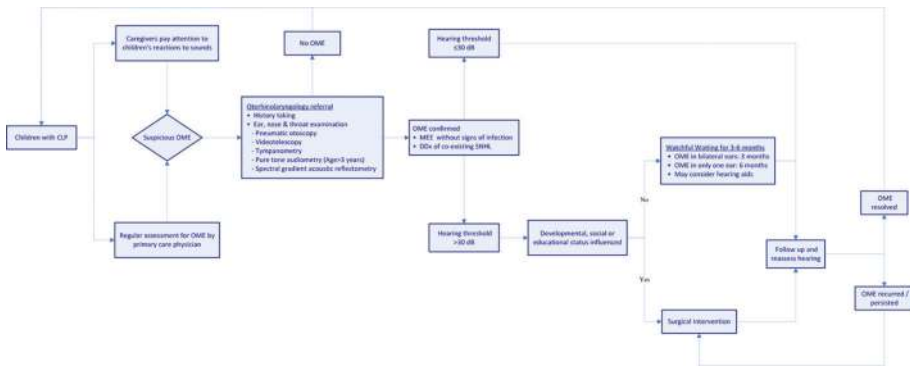
Figure 1. Flowchart of recommended management guidance for OME in CLP children. OME, otitis media with effusion; CLP, cleft lip/palate; MEE, middle ear effusion; DDX, differential diagnosis; dB, decibel; SNHL, sensorineural hearing loss.

11. Summary

Otitis media with effusion associated with Eustachian tube dysfunction can seriously affect hearing in children with CLP, which can lead to linguistic and speech disorders, and ultimately to the disruption of learning and development. Compared with watchful waiting or hearing aids, VTI has been shown to improve hearing in more than half of CLP children 5–15 years after surgery. VTI and the conservative approach do not appear to differ with regard to speech and language outcomes. CLP children that undergo VTI present a higher risk of complications than do children without VTI. It has been shown that VTI is beneficial in helping CLP patients to recover from OME. There is insufficient evidence with regard to the timing of VTI (e.g., prophylactic insertion during repair of lip or palate). This summary is based on underpowered studies, and the evidence for each outcome is inconclusive. The lack of concrete evidence regarding the optimal treatment for OME in CLP children should prompt a relatively conservative approach. Most importantly, the needs of children and their parents must be taken into consideration. Only a consensus between patients/parents and surgeons regarding the most suitable treatment strategy for OME can ensure the greatest benefits.

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References

[1] Lilja J. Cleft lip and palate surgery. *Scand J Surg* 2003; 92:269–273.

[2] Ponduri S, Bradley R, Ellis PE, Brookes ST, Sandy JR, Ness AR. The management of otitis media with early routine insertion of grommets in children with cleft palate – a systematic review. *Cleft Palate Craniofac J* 2009; 46:30–38.

[3] Kuo CL, Lien CF, Chu CH, Shiao AS. Otitis media with effusion in children with cleft lip and palate: a narrative review. *Int J Pediatr Otorhinolaryngol* 2013; 77:1403–1409.

[4] Szabo C, Langevin K, Schoem S, Mabry K. Treatment of persistent middle ear effusion in cleft palate patients. *Int J Pediatr Otorhinolaryngol* 2010; 74:874–877.

[5] Dhillon RS. The middle ear in cleft palate children pre and post palatal closure. *J R Soc Med* 1988; 81:710–713.

[6] Sharma RK, Nanda V. Problems of middle ear and hearing in cleft children. *Indian J Plast Surg* 2009; 42(Suppl):S144–S148.

[7] Bluestone CD, Klein JO. Pediatric otolaryngology. In: Bluestone CD, Stool SE, Alper CM (eds). Philadelphia: Saunders, 2003:474–685.

[8] Kuo CL, Wang MC, Chu CH, Shiao AS. New therapeutic strategy for treating otitis media with effusion in postirradiated nasopharyngeal carcinoma patients. *J Chinese Med Assoc* 2012; 75:329–334.

[9]   Chang CW, Yang YW, Fu CY, Shiao AS. Differences between children and adults with otitis media with effusion treated with CO_2 laser myringotomy. *J Chin Med Assoc* 2012; 75:29–35.

[10]   Takasaki K, Sando I, Balaban CD, Ishijima K. Postnatal development of eustachian tube cartilage. A study of normal and cleft palate cases. *Int J Pediatr Otorhinolaryngol* 2000; 52:31–36.

