Balloon Eustachian Tuboplasty (BET) in Children: A Retrospective Multicenter Analysis

Article *in* Otology & Neurotology · July 2020

DOI: 10.1097/MAO.0000000000002789

20 authors, including:

Michelle lea Tisch
Aspen University
29 PUBLICATIONS **19** CITATIONS
SEE PROFILE

Goetz F Lehnerdt
University of Duisburg-Essen
18 PUBLICATIONS **528** CITATIONS
SEE PROFILE

Carsten V Dalchow
Hospital Frankfurt Hoechst
64 PUBLICATIONS **886** CITATIONS
SEE PROFILE

Holger H Sudhoff
Klinikum Bielefeld
526 PUBLICATIONS **5,080** CITATIONS
SEE PROFILE

Original Study

Balloon Eustachian Tuboplasty (BET) in Children: A Retrospective Multicenter Analysis

*Matthias Tisch, *†Susanne Maier, ‡Serena Preyer, ‡Savvas Kourtidis, §Goetz Lehnerdt, §Sebastian Winterhoff, ||¶Carsten V. Dalchow, ||Friederike Mueller-Jenckel, #Holger H. Sudhoff, #Stefanie Schröder, ††Assen Koitschev, ††Peter Amrhein, ‡‡Karl-Ludwig Bruchhage, ‡‡Anke Leichtle, §§||||Christian Güldner, ¶¶Juergen Grulich-Henn, ##Katrin Jensen, ##Moritz Pohl, ***Peter K. Plinkert, and ***Sara Euteneuer

*Department of Otorhinolaryngology, Head- and Neck Surgery, Bundeswehrkrankenhaus Ulm; †Department of Traumatology, Ulm University Medical Center, Ulm; ‡Department of Otorhinolaryngology, Head- and Neck Surgery, Evangelisches Diakonissenkrankenhaus Karlsruhe-Rüppurr, Karlsruhe; §Department of Otorhinolaryngology, Head- and Neck Surgery, Klinikverbund St. Antonius und St. Josef, Wuppertal; ||Department of Otorhinolaryngology, Head- and Neck Surgery, University Medical Center Hamburg-Eppendorf (UKE), Hamburg; ¶Department of Otorhinolaryngology, Head- and Neck Surgery, Klinikum Frankfurt Hoechst, Frankfurt; #Department of Otorhinolaryngology, Head- and Neck Surgery, Klinikum Bielefeld, Bielefeld; **Department of Otorhinolaryngology, Head- and Neck Surgery. ''Otto Koerner'', Rostock University Medical Center, Rostock; ††Department of Otorhinolaryngology, Head- and Neck Surgery, Klinikum Stuttgart, Olgahospital, Stuttgart; ‡‡Department of Otorhinolaryngology, Head- and Neck Surgery, University Medical Center Schleswig-Holstein, Campus Lübeck, Lübeck; §§Department of Otorhinolaryngology, Head- and Neck Surgery, University Hospital of Giessen and Marburg (UKGM), Philipps-University of Marburg, Marburg; ||||Department of Otorhinolaryngology, Head- and Neck Surgery, Klinikum Chemnitz gGmbH, Chemnitz; ¶¶Department of Pediatrics, Division of General Pediatrics, Neuropediatrics, Metabolism, Gastroenterology and Nephrology, Heidelberg University Hospital; ##Institute of Medical Biometry and Informatics, University of Heidelberg; and ***Department of Otorhinolaryngology, Head- and Neck Surgery, Heidelberg University Hospital, Heidelberg, Germany

Objective: Generation of pilot data for planning of prospective BET-studies for treatment of dilatory Eustachian tube (ET) dysfunction in children.
Study Design: Retrospective multicenter analysis.
Setting: Nine ENT departments at tertiary care teaching hospitals.
Patients: 4–12-year-old children with chronic otitis media with effusion (COME) for more than 3 months or more than 3 episodes of acute otitis media during the last year, having failed standard surgical therapy at least once.
Intervention: BET with or without paracentesis, ventilation tube insertion, or tympanoplasty.
Main outcome measures: Tympanic membrane appearance, tympanometry, and hearing threshold.
Results: Two hundred ninety-nine ETs of 167 children were treated. Mean age was 9.1 years (95% confidence interval [95% CI]: 8.7–9.4 yr). In 249 ears (83.3%), COME and/or retraction of the tympanic membrane were the indication for BET. Median hearing threshold was 20 dB HL (95% CI: 0–46 dB). One hundred fifty-five ears (51.8%, 95% CI: 46.1–57.4%) showed a tympanogram type B. Treatment consisted of BET without other interventions (''BET–only'') in 70 children, 128 ears. Median length of follow-up for 158 (94.6%) children was 2.6 months (95% CI: 0.3–16.1 mo). After treatment, the tympanic membrane appeared normal in 196 ears (65.6%, 95% CI: 60.0–70.8%, $p < 0.001$). Median hearing threshold improved to 10 dB HL (95% CI: 0–45 dB, $p < 0.001$). Tympanograms shifted toward type A and C (type A: 39.1%, 95% CI: 33.7–44.7, $p < 0.001$). These

Address correspondence and reprint requests to Matthias Tisch, M.D., Department of Otorhinolaryngology, Head- and Neck Surgery, Bundeswehrkrankenhaus Ulm, Oberer Eselsberg 40, 89081 Ulm, Germany; E-mail: matthias.tisch@hals-nasen-ohren.net; Sara Euteneuer, M.D., Department of Otorhinolaryngology, Head- and Neck Surgery, Heidelberg University Hospital, In Neuenheimer Feld 400, 69120 Heidelberg, Germany; E-mail: sara.euteneuer@med.uni-heidelberg.de

M.T., S.P., G.L., C.V.D., H.H.S., K.-L.B., C.G., and J.G.-H. conceived the project, treated patients, and acquired data. S.M., S.K., S.W., F.M.-J., S.S., A.K., P.A., A.L., and P.K.P. treated patients and acquired data. K.J. and M.P. gave statistical advice and helped with data analysis. S.E. conceived the project, treated patients, acquired data, conceptualized and designed the study, obtained ethical approval, coordinated and supervised data acquisition, pooled data, carried out the statistical analysis and drafted the initial manuscript. All authors reviewed and revised the manuscript critically for important intellectual content, approved the final manuscript version to be published, and agree to be accountable for all aspects of the work.

This research project was carried out without any specific internal or external funding support. M.T., S.P., S.K., S.W., G.L., C.V.D., H.H.S., S.S., P.A., K.L.B., A.L., C.G., J.G.H., and S.E. received reimbursements for travel expenses from the manufarcurer of the Eustachian tube balloon utilized in this study (Spiggle & Theis Medizintechnik, Overath, Germany). C.V.D., H.H.S., and S.E. received financial support for holding symposia from Spiggle & Theis Medizintechnik. In addition, C.V.D. received consulting fees, S.S. financial support for another clinical study, and H.H.S. grant support form Spiggle & Theis Medizintechnik. All other authors have indicated that they have no financial competing interests, or other relationships that might lead to bias relevant to this manuscript.

DOI: 10.1097/MAO.0000000000002789

improvements were also observed in subgroup analyses of ''BET-only'' treatment and the indication of ''COME'' respectively.
Conclusion: BET is improving a variety of dilatory ET dysfunction-related ear diseases in children. This study provides detailed data for design and planning of prospective studies on BET in children. **Key Words:** Balloon Eustachian tuboplasty—BET—Children—Chronic otitis media with effusion—COME—Eustachian tube dysfunction—Ventilation tubes.