[11]   Stool SE, Randall P. Unexpected ear disease in infants with cleft palate. *Cleft Palate J* 1967; 4:99–103.

[12]   Bluestone CD. Studies in otitis media: children's hospital of Pittsburgh-University of Pittsburgh progress report–2004. *Laryngoscope* 2004; 114:1–26.

[13]   Rajion ZA, Al-Khatib AR, Netherway DJ, et al. The nasopharynx in infants with cleft lip and palate. *Int J Pediatr Otorhinolaryngol* 2012; 76:227–234.

[14]   Kemaloglu YK, Kobayashi T, Nakajima T. Analysis of the craniofacial skeleton in cleft children with otitis media with effusion. *Int J Pediatr Otorhinolaryngol* 1999; 47:57–69.

[15]   Rosenfeld RM, Goldsmith AJ, Tetlus L, Balzano A. Quality of life for children with otitis media. *Arch Otolaryngol Head Neck Surg* 1997; 123:1049–1054.

[16]   Sheahan P, Blayney AW, Sheahan JN, Earley MJ. Sequelae of otitis media with effusion among children with cleft lip and/or cleft palate. *Clin Otolaryngol Allied Sci* 2002; 27:494–500.

[17]   Robinson PJ, Lodge S, Jones BM, Walker CC, Grant HR. The effect of palate repair on otitis media with effusion. *Plast Reconstr Surg* 1992; 89:640–645.

[18]   Sheahan P, Miller I, Sheahan JN, Earley MJ, Blayney AW. Incidence and outcome of middle ear disease in cleft lip and/or cleft palate. *Int J Pediatr Otorhinolaryngol* 2003; 67:785–793.

[19]   Chu KM, McPherson B. Audiological status of Chinese patients with cleft lip/palate. *Cleft Palate Craniofac J* 2005; 42:280–285.

[20]   Phua YS, Salkeld LJ, de Chalain TM. Middle ear disease in children with cleft palate: protocols for management. *Int J Pediatr Otorhinolaryngol* 2009; 73:307–313.

[21]   Viswanathan N, Vidler M, Richard B. Hearing thresholds in newborns with a cleft palate assessed by auditory brain stem response. *Cleft Palate Craniofac J* 2008; 45:187–192.

[22]   Bluestone CD, Beery QC, Cantekin EI, Paradise JL. Eustachian tube ventilatory function in relation to cleft palate. *Ann Otol Rhinol Laryngol* 1975; 84:333–338.

[23]   Goudy S, Lott D, Canady J, Smith RJ. Conductive hearing loss and otopathology in cleft palate patients. *Otolaryngol Head Neck Surg* 2006; 134:946–948.

[24]   Harris L, Cushing SL, Hubbard B, Fisher D, Papsin BC, James AL. Impact of cleft palate type on the incidence of acquired cholesteatoma. *Int J Pediatr Otorhinolaryngol* 2013, http://dx.doi.org/10.1016/j.ijporl.2013.01.020.

[25] D'Mello J, Kumar S. Audiological findings in cleft palate patients attending speech camp. *Indian J Med Res* 2007; 125:777–782.

[26] Schonweiler R, Lisson JA, Schonweiler B, et al. A retrospective study of hearing, speech and language function in children with clefts following palatoplasty and veloplasty procedures at 18–24 months of age. *Int J Pediatr Otorhinolaryngol* 1999; 50:205–217.

[27] Rosenfeld RM, Culpepper L, Doyle KJ, et al. Clinical practice guideline: Otitis media with effusion. *Otolaryngol Head Neck Surg* 2004; 130:S95–S118.

[28] Chen YW, Chen KT, Chang PH, Su JL, Huang CC, TJ. L. Is otitis media with effusion almost always accompanying cleft palate in children? The experience of 319 Asian patients. *Laryngoscope* 2012; 122:220–224.

[29] Bess FH, Klee T, Culbertson JL. Identification, assessment, and management of children with unilateral sensorineural hearing loss. *Ear Hear* 1986; 7:43–51.

[30] Smith RM, McWilliams BJ. Creative thinking abilities of cleft palate children. *Cleft Palate J* 1966; 3:275–283.

[31] Paradise JL, Bluestone CD. Early treatment of the universal otitis media of infants with cleft palate. *Pediatrics* 1974; 53:48–54.

[32] Luthra S, Singh S, Nagarkar AN, Mahajan JK. The role of audiological diagnostics in children with cleft lip & palate (CLP). *Int J Pediatr Otorhinolaryngol* 2009; 73:1365–1367.

[33] Guo YC, Shiao AS. Diagnostic methods for otitis media with effusion in children. *Zhonghua Yi Xue Za Zhi (Taipei)* 2002; 65:372–377; discussion 363–374.

[34] Wimmer E, Toleti B, Berghaus A, Baumann U, Nejedlo I. Impedance audiometry in infants with a cleft palate: the standard 226-Hz probe tone has no predictive value for the middle ear condition. *Int J Pediatr Otorhinolaryngol* 2010; 74:586–590.

[35] Halloran DR, Hardin JM, Wall TC. Validity of pure-tone hearing screening at well-child visits. *Arch Pediatr Adolesc Med* 2009; 163:158–163.

[36] Schwartz DM, Schwartz RH. Validity of acoustic reflectometry in detecting middle ear effusion. *Pediatrics* 1987; 79:739–742.

[37] Oyiborhoro JM, Olaniyan SO, Newman CW, Balakrishnan SL. Efficacy of acoustic otoscope in detecting middle ear effusion in children. *Laryngoscope* 1987; 97:495–498.

[38] Pellett FS, Cox LC, MacDonald CB. Use of acoustic reflectometry in the detection of middle ear effusion. *J Am Acad Audiol* 1997; 8:181–187.

[39] Alt A. Heilunger Taubstummheit erzielte durch Bersitung einer otorrhooe einer angibornen Gaummenspalte. *Arch Augenheilkd* 1878; 7:211–213.

[40] Muntz HR. An overview of middle ear disease in cleft palate children. *Facial Plast Surg* 1993; 9:177–180.

[41] Flynn T, Lohmander A, Moller C, Magnusson L. A longitudinal study of hearing and middle ear status in adolescents with cleft lip and palate. *Laryngoscope* 2013; 123:1374–1380.

[42] Rynnel-Dagoo B, Lindberg K, Bagger-Sjoback D, Larson O. Middle ear disease in cleft palate children at three years of age. *Int J Pediatr Otorhinolaryngol* 1992; 23:201–209.

[43] Smith TL, DiRuggiero DC, Jones KR. Recovery of eustachian tube function and hearing outcome in patients with cleft palate. *Otolaryngol Head Neck Surg* 1994; 111:423–429.

[44] Robson AK, Blanshard JD, Jones K, Albery EH, Smith IM, Maw AR. A conservative approach to the management of otitis media with effusion in cleft palate children. *J Laryngol Otol* 1992; 106:788–792.

[45] NICE Clinical Guideline: *Surgical Management of Otitis Media with Effusion in Children*: National Collaborating Centre for Women's and Children's Health (UK), 2008, http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0009526/.

[46] Gani B, Kinshuck AJ, Sharma R. A review of hearing loss in cleft palate patients. *Int J Otolaryngol* 2012; 2012:548698.

[47] Alper CM, Losee JE, Mandel EM, Seroky JT, Swarts JD, Doyle WJ. Pre- and post-palatoplasty Eustachian tube function in infants with cleft palate. *Int J Pediatr Otorhinolaryngol* 2012; 76:388–391.

[48] Andrews PJ, Chorbachi R, Sirimanna T, Sommerlad B, Hartley BE. Evaluation of hearing thresholds in 3-month-old children with a cleft palate: the basis for a selective policy for ventilation tube insertion at time of palate repair. *Clin Otolaryngol Allied Sci* 2004; 29:10–17.

[49] Ahn JH, Kang WS, Kim JH, Koh KS, Yoon TH. Clinical manifestation and risk factors of children with cleft palate receiving repeated ventilating tube insertions for treatment of recurrent otitis media with effusion. *Acta Otolaryngol* 2012; 132:702–707.

[50] Klockars T, Rautio J. Early placement of ventilation tubes in cleft lip and palate patients: does palatal closure affect tube occlusion and short-term outcome? *Int J Pediatr Otorhinolaryngol* 2012; 76:1481–1484.