Otol Neurotol **41:**xxx–xxx, 2020.

Dilatory Eustachian tube dysfunction (ETD) and related diseases, like chronic otitis media with effusion (COME or ''glue ear'') or acute otitis media, are common in children. Incidences peak at 2 to 6 years of age before ET maturation is complete (1), with some children being persistently affected into later childhood and even teenage age. In most children, symptoms resolve spontaneously. However, if natural resolution does not occur, or the child does not respond to medical therapy and/or ventilation training within 3 months, paracentesis and placement of ventilation tubes (grommets, VTs) are recommended by pediatric and otolaryngologic societies worldwide. Adhering to these recommendations, about 5% of all children in central European countries have received paracentesis and VTs at least once before reaching teenage age (2–4).

Reasons for recurrent or persistent dilatory ETD and its related diseases, particularly in children, are the frequent upper respiratory infections with concurrent mucosal swelling and hyperplasia of the local lymphatic tissue (adenoids). However, medical treatments with antibiotics, antihistamins, or steroids have proven to be ineffective for COME (5,6). Compared to VT placement alone, concurrent adenoidectomy has been shown to half the rate of recurrent COME (33 versus 14%) in 3.5 to 7 year olds at 1 year after intervention, a time when all short-term VTs had spontaneously been extruded (7).

The children without surgical success after initial VT placement and suffering from persistent dilatory ETD are at risk to continue an ''otologic career,'' including multiple revision surgeries and/ or tympanoplasty. In addition, VTs bear a risk for complications like tympanosclerosis, possibly associated with persistent conductive hearing impairment, recurrent and chronic otorrhea, and permanent perforations of the tympanic membrane (7,8). Therefore, there is a need for alternative treatment options, especially in those children with recurrent disease failing primary surgery. Recently, balloon dilation of the Eustachian tube or ''balloon Eustachian tuboplasty'' (BET) has come forward as a less invasive alternative treatment option in adults, aiming to improve the underlying dilatory ETD itself. BET was first introduced in 2009 simultaneously in Finland and in Germany (9,10). During the BET procedure, a single use balloon catheter is inserted into the ET via its nasopharyngeal opening with endoscopic assistance in local or general anesthesia, inflated to a pressure level of 10 or 12 bars, generally held for 2 minutes, and then removed after deflation (TubaVent catheter, Spiggle & Theis Medizintechnik, Overath, Germany; Acclarent AERAEustachian Tube Balloon System, Acclarent Inc., Menlo Park, CA; XprESS LoProfile; Entellus Medical, Inc., Plymouth, MN). Prospective licensing trials in the US, as well as multinational retrospective cohort studies in adult patients, have shown an improvement of various symptoms and ear diseases arising from chronic dilatory ETD, including COME, in approximately 70 to 80% of patients (11–23). These data on outcome in adult patients, confirmed by our own observations, motivated the authors to offer BET as an off-label second-line treatment to children. To overcome the limits of the small number of children treated per individual department (24–28), the authors pooled their data to enable statistical evaluation of BET treatment in children.

METHODS

Objective/Aim

This very first retrospective multicenter study of BET treatment in children aims to provide the pilot data, necessary for planning prospective studies to thoroughly evaluate BET in children in the future. The primary objective of this study was to evaluate BET treatment effectiveness to resolve middle ear diseases in children due to chronic dilatory ETD. The secondary objective was to specifically investigate BET efficiency in clearance of COME. Both objectives intend to provide pilot data for a BET-arm in prospective confirmatory trials in children. In accordance with current concepts of clinical presentation and diagnosis of ETD (29–31), as well as meta-analyses of COME (32), appearance of the tympanic membrane during microscopic otoscopy, tympanograms, and hearing thresholds were chosen as main outcome criteria for resolution of disease. Results are reported according to the guidelines for reporting of observational studies by the EQUATOR network (STROBE-statement).

Study Design and Setting

This study was carried out in accordance with the Declaration of Helsinki. Ethical approval for this retrospective multicenter analysis was obtained from Heidelberg University institutional ethical review board (S-010/2015, PI: S. Euteneuer). Children included in this study were treated at 9 German secondary and tertiary referral otorhinolaryngology departments between March 2011 and August 2014: Bundeswehrkrankenhaus Ulm, Evangelisches Diakonissenkrankenhaus Karlsruhe-Rüppurr, Klinikverbund St. Antonius und St. Josef Wuppertal, University Medical Center Hamburg-Eppendorf, Klinikum Bielefeld, Olgahospital - Klinikum Stuttgart, University Hospital Luebeck, University Hospital Giessen-Marburg and Heidelberg University Hospital.

Standardized retrospective retrieval of the following criteria, i.e., age, allergies, pre-BET medical and surgical history, indication for BET, concomitant surgical procedures, appearance of the tympanic membrane, tympanograms, hearing thresholds, ability to perform Valsalva's Maneuver, follow-up intervals, and guardians satisfaction after treatment, was performed locally at the participating departments from medical

records. Subsequently, data were anonymized and pooled for statistical analysis. In case of multiple post BET follow-up examinations, data from the most recent examination were utilized.

Characteristics of Participants: Inclusion and Exclusion Criteria

All children included in the current analysis had failed first-line medical (antibiotics, corticosteroids) and surgical standard therapy, having received at least one surgical intervention (adenoidectomy and/ or paracentesis and/or VT placement) for chronic dilatory ETD-related disease in the past. Further criteria for inclusion were age between 4 and 12 years at the time of BET; either presence of COME for more than 3 months (once again), or more than 3 episodes of AOM during the past year before BET, presence of chronic suppurative otitis media (CSOM), chronic epitympanic otitis media (cholesteatoma) or mesotympanic retractions pockets up to full atelectasis; no previous BET treatment.

Exclusion criteria were presence of cystic fibrosis, Down syndrome, cleft lip and palate, fibrous dysplasia, malignant disease, immunodeficiency, neuromuscular disorders and syndromic dysmorphism of the head and concomitant adenoidectomy at the time of BET.

Paracentesis, VT placement, tympanoplasty, and radiofrequency therapy of inferior turbinate synchronous with the BET were allowed. Synchronous revision-adenoidectomy was not allowed, reflecting the authors' opinion, that adenoids are a source of chronic inflammation at the ET pharyngeal orifice and therefore dilatory ETD, and should have been treated before such an intervention.

A clinical and physical examination by a pediatrician was performed before the children were included.