[51] Valtonen H, Dietz A, Qvarnberg Y. Long-term clinical, audiologic, and radiologic outcomes in palate cleft children treated with early tympanostomy for otitis media with effusion: a controlled prospective study. *Laryngoscope* 2005; 115:1512–1516.

[52] Ovesen T, Blegvad-Andersen O. Alterations in tympanic membrane appearance and middle ear function in 11-year-old children with complete unilateral cleft lip and palate compared with healthy age-matched subjects. *Clin Otolaryngol Allied Sci* 1992; 17:203–207.

[53] He Y, Xu H, Zhen Q, Liao X, Xu L, Zhen Y. The influence of palatoplasty and tympanotomy on middle ear function in cleft palate patients. *Hua Xi Kou Qiang Yi Xue Za Zhi* 2001; 19:243–245.

[54] Koempel JA, Kumar A. Long-term otologic status of older cleft palate patients. *Indian J Pediatr* 1997; 64:793–800.

[55] Fria TJ, Paradise JL, Sabo DL, Elster BA. Conductive hearing loss in infants and young children with cleft palate. *J Pediatr* 1987; 111:84–87.

[56] Frable MA, Brandon GT, Theogaraj SD. Velar closure and ear tubings as a primary procedure in the repair of cleft palates. *Laryngoscope* 1985; 95:1044–1046.

[57] Moller P. Hearing, middle ear pressure and otopathology in a cleft palate population. *Acta Otolaryngol* 1981; 92:521–528.

[58] Zheng Q, Xu H, He Y. Effects of tympanotomy and pressure equilibrium tube insertion during palatoplasty on prognoses of otitis media with effusion. *Hua Xi Kou Qiang Yi Xue Za Zhi* 2003; 21:28–30.

[59] Broen PA, Moller KT, Carlstrom J, Doyle SS, Devers M, Keenan KM. Comparison of the hearing histories of children with and without cleft palate. *Cleft Palate Craniofac J* 1996; 33:127–133.

[60] Hubbard TW, Paradise JL, McWilliams BJ, Elster BA, Taylor FH. Consequences of unremitting middle-ear disease in early life. Otologic, audiologic, and developmental findings in children with cleft palate. *N Engl J Med* 1985; 312:1529–1534.

[61] Kwan WM, Abdullah VJ, Liu K, van Hasselt CA, Tong MC. Otitis media with effusion and hearing loss in chinese children with cleft lip and palate. *Cleft Palate Craniofac J* 2011; 48:684–689.

[62] Hornigold R, Morley A, Glore RJ, Boorman J, Sergeant R. The long-term effect of unilateral t-tube insertion in patients undergoing cleft palate repair: 20-year follow-up of a randomised controlled trial. *Clin Otolaryngol* 2008; 33:265–268.

[63] Chen JL, Messner AH, Curtin G. Newborn hearing screening in infants with cleft palates. *Otol Neurotol* 2008; 29:812–815.

[64] Li W, Shang W, Yu AH, et al. Early treatment of middle ear disease in cleft palate infants. *Hua Xi Kou Qiang Yi Xue Za Zhi* 2007; 25:458–462.

[65] Liu L, Sun YG, Ma L, Zhao W, Wu R. Effect of ventilation tube insertion on otitis media with effusion in cleft palate children. *Zhonghua Er Bi Yan Hou Ke Za Zhi* 2004; 39:216–218.

[66] Maheshwar AA, Milling MA, Kumar M, Clayton MI, Thomas A. Use of hearing aids in the management of children with cleft palate. *Int J Pediatr Otorhinolaryngol* 2002; 66:55–62.

[67] Gordon AS, Jean-Louis F, Morton RP. Late ear sequelae in cleft palate patients. *Int J Pediatr Otorhinolaryngol* 1988; 15:149–156.

[68] Potsic WP, Cohen M, Randall P, Winchester R. A retrospective study of hearing impairment in three groups of cleft palate patients. *Cleft Palate J* 1979; 16:56–58.

[69] Merrick GD, Kunjur J, Watts R, Markus AF. The effect of early insertion of grommets on the development of speech in children with cleft palates. *Br J Oral Maxillofac Surg* 2007; 45:527–533.

[70] Kobayashi H, Sakuma T, Yamada N, Suzaki H. Clinical outcomes of ventilation tube placement in children with cleft palate. *Int J Pediatr Otorhinolaryngol* 2012; 76:718–721.

[71] Shaw R, Richardson D, McMahon S. Conservative management of otitis media in cleft palate. *J Craniomaxillofac Surg* 2003; 31:316–320.

[72] Freeland AP, Evans DM. Middle ear disease in the cleft palate infant: its effect on speech and language development. *Br J Plast Surg* 1981; 34:142–143.

[73] Spilsbury K, Ha JF, Semmens JB, Lannigan F. Cholesteatoma in cleft lip and palate: a population-based follow-up study of children after ventilation tubes. *Laryngoscope* 2013; 123:2024–2029.

[74] Kay DJ, Nelson M, Rosenfeld RM. Meta-analysis of tympanostomy tube sequelae. *Otolaryngol Head Neck Surg* 2001; 124:374–380.

[75] Golz A, Goldenberg D, Netzer A, et al. Cholesteatomas associated with ventilation tube insertion. *Arch Otolaryngol Head Neck Surg* 1999; 125:754–757.

[76] Herdman R, Wright JL. Grommets and cholesteatoma in children. *J Laryngol Otol* 1988; 102:1000–1002.

[77] Hellstrom S, Groth A, Jorgensen F, et al. Ventilation tube treatment: a systematic review of the literature. *Otolaryngol Head Neck Surg* 2011; 145:383–395.

[78] Moller P. Selective use of ventilating tubes in the treatment of secretory otitis media and retractions of the eardrum. *Acta Otolaryngol* 1982; 94(Suppl 386):158–160.

[79] Curtin G, Messner AH, Chang KW. Otorrhea in infants with tympanostomy tubes before and after surgical repair of a cleft palate. *Arch Otolaryngol Head Neck Surg* 2009; 135:748–751.

[80] Shapiro RS. Otologic findings in an Inuit population of cleft palate children. *J Otolaryngol* 1988; 17:101–102.

[81] Yamamoto Y, Takahashi K, Morita Y, Takahashi S. Clinical behavior and pathogenesis of secondary acquired cholesteatoma with a tympanic membrane perforation. *Acta Otolaryngol* 2013; 133:1035–1039.

[82] Kuo CL, Shiao AS, Yung M, et al. Updates and knowledge gaps in cholesteatoma research. *BioMed Res Int* 2015; 2015:854024.

[83] Kuo CL. Etiopathogenesis of acquired cholesteatoma: prominent theories and recent advances in biomolecular research. *Laryngoscope* 2015; 125:234–240.

[84] Kuo CL, Liao WH, Shiao AS. A review of current progress in acquired cholesteatoma management. *Eur Archives Oto-Rhino-Laryngol Off J Eur Fed Oto-Rhino-Laryngol Soc* 2015; 272:3601–3609.

[85] Kuo CL. *Chapter 12. Recent Advances in Understanding Pathogenesis of Acquired Cholesteatoma. Recent Advances in Otolaryngology Head and Neck Surgery*. India: Jaypee Brothers Medical Publishers. 2016, Vol. 5, pp. 167–190.

[86] Kuo CL. In reference to A new theory on the pathogenesis of acquired cholesteatoma: mucosal traction. *Laryngoscope* 2016; 126:E132.

[87] Vlastarakos PV, Nikolopoulos TP, Korres S, Tavoulari E, Tzagaroulakis A, Ferekidis E. Grommets in otitis media with effusion: the most frequent operation in children. But is it associated with significant complications? *Eur J Pediatr* 2007; 166:385–391.

[88] Caglar O, Bulbul F, Sennaroglu L. Incidence of otitis media with effusion and long-term clinical findings in children with cleft lip and palate types. *Kulak Burun Bogaz Ihtis Derg* 2013; 23:268–274.

[89] Kuscu O, Gunaydin RO, Icen M, et al. The effect of early routine grommet insertion on management of otitis media with effusion in children with cleft palate. *J Craniomaxillofac Surg* 2015; 43:2112–2115.

[90] Lithovius RH, Lehtonen V, Autio TJ, et al. The association of cleft severity and cleft palate repair technique on hearing outcomes in children in northern Finland. *J Craniomaxillofac Surg* 2015; 43:1863–1867.

[91] Huang CY, Wu CS, Tang CH, Wang MC, Kuo TY, Tu TY. Palatoplasty decreases the re-insertion rate of middle ear ventilation tube in cleft palate children – a population-based birth cohort study. *Acta Otolaryngol* 2016; 136:768–774.