Intervention: BET Procedure

Preoperative informed consent was obtained from the parents or legal guardians after profound discussion of all treatment alternatives (i.e., paracentesis, VT placement) and offering BET as an individual off-label-treatment: The BET balloon catheter used in the current study (TubaVent catheter, Spiggle & Theis, Overath, Germany) had been accredited in Germany (CE marked) in 2010 for use in adults. During a regular accreditation renewal in 2014, the catheter was approved for use in children ''at the attending physician's discretion.'' BET was performed in general anesthesia as an inpatient procedure with overnight monitoring. All children were treated with the standard TubaVent balloon catheter (dimensions: length 20 mm, diameter 3.28 mm) and its designated combined insertion instrument (both Spiggle & Theis, Overath, Germany), the later limiting the insertion depth of the balloon catheter to the cartilaginous portion of the ET even in the youngest children included in this study: During ET maturation, lengthening of the cartilaginous portion occurs mainly in the first 3 years of life, while the bony portion continues to lengthen until maturation is completed at the age of 6 to 7 years. In current computed tomography studies, every child investigated at the age of 4 years or older had a cartilaginous ET portion length of more than 20 mm (33–35). The surgical technique of BET varied between participating centers. Either a transnasal or a transoral approach was used. In the transnasal approach, the balloon catheter, loaded into its designated insertion instrument, was inserted through the ipsilateral nasal cavity, its positioning into the nasopharyngeal Eustachian tube orifice visualized by a Hopkins rod endoscope (Karl Storz, Tuttlingen, Germany), inserted though the ipsi- or contralateral nasal cavity. Video images were displayed on a monitor (Karl Storz, Tuttlingen, Germany). In the transoral approach, the balloon catheter loaded into its designated insertion instrument was inserted through the ipsilateral nasal cavity while its positioning in the Eustachian tube orifice was visualized transorally by a 120° Hopkins rod endoscope (Karl Storz, Tuttlingen, Germany). In all patients, the balloon catheter was inflated with sterile 0.9% saline solution to 10 bars, and held for 2 minutes before deflating and removal under endoscopic control.

Main Outcome Measures: Diagnostic Tests

Tympanometry was performed using calibrated standardized tympanometers. Tympanograms were classified as types A, B, C according to the Jerger classification. Hearing thresholds were determined in dB HL either by pure-tone audiometry or age-adapted conditional audiometry depending on the age of the child. The air conduction thresholds at 1 kHz were chosen for evaluation in this study. The ability to perform Valsalva's Maneuver was judged by visibility of tympanic membrane motion during microscopic otoscopy. No visible tympanic membrane motion was qualified as ''negative'' Valsalva's maneuver; visible tympanic membrane motion was qualified as a ''positive'' one.

Statistical Analysis

Data were analyzed by using Statistica 5.1 (StatSoft (Europe) GmbH, Hamburg, Germany) and SAS 9.4 TS Level1M3 (SAS Institute Inc., Cary, NC). Quantitative variables (i.e., age, hearing thresholds, follow-up interval) were tested for normal distribution using the Kolmogorov–Smirnov test. Depending on their distribution, results are expressed either as median and quartiles or mean and standard error of the mean (SEM) and the appendent 95% confidence intervals (95% CIs). Comparisons before and after treatment were either performed by a paired *t*-test or by Wilcoxon's signed-rank test, respectively. Comparisons between groups were done by independent samples *t* test, Mann–Whitney *U* test, or multivariate analysis of variance (ANOVA).

Percentages are given in relation to either the total number of children ($N = 167$) or the total number of treated ears ($N = 299$) with their respective 95% CIs, the later calculated according to the Wilson method without continuity correction.

Paired categorical data (i.e., appearance of the tympanic membrane during otoscopy, tympanograms, ability to perform Valsalva's Maneuver) before and after treatment were analyzed by 2-way contingency tables and Bowker's test for symmetry. To evaluate treatment effects caused by BET itself, and not by the concomitant surgical procedures (i.e., paracentesis, VT placement, tympanoplasty), the ears treated by ''BET-only'' and by ''BET-plus'' concomitant surgical procedure were evaluated in a subsequent subgroup analysis. To evaluate the effect of maturation status of the ET at the time of treatment, we compared children aged < 7 years with children aged ≥ 7 years in subgroup analysis. Subgroups were compared by contingency tables and Pearson's chi–square test. Missing data (MD) were included in the respective contingency tables, but not into the statistical analysis. In all cases a two-tailed p value less than 0.05 was considered to be significant. The same statistical methods were used to evaluate BET efficacy in the subgroup of children with COME.

RESULTS

One hundred sixty-seven children, between 4 and 12 years of age, received 299 BET procedures during

the 3.5 years recruiting period. The mean age at the time of BET was 9.1 years (95% CI: 8.7–9.4 yr). One hundred thirty-two children were treated bilaterally (79.0%), 35 children (21.0%) unilaterally.

Every child had received at least one surgical intervention before BET, most children had received multiple. One hundred forty children (83.6%) had received an adenoidectomy before BET. Paracentesis or short-term VT insertions had been carried out at least once in 248 of 299 ears (82.9%). Tympanoplasty had been carried out in 69 ears (23.0%) before BET. Eleven children (6.6%) had been diagnosed with allergies.

The main indications for BET were persistent COME and/or tympanic membrane retraction in 249 ears (83.3%). A history of recurrent AOM by itself, or in combination with COME and tympanic membrane retraction, seemed not to play a prominent role in the current cohort, contributing to the indication for BET in only 28 ears (9.4%). In 39 ears (13%) advanced ear diseases, i.e., CSOM or cholesteatoma, were stated as reasons for BET.

Diagnostic Findings Before BET

Consistent with the specified indications, COME and/or tympanic membrane retraction were observed in 83.3% of microscopic otoscopic examinations at the time of BET (Table 1A, rows). In five ears (1.7%), VTs were still in place. Four ears (1.3%)—with the indication ''recurrent AOM''—revealed normal tympanic membranes during microscopic otoscopic examination at the time of BET (Table 1A, rows). Consistently type B was the bestriding type of tympanogram (155 ears, 51.8%, Table 2A, rows) before BET, followed by type C (69 ears, 23.1%). A type A tympanogram was found only in 34 ears (11.4%). In 41 ears (13.7), data were missing, or pressure buildup was not possible due to a perforated tympanic membrane in CSOM, cholesteatoma, or with VTs in place. The median air conduction hearing threshold at 1 kHz before BET was 20 dB HL (95% CI: 0–46 dB; Fig. 1''All''). Valsalva's Maneuver results were merely available in 132 ears (44.1%), being negative in 117 ears and positive in 15 ears.

Concomitant Procedures and Complications

As stated in the Methods section, surgeons were allowed to carry out paracentesis, VT placement, tympanoplasty, and radiofrequency therapy of inferior turbinate synchronous with the BET. In 171 ears (57.2%) BET was accompanied by either paracentesis (41 ears, 13.7%), VT placement (94 ears, 31.4%), or tympanoplasty (36 ears, 12.0%). In 128 ears (42.8%) BET was the only intervention. In addition, eight children (4.8% of 167) received bilateral inferior turbinate reductions. In the five ears (1.7%) having tubes in place, they were removed during BET. Two of five ears received no further ear intervention, three of five ears received synchronous tympanoplasty type I. No serious BET-related complications occurred. Four children (2.4%) suffered mild anterior epistaxis, promptly responsive to xylometazoline nasal drops administered in the recovery room.

Primary Objective: BET Treatment for Resolution of Middle Ear Diseases

Comparison of Diagnostic Findings Before and After Treatment

One hundred fifty-eight children attended follow-up visits at participating centers (follow-up rate: 94.6%) (Tables 1A, 2A, Fig. 1). They had received 282 BET procedures. Given the multicenter retrospective study-design with different follow-up procedures in place in participating centers, results could not be stratified to specific follow-up intervals, e.g., 6 weeks, 3 months, 1 year, etc. The median follow-up interval was 2.6 months (95% CI: 0.3–16.1 mo), the maximum follow-up of 16.9 months, with the length of follow-up interval ensuing an exponential distribution function.