[92] Kuo CL. A critical appraisal of ventilation tube insertion in children with cleft palate. *JAMA Otolaryngol Head Neck Sur* 2015; 141:189–190.

[93] Kuo CL, Tsao YH, Shiao AS. Critical reassessment of the probability of receiving additional ventilation tube insertion for recurrent otitis media with effusion in children with cleft palate. *Acta Otolaryngol* 2015; 135:519–520.

[94] Rosenfeld RM, Shin JJ, Schwartz SR, et al. Clinical practice guideline: otitis media with effusion executive summary (update). *Otolaryngol Head Neck Surg* 2016; 154:201–214.

[95] Browning GG, Rovers MM, Williamson I, Lous J, Burton MJ. Grommets (ventilation tubes) for hearing loss associated with otitis media with effusion in children. Cochrane Database of Systematic Reviews 2010, Issue 10. Art. No.: CD001801. DOI: 10.1002/14651858.CD001801.pub3

[96] Sheahan P, Blayney AW. Cleft palate and otitis media with effusion: a review. *Rev Laryngol Otol Rhinol (Bord)* 2003; 124:171–177.

[97] Paradise JL. Middle ear problems associated with cleft palate. An internationally-oriented review. *Cleft Palate J* 1975; 12:17–22.

[98] Yules RB. Current concepts of treatment of ear disease in cleft palate children and adults. *Cleft Palate J* 1975; 12:315–322.

[99]   Rosenfeld RM, Schwartz SR, Pynnonen MA, et al. Clinical practice guideline: tympa-
nostomy tubes in children. *Otolaryngol Head Neck Surg* 2013; 149:S1–S35.

[100]   Wallace IF, Berkman ND, Lohr KN, Harrison MF, Kimple AJ, Steiner MJ. Surgical treat-
ments for otitis media with effusion: a systematic review. *Pediatrics* 2014.

[101]   Berkman ND, Wallace IF, Steiner MJ, et al. Otitis media with effusion: comparative
effectiveness of treatments. *Comparative Effectiveness Review No. 101 (Prepared by the RTI-
UNC Evidence-based Practice Center under Contract No. 290-2007-10056-1).* 2013.

[102]   McDonald S, Langton Hewer CD, Nunez DA. Grommets (ventilation tubes) for recurrent
acute otitis media in children. Cochrane Database of Systematic Reviews 2008, Issue 4.
Art. No.: CD004741. DOI: 10.1002/14651858.CD004741.pub2.

[103]   Perera R, Haynes J, Glasziou PP, Heneghan CJ. Autoinflation for hearing loss associ-
ated with otitis media with effusion. Cochrane Database of Systematic Reviews 2006,
Issue 4. Art. No.: CD006285. DOI: 10.1002/14651858.CD006285.

[104]   van den Aardweg MTA, Schilder AGM, Herkert E, Boonacker CWB, Rovers MM.
Adenoidectomy for otitis media in children. Cochrane Database of Systematic Reviews
2010, Issue 1. Art. No.: CD007810. DOI: 10.1002/14651858.CD007810.pub2.

[105]   van Zon A, van der Heijden GJ, van Dongen TMA, Burton MJ, Schilder AGM.
Antibiotics for otitis media with effusion in children. Cochrane Database of Systematic
Reviews 2012, Issue 9. Art. No.: CD009163. DOI: 10.1002/14651858.CD009163.pub2.

[106]   Higgins JPT, Green S (eds). *Cochrane Handbook for Systematic Reviews of Interventions
Version 5.1.0* [updated March 2011]. The Cochrane Collaboration, 2011. Available from
http://handbook.cochrane.org.

[107]   Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic
reviews and meta-analyses of studies that evaluate health care interventions: explana-
tion and elaboration. *PLoS Med* 2009; 6:e1000100.

[108]   Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review
and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Rev* 2015; 4:1.

[109]   Kuo CL, Tsao YH, Cheng HM, et al. Grommets for otitis media with effusion in chil-
dren with cleft palate: a systematic review. *Pediatrics* 2014; 134:983–994.

[110]   Smallridge J, Hall AJ, Chorbachi R, et al. Functional outcomes in the Cleft Care UK study–
Part 3: oral health and audiology. *Orthodontics Craniofacial Res* 2015; 18(Suppl 2):25–35.