Post BET treatment, tympanic membranes appearance had changed (Table 1A, columns, $p < 0.001$): In 196 ears (65.6%) the tympanic membrane appeared normal. Findings of COME and/or retraction of the tympanic membrane were notably reduced to 23.4% of ears at follow-up. Episodes of recurrent COME during the follow-up interval were reported in 41 ears (13.7%). Twenty-six of these were treated with VT insertion. However, only 5 VTs were still in place at the last follow-up visit (Table 1A).

Median air conduction hearing threshold at 1 kHz improved from 20 to 10 dB HL after BET (95% CI: 0–45 dB; Wilcoxon's signed-rank test: $p < 0.001$, Fig. 1). This improvement could indeed be attributed to therapy, but not to selective missing data from children hearing worse before (Man–Whitney U test $p = 0.06$). Tympanogram type shifted from types B and C before toward type A after treatment (see Table 2A, $p < 0.001$): 90 ears with type B and C tympanograms before treatment showed type A tympanograms thereafter, including 4 of the 5 ears with tube-removal. Like before treatment, Valsalva's maneuver results after treatment were documented in only 42% (126) of children's ears. Of these, 82 were positive and 44 were negative after therapy, whereas there had been 117 negative and 15 positive Valsalva's maneuvers before.

Guardian's satisfaction with treatment was documented in medical records of 135 children (80.1%): 82 were highly satisfied, 32 were satisfied, 20 guardians were undecided and only one child's guardians were unsatisfied.

Obviously, the concomitant performance of paracentesis, VT placement as well as tympanoplasty in 57.2% of ears interacts on these treatment results. To further elaborate the effect caused by BET itself, and not by the concomitant surgical procedures (i.e., paracentesis, VT-placement, tympanoplasty), we conducted a subsequent subgroup analysis of ears treated by ''BET-only'' and by ''BET -plus'' concomitant surgical ear procedure.

TABLE 1. *Tympanic membrane (TM) findings before and after treatment.*

A All

	After Treatment								
	Normal	COME	Retraction	CSOM/ Cholesteatoma	VT	MD (Incl. Lost Follow-Up)	Row Total	Row %	Row 95% CI
Before BET									
Normal	2	2	0	0	0	0	4	1.3	(0.5–3.3)
COME	62	20	7	0	4	6	99	33.1	(28.0–38.6)
Retraction	77	3	23	4	1	8	116	38.8	(33.5–44.4)
COME and retraction	21	7	5	1	0	0	34	11.4	(8.3–15.5)
CSOM/cholesteatoma	21	1	2	3	0	5	32	10.7	(7.7–14.7)
VT	5	0	0	0	0	0	5	1.7	(0.7–3.9)
MD	8	0	0	0	0	1	9	3.0	(1.6–5.6)
Column total	196	33	37	8	5	20	299	100.0	
Column %	65.6	11.0	12.4	2.7	1.7	6.7	100.0	100.0	
Column 95% CI	(60.0–70.8)	(7.9–15.1)	(9.1–16.6)	(1.4–5.2)	(0.7–3.9)	(4.4–10.1)			

B BET-Only

	After Treatment								
	Normal	COME	Retraction	CSOM/ Cholesteatoma	VT	MD (Incl. Lost Follow-Up)	Row Total	Row %	Row 95% CI
Before BET									
Normal	2	2	0	0	0	0	4	3.1	(1.2–7.7)
COME	23	2	0	0	0	1	26	20.3	(14.2–28.1)
Retraction	36	2	15	2	0	5	60	46.9	(38.5–55.5)
COME and retraction	5	3	4	1	0	0	13	10.2	(6.1–16.7)
CSOM/cholesteatoma	11	1	0	2	0	1	15	11.7	(7.2–18.4)
VT	2	0	0	0	0	0	2	2.3	(0.8–6.6)
MD	8	0	0	0	0	0	8	6.3	(3.2–11.9)
Column total	87	10	19	5	0	7	128	100.0	
Column %	68	7.8	14.8	3.9	0	5.5	100.0	100.0	
Column 95% CI	(59.5–75.5)	(4.3–13.8)	(9.7–22.0)	(1.7–8.8)	(0.0–2.9)	(2.7–10.9)			

C BET-Plus

	After Treatment								
	Normal	COME	Retraction	CSOM/ Cholesteatoma	VT	MD (Incl. Lost Follow-Up)	Row Total	Row %	Row 95% CI
Before BET									
Normal	0	0	0	0	0	0	0	0	(0.0–2.2)
COME	39	18	7	0	4	5	73	42.7	(35.5–50.2)
Retraction	41	1	8	2	1	3	56	32.8	(26.2–40.1)
COME and retraction	16	4	1	0	0	0	21	12.3	(8.2–18.1)
CSOM/cholesteatoma	10	0	2	1	0	4	17	11.7	(7.7–17.4)
VT	3	0	0	0	0	0	3	1.8	(0.6–5.1)
MD	0	0	0	0	0	1	1	0.6	(0.1–3.3)
Column total	109	23	18	3	5	13	171	100.0	
Column %	63.7	13.5	10.5	1.8	2.9	7.6	100.0	100.0	
Column 95% CI	(56.3–70.5)	(9.2–19.4)	(6.7–16.0)	(0.6–5.1)	(1.2–6.6)	(4.5–12.6)			

Findings are given in all ears (A), as well as the subgroups of ears treated with ''BET-only'' (B) and treated with BET and other concomitant procedures (''BET-plus'', C). Numbers of ears with the respective TM findings before treatment are detailed in rows. Numbers of ears with the respective TM findings after treatment are detailed in columns. Proportion of the respective TM findings (%) relative to all TM findings before and after treatment respectively are given at the table's frame along with the respective 95% confidence intervals (95% CIs). Missing data (MD) are included in the table but not into statistical analysis. Treatment changed TM findings in the total collective (A) as well as in subgroups (B and C, all Bowker's test: $p < 0{,}001$). Subgroups differed in their TM findings before therapy (rows in B and C, $\chi 2 = 24.0$, $p < 0.001$).

BET indicates balloon Eustachian tuboplasty; COME, chronic otitis media with effusion; CSOM, chronic suppurative otitis media; VT, ventilation tube.

TABLE 2. *Type of tympanogram before and after treatment*

A All

	After BET						
	Type A	Type B	Type C	MD (Incl. lost Follow-Up)	Row Total	Row %	Row 95% CI
Before BET							
Type A	22	5	3	4	34	11.4	(8.3–15.5)
Type B	64	43	14	34	155	51.8	(46.1–57.4)
Type C	26	7	14	22	69	23.1	(18.7–28.2)
MD	5	5	1	30	41	13.7	(10.3–18.1)
Column total	117	60	32	90	299	100.0	
Column %	39.1	20.1	10.7	30.1	100.0	100.0	
Column 95% CI	(33.7–44.7)	(15.9–25.0)	(7.7–14.7)	(25.2–35.5)			

B BET-Only

	After BET						
	Type A	Type B	Type C	MD (Incl. Lost Follow-Up)	Row Total	Row %	Row 95% CI
Before BET							
Type A	18	5	1	4	28	21.9	(15.6–29.8)
Type B	23	16	5	8	52	40.6	(32.5–49.3)
Type C	15	4	8	5	32	25.0	(18.3–33.2)
MD	4	3	1	8	16	12.5	(7.8–19.3)
Column total	60	28	15	25	128	100.0	
Column %	46.9	21.9	11.7	19.5	100.0	100.0	
Column 95% CI	(38.4–55.5)	(15.6–29.8)	(7.2–18.4)	(13.6–27.2)			

C BET-Plus

	After BET						
	Type A	Type B	Type C	MD (Incl. Lost Follow-Up)	Row Total	Row %	Row 95% CI
Before BET							
Type A	4	0	2	0	6	3.5	(1.6–7.4)
Type B	41	27	9	26	103	60.2	(52.7–67.2)
Type C	11	3	6	17	37	21.6	(16.1–28.4)
MD	1	2	0	22	25	14.6	(10.1–20.7)
Column total	57	32	17	65	171	100.0	
Column %	33.3	18.7	9.9	38	100.0	100.0	
Column 95% CI	(26.7–40.7)	(13.6–25.2)	(6.3–15.3)	(31.1–45.5)			

Findings are given in all ears (A), as well as in the subgroups of ears treated with ''BET-only'' (B) and treated with BET and other concomitant procedures (''BET-plus'', C). Numbers of ears with the respective type of tympanogram before treatment are detailed in rows. Numbers of ears with the respective type of tympanogram after treatment are detailed in columns. Proportion of the respective type of tympanogram (%) relative to all tympanograms before and after treatment respectively are given at the table's frame along with the respective 95% confidence intervals (95% CIs). Missing data (MD) are included in the table but not into statistical analysis. Treatment changed the type of tympanogram in the total collective (A) as well as in subgroups (B and C, all Bowker's test: $p < 0.001$). Subgroups differed in their TM findings before therapy (rows in B and C, $\chi 2 = 27.7$, $p < 0.001$).

BET indicates balloon Eustachian tuboplasty.

Findings After Isolated BET Treatment (''BET-Only,'' Tables 1B and 2B, Fig. 1) Versus BET Plus Concomitant Surgical Procedure (''BET-Plus,'' Tables 1C and 2C, Fig. 1)

In 128 ears (42.8%), BET or BET with VT removal (2 ears) were the only intervention, hereafter referred to as ''BET-only'' group (Table 1B). In 171 of 299 ears (57.2%) BET was combined with paracentesis (41 ears, 13.7%), VT placement (94 ears, 31.4%), or tympanoplasty (34 ears, 11.4%; including 3 ears with VT removal), hereafter referred to as ''BET-plus'' group (Table 1C).

The general pretreatment characteristics between groups differed significantly: Children treated with ''BET-only'' tended to be older (9.7 versus 8.6 yr, $p < 0.001$). Relatively more retractions but less COMEs were seen in ''BET-only''

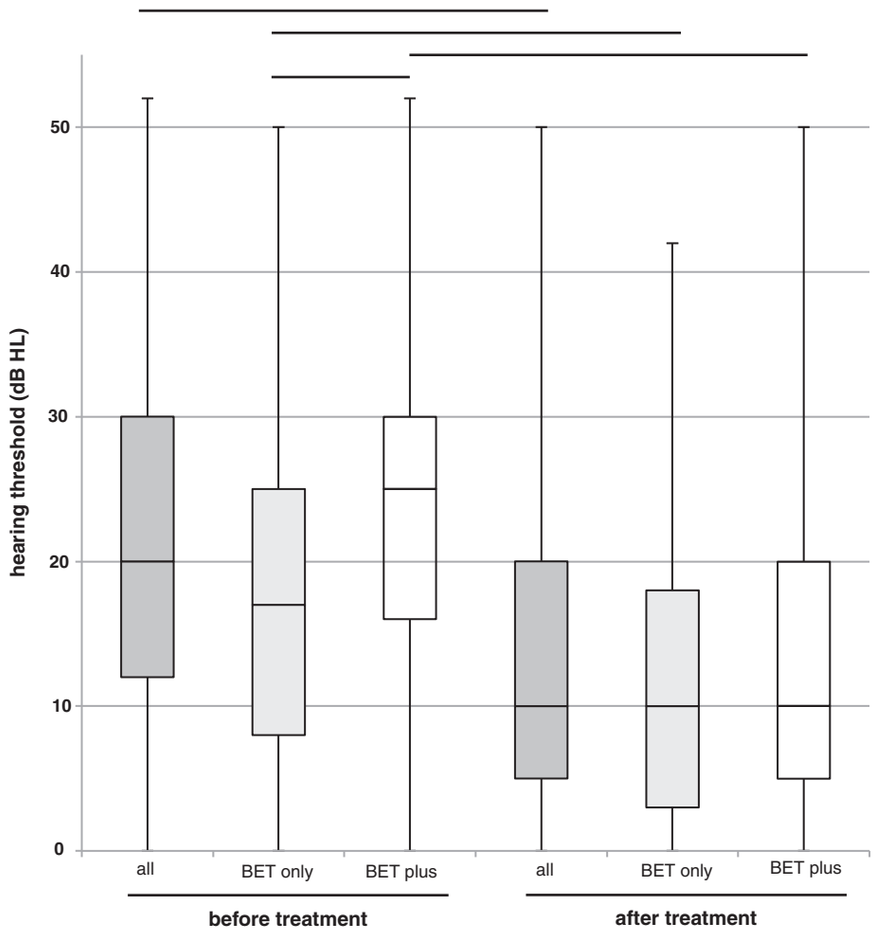

FIG. 1. Hearing thresholds before and after treatment. Thresholds before and after treatment are given as mean and quartiles (boxes) with minimum and maximum values (whiskers). Thresholds are detailed in all ears (dark gray, N = 285 and N = 196), as well as in the subgroups of ears treated with "BET-only" (light gray, N = 126 and N = 99) and with "BET-plus" (transparent, N = 159 and N = 97). Median threshold before therapy was higher in "BET-plus" than in "BET-only" treated ears (U = 6744, $p < 0.001$). Thresholds after treatment were reduced in the total collective as well as in the subgroups (Wilcoxon's test, all $p < 0.001$). Congruently, mean reduction of individual thresholds (in ears with both the before and after treatment thresholds available) was higher in "BET-plus" than in "BET-only" treated ears (N = 195, U = 3,933, $p = 0.04$).

treated ears compared with the ''BET-plus'' treated ears (Table 1B, C). Hearing thresholds before therapy tended to be lower in ''BET-only'' treated ears (median 17 dB versus 25 dB, $p < 0.001$), and tympanograms were more likely to be type A and less likely to be type B before therapy (Table 2B, C). In the few ears documented, the ability to perform Valsalva's maneuver did not differ between groups.

The length of follow-up was similar in both groups (median 2.3 mo in ''BET-only'' versus 2.6 mo in ''BET-plus''). In both ''BET-only'' and in ''BET-plus'' groups, findings of COME and/or retraction of the tympanic membrane were notably reduced, with the tympanic membrane appearance returning to normal (68.0 versus 63.2%, Table 1B, C). Hearing thresholds significantly improved to a median of 10 dB hearing level in both groups (both $p < 0.001$, Figure 1). In ''BET-only'' as well as in ''BET-plus'' treated ears, type A tympanograms were increased after treatment while the rate of type B declined (Table 2B, C). The ability to perform Valsalva's maneuver was documented only in 42% of patients after treatment. In the ''BET-only'' treated group, Valsalva's maneuvers were positive in 33 of 58 ears after BET. In the ''BET-plus'' treated group, 49 of 68 became positive after treatment. The parents or legal guardians, respectively, were equally satisfied with their children's treatment in both groups.

Secondary Objective: BET Treatment for Resolution of COME

Comparison of Diagnostic Findings Before and After Treatment (Tables 3 and 4, Figure 2)

In 144 ears (48.2%), COME was stated as the indication for BET. Presence of effusion, with or without retraction of the tympanic membrane, was confirmed in 133 of these 144 ears directly before BET

TABLE 3. *Tympanic membrane (TM) findings in ears with COME after treatment*

	All			BET-Only			BET-Plus		
	N	%	95% CI	N	%	95% CI	N	%	95% CI
Column total	105	100		26	100		79	100	
Normal	65	62	(52–71)	19	73	(54–86)	46	58	(47–68)
COME	20	19	(13–28)	1	4	(1–19)	19	24	(16–35)
Retraction	12	11	(7–19)	4	15	(6–34)	8	10	(5–19)
CSOM/cholesteatoma	1	1	(0–5)	1	4	(1–19)	0	0	(0–5)
VT	4	4	(1–9)	0	0	(0–13)	4	5	(2–12)
MD (incl. lost follow-up)	3	3	(1–8)	1	4	(1–19)	2	3	(1–9)

Numbers of ears with respective TM findings after treatment are given in all children (left columns), in children treated with ''BET-only'' (middle columns), and children treated with balloon Eustachian tuboplasty (BET) and other concomitant procedures (''BET-plus'', right columns). Proportions of the respective TM findings (%) are given along with the respective 95% confidence intervals (95% CIs). Before treatment all ears showed chronic otitis media with effusion (COME). Missing data (MD) are included in the table but not into statistical analysis. Treatment changed TM findings in the total collective as well as in subgroups. Subgroups differed in their TM findings after therapy ($\chi 2 = 19.2$, $p = 0.04$).

CSOM indicates chronic suppurative otitis media.

(Table 1). Tympanograms before treatment had been performed in 116 of these ears. Surprisingly, despite the otoscopic finding of COME, 11 ears showed type A tympanograms. These ears were excluded from the COME-subgroup analysis. Consequently, 105 ears from 66 children, with effusion during microscopic otoscopy and type B or C tympanograms, were included in the COME-subgroup analysis.

Their mean age was 8.3 ± 0.3 years (95% CI: 7.7–8.9 yr). Four children (6%) had been diagnosed with allergies. 88% (95% CI: 78–94%) of children with COME had received a previous adenoidectomy. 96% (95% CI: 91–99%) of their ears had been treated with paracentesis with or without VTs at least once. The vast majority of them had received multiple surgical interventions, with the maximum amount of 6 paracentesis and VT insertions per ear. The median follow-up interval was 2.5 months (95% CI: 0.2–15.2 mo).

Median hearing threshold in the COME subgroup was 25 dB HL (95% CI: 2–45 dB) before treatment, improving to a median of 10 dB HL (95% CI: 0–40 dB) after treatment (Fig. 2, $p < 0.001$). In the 61 ears with paired pre- and postoperative hearing thresholds available, the individual hearing threshold improved by 10 dB HL (median, 95% CI: −38 to 5 dB). Microscopic otoscopy at follow-up revealed a clearance rate of middle ear effusion resulting in a normal tympanic membrane in 62% (95% CI: 52–71%) of ears (Table 3). Post treatment tympanograms shifted toward a normal type A in 45% of ears (95% CI: 36–54), while 25% stayed types B and C (Table 4A). The ability to perform Valsalva's maneuver was only documented in nearly half (54) of ears with COME before treatment. Of these 48 were negative. After treatment only 16 of 51 were still negative.

During the follow-up, recurrent middle ear effusion was observed in 27 ears (26%, 95% CI: 18–35%). Sixteen ears were therefore treated with VT insertions during follow-up. Four of these were still in place at the most recent follow-up (Table 3). Forty-six of 66 children's guardians were ''content'' or ''very content'' with treatment.

As with the total collective, concomitant performance of paracentesis, VT placement as well as tympanoplasty interacts on these treatment results in children with COME. To further elaborate the effect caused by BET itself, we once again conducted subgroup analysis of ears treated by ''BET-only'' and by ''BET -plus'' concomitant surgical procedures.

Effect of Isolated BET Treatment Versus ''BET-Plus'' Treatment in Resolution of COME

As for the other BET indications, not all ears were treated with BET only (N = 26, 25%), but with simultaneous paracentesis (N = 26, 25%) or VTs (N = 53, 50%) respectively, the latter two groups hence referred to as ''BET-plus'' COME group. Notably, in the ''BET-only'' COME subgroup, more ears had previously been treated with a tympanoplasty (6/26 ears, 23%, 95% CI: 7–39%) than in the ''BET-plus'' COME subgroup (4/79 ears, 5%, 95% CI: 0–10%, $\chi 2 = 7.3$, $p = 0.007$). Rates of previous paracentesis and VT placements per ear were comparable in both COME subgroups, as was the rate of previous adenoidectomy in the respective children. Children treated with ''BET-only'' for COME tended to be older (N = 16, 9.4 ± 0.6 yr, 95% CI: 5.0–12.9 yr) than children that were treated by ''BET-plus'' (N = 50, 7.9 ± 0.3 yr, 95% CI: 4.1–12.2 yr, t = 2.28, $p < 0.03$). Otherwise characteristics before treatment, like presence of allergies in children, tympanogram type (Table 4), median hearing threshold (Fig. 2), and the ability to perform Valsalva's maneuver per ear did not differ between ''BET-only'' and ''BET-plus'' COME subgroups. Length of follow-up was comparable (''BET-only'' COME: median 2.1 mo, 95% CI: 0.4–12.6 mo; ''BET-plus'' COME: median 2.6 months, 95% CI: 0.1–16.9 mo, $p = 0.87$).

The clearance rate of middle ear effusion, as determined by a normal tympanic membrane during microscopic

TABLE 4. *Type of tympanogram in ears with COME before and after treatment*

A All

	After BET						
	Type A	Type B	Type C	MD (Incl. Lost Follow-Up)	Row Total	Row %	Row 95% CI
Before							
Type A	0	0	0	0	0	0	0
Type B	38	19	4	12	73	70	(60–78)
Type C	8	1	2	10	21	20	(13–29)
MD	1	0	0	10	11	10	(6–18)
Column total	47	20	6	32	105	100.0	
Column %	45.0	19.0	6.0	30.0	100.0	100.0	
Column 95% CI	(36–54)	(13–28)	(3–12)	(22–40)			

B BET-only

	After BET						
	Type A	Type B	Type C	MD (Incl. Lost Follow-Up)	Row Total	Row %	Row 95% CI
Before							
Type A	0	0	0	0	0	0	0
Type B	8	3	0	3	14	54	(35–71)
Type C	6	1	1	0	8	31	(17–50)
MD	1	0	0	3	4	15	(6–34)
Column total	15	4	1	6	26	100.0	
Column %	58	15	4	23	100.0	100.0	
Column 95% CI	(39–78)	(6–34)	(1–19)	(11–42)			

C BET-plus

	After BET						
	Type A	Type B	Type C	MD (Incl. Lost Follow-Up)	Row Total	Row %	Row 95% CI
Before							
Type A	0	0	0	0	0	0	0
Type B	30	16	4	9	59	75	(64–83)
Type C	2	0	1	10	13	16	(10–26)
MD	0	0	0	7	7	9	(4–17)
Column total	32	16	5	26	79	100.0	
Column %	41	20	6	33	100.0	100.0	
Column 95% CI	(30–52)	(13–30)	(3–14)	(24–44)			

Findings are given in all children (A), in children treated with ''BET-only'' (B) and in children treated with BET and other concomitant procedures (''BET-plus'', C). Numbers of ears with the respective type of tympanogram before treatment are detailed in rows. Numbers of ears with the respective type of tympanogram after treatment are detailed in columns. Proportion of the respective type of tympanogram (%) relative to all tympanograms before and after treatment respectively are given at the table's frame along with the respective 95% confidence intervals (95% CIs). Missing data (MD) are included in the table but not into statistical analysis. Treatment changed the type of tympanogram in the total collective (A) as well as in subgroups (B and C, all Bowker's test: $p < 0.002$). However, subgroups did not differ regarding their type of tympanograms before and after therapy.

BET indicates balloon Eustachian tuboplasty.

otoscopy, was slightly higher in ears treated with ''BET-only'' (73%, 95% CI: 54–86%) than with ''BET-plus'' (58%, 95% CI: 47–68%), $\chi 2 = 9.8$, $p = 0.04$, Table 3). Hearing thresholds and tympanograms improved similarly in both subgroups (Fig. 2, Table 4B, C).

Recurrent middle ear effusion during the follow-up interval occurred more often in the ''BET-plus'' than in the ''BET-only'' COME subgroup (30% (95% CI: 20–41%) versus 12% (95% CI: −1 to 24%), $\chi 2 = 8.2$, $p = 0.02$). Thus VT insertions during the follow-up interval occurred in the ''BET-plus'' COME subgroup but not the ''BET-only'' COME subgroup (16/79, 20% (95% CI: 11–29%) versus 0/26, $\chi 2 = 11.0$, $p = 0.004$). Guardian's satisfaction with treatment was similar across groups.

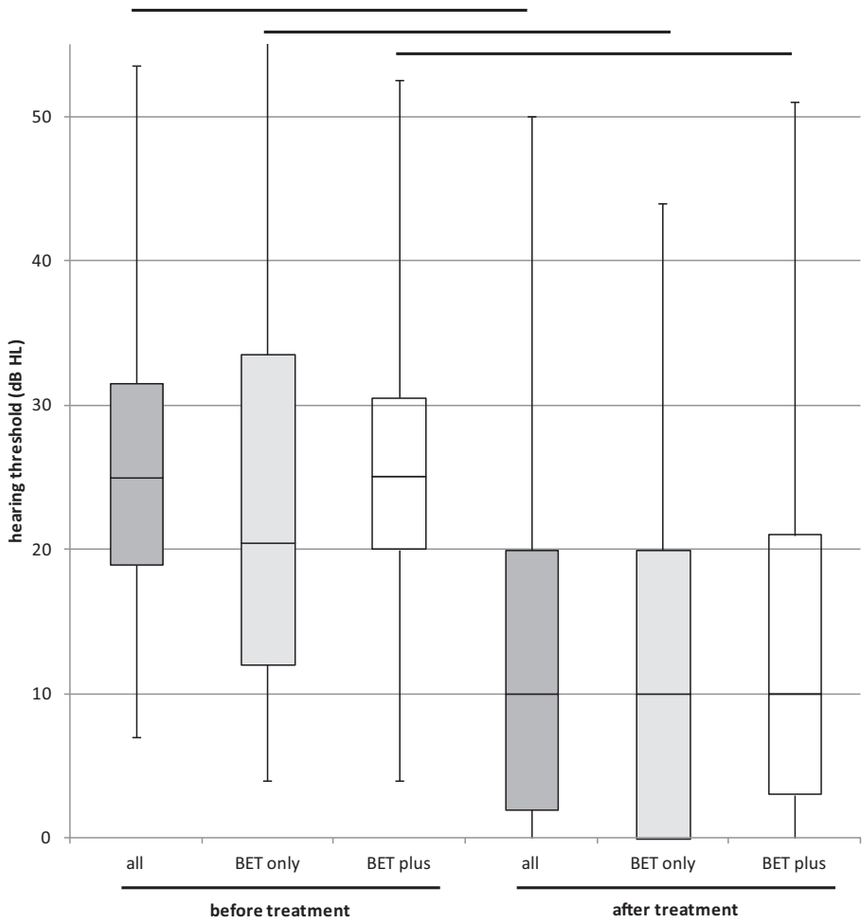

FIG. 2. Hearing thresholds in ears with COME before and after treatment. Thresholds before and after treatment are given as mean and quartiles (boxes) with minimum and maximum values (whiskers). Thresholds are detailed in all ears (dark gray, N = 96 and N = 61), as well as in the subgroups of ears treated with "BET-only" (light gray, N = 24 and N = 18) and with "BET-plus" (transparent, N = 72 and N = 43). Median thresholds before and after therapy did not differ in "BET-plus" and "BET-only" treated ears (Mann–Whitney *U*: $p > 0.2$ and $p > 0.5$). Thresholds after treatment were reduced in the total collective as well as in the subgroups (Wilcoxon's test, all $p < 0.001$). Mean reduction of individual thresholds (in ears with both the before and after treatment thresholds available) was comparable in "BET-plus" and in "BET-only" treated ears (N = 61, U = 312, $p > 0.2$).

Effect of BET Treatment in Resolution of COME Before and After Maturation of the ET

ET tube configuration and function matures around 6 to 7 years of age (1,45). Therefore, one might speculate that the child's age at the time of treatment interacts with BET efficiency in clearance of COME. We therefore further investigated the above-reported treatment results by comparing children aged < 7 years with children aged ≥7 years at the time of BET treatment. Twenty children with COME (33 ears) were treated before the age of 7 years (''BET-only'': 5 ears, ''BET-plus'': 28 ears), while 46 children with COME (72 ears) were treated when children were ≥7 years of age (''BET-only'': 21 ears, ''BET-plus'': 51 ears; $\chi^2 = 2.3$, $p > 1.2$). All of the younger children with COME had undergone previous adenoidectomy, while only 38 (83%, 95% CI: 72–92%) of the children with COME ≥7 years had ($\chi^2 = 4.0$, $p > 0.05$). Their ears did not differ regarding the percentage of previous paracentesis, VT placements, or tympanoplasty. Median hearing threshold before treatment was 25 dB HL in both age groups (<7 yr 95% CI: 12–45 dB, ≥7 yr 95% CI: 0–48 dB, U = 838.5, $p > 0.4$). Two children in each age group had been diagnosed with allergies ($\chi 2 = 0.8$, $p > 0.4$). Median length of follow-up was comparable in both age groups (<7 yr: 1.9 mo, 95% CI: 0.1–10.7 mo; ≥7 yr: 2.8 mo, 95% CI 0.5–16.9 mo, U = 319, $p = 0.09$).

Hearing thresholds improved comparably regardless of BET treatment modality (''BET-only'' or ''BET-plus'') or of age-group (2 × 2 ANOVA, interaction effect, F = 1.1, $p > 0.3$). The clearance rate of middle ear effusion, as determined by a normal tympanic membrane during microscopic otoscopy, in ''BET-only'' treated COME ears did not depend on the age at the time of treatment (<7 yr: 60%, 95% CI: 17–103%; ≥7 yr: 80%, 95% CI: 62–98%, $\chi 2 = 3.0$,

$p = 0.6$). In ''BET-plus'' treated ears however, children < 7 years showed a higher rate of normal appearing tympanic membranes than children ≥ 7 years (<7 yr: 85%, 95% CI: 71–98%; ≥ 7 yr: 47%, 95% CI: 33–61%, $\chi 2 = 11.6$, $p = 0.02$). Correspondingly, ''BET-plus'' treated children with COME < 7 years showed higher rates of type A tympanograms at the end of follow-up than ''BET-plus'' treated children with COME ≥ 7 years (<7 yr: 82%, 95% CI: 66–98%; ≥ 7 yr: 45%, 95% CI: 28–63%, $\chi 2 = 8.4$, $p = 0.01$). Valsalva's maneuver results had only been documented in 51 of the 105 COME ears, 35 (69%) of these in children ≥ 7 years. In these older children with COME, rates of positive Valsalva's maneuvers were comparable after ''BET-only'' (62%, 95% CI: 35–88%) and ''BET-plus treatment (73%, 95% CI: 54–91%, $\chi 2 = 0.5$, $p = 0.5$). Children's parents were equally content with treatment regardless of BET treatment modality (''BET-only'' or ''BET-plus'') or of their child's age group.

DISCUSSION

The current study is the very first to present a large multicenter analysis of BET treatment effects in children. So far, there are no results from prospective BET trials available in children. Just recently, one prospective study has started recruiting 4 to 10-year-old children with otoscopic COME, and type B tympanograms for adenoidectomy, myringotomy, and VT placement on both ears, with BET being randomly assigned on one ear in addition (ClinicalTrials.gov-Identifier: NCT03499015). We are aware of six publications from four single centers exclusively reporting on BET in children (24–28,36). However, three of these publications are non-English language, and the publication of Jenkel et al. (24) focuses on the diagnostic tool of tubomanometry rather than BET treatment itself. Data from Jenckel, Leichtle, Maier et al. (24–26) contributed to the current study.

In this multicenter retrospective study, BET was safely feasible in children 4 years and older using one of the currently marketed standard balloon systems with a balloon length of 20 mm. The only adverse event observed was mild anterior epistaxis at a rate of 2.4% (95% CI: 0–5%), promptly responsive to xylomeazoline nasal drops administered in the recovery room. We are pointing out that we specifically excluded children with suspected anatomical variations or hints for dysmaturation of the ET form this study. When considering BET in these children, we strongly recommend preintervention tomographic imaging to evaluate not only the length of the cartilaginous portion of the ET, to ensure dilation of only the later, but also the course of the internal carotid artery in relation to cartilaginous portion of the ET, to prevent any risk for injury. In the present study, BET has been performed as an in-patient procedure in general anesthesia with an over-night stay in hospital to monitor for possible development of emphysema of the head and neck in the rare case of mucosa lesioning during catheter insertion (37). However, this later provision is to be challenged, based on the low incidence and courses of the few emphysemas encountered (up to 0.5%) (37), as well as the feasibility of BET in local anesthesia at least in adults (13,38).

Median follow-up in our pediatric collective was rather short (2.6 mo), though the range of follow-up extended well beyond 1 year (95% CI: 0.3–16.1 mo). In a prospective interventional trial of BET in treatment of COME however, a 1-year follow-up interval should be instantiated as a minimum, given the chronic nature of the condition studied. The few prospective licensing trails investigating BET in adults have in fact shown that the short-term effects seen 6 weeks after BET sustained for up to 1 year (11–13), suggesting the currently presented short-term data are indeed useful for planning of longer-term studies.

Further limitations due to the retrospective study design include variations between centers in their diagnostic criteria of allergies (i.e., structured past medical history, allergen-specific serum IgE, in-vivo skin testing), as well as their rigor to discern children showing tympanic membrane retractions contemporaneously with COME. Evidently, in a future prospective study the exact diagnostic criteria need to be stipulated. Furthermore, in a prospective setting, surgeons and guardians have to be aware that BET might not be accomplishable in the presence of enlarged adenoids. The later not only negatively impact ET function by themselves, but also prevent safe identification of the ET's pharyngeal orifice for balloon catheter insertion. In conformity with others (39), it is the authors' opinion that adenoids should be removed before a novel invasive intervention like BET.

However, even if the exact mechanism producing BET's treatment effect is currently still under debate, reduction of inflammatory lymphoid tissue at the ET orifice, not previously safely accessible even by endoscopic adenoidectomy techniques, seems an attractive explanation. Indeed, the one histopathologic case series published has shown replacement of lymphocytic submucosal infiltrate by thinner fibrous tissue in adult patients biopsied pre- and post-BET (40). Another mechanism of BET-action discussed is the extraction of mucous accumulated in the ET, thereby lowering the increased opening resistance due to ET-clearance failure (29,40,41). Viral upper respiratory infections with increased mucous production are frequent in children, and well known to negatively impact ET function (42). Both the reduction of the mucosal inflammatory load and mucosal adhesion by BET seem to be important mechanisms of action particularly in pediatric patients.

This study was conducted in children 4 to 12 years of age, presenting with recurrent symptomatic ear disease due to persistent ETD. Microscopic otoscopy, tympanometry, hearing threshold, and, in some of the participating centers, the ability to perform Valsalva's maneuver were chosen as diagnostic and outcome criteria. This reflects the consensus that there is no single ''gold standard'' test in clinical practice for diagnosis of ET function as well as evaluation of interventions on ETD

(29–31). In most COME clinical trials, otoscopy and tympanometry are chosen diagnostic tests for inclusion, while hearing threshold is used as a primary outcome parameter (7,32). For the purpose of clinical trials in ETD, expert panels recommended otoscopy, tympanometry, and pure-tone audiometry as outcome criteria (29,30). As opposed to these tests, questionnaire-based patient reported outcome measures of ETD, like the ETDQ-7 (43), or composite measures like the ETS-7 (44), will have questionable reliability in children when proxies are the primary responders.

Per inclusion criteria of the current study, children all underwent previous adenoidectomy, paracentesis, and/or ventilation tube insertions. Their mean age was 8.3 years (95% CI: 7.7–8.9 yr), a time when most children have ''outgrown'' their risk for otitis media and ET function is mature (1,45). However, they still presented with recurrent disease, mainly COME and tympanic membrane retraction, and a mean hearing threshold of 20 dB HL. In line with the exploratory ''pilot-data-mining'' aim of the current study, we did not exclude children nonetheless presenting with type A tympanograms (34 ears 11.4%) from the primary objective's analysis. This reflects the current uncertainty in the ENT community on how to address chronic persistent dilatory ETD versus chronic intermittent ETD, as seen in chronic tympanic membrane retraction and other advanced ear diseases. In future prospective studies investigating BET treatment efficiency, in tympanic membrane retraction e.g., presence of type B and C tympanograms at the time of treatment will most likely be regarded as requisite for inclusion.

While ''watchful waiting'' is proposed in younger children with shorter duration of COME symptoms, there is consensus in the literature and guidelines about the recommendation for VTs in this study's patient collective (46–48). Meanwhile, VTs only provide passive aeration of the middle ear via the outer ear canal, and do not address the underlying dilatory ETD. The authors therefore felt comfortable offering ''off-label'' BET to these children in a causal treatment approach. There was uncertainty among the authors and the children's guardians, if BET should be offered as sole intervention or be chaperoned by paracentesis or VTs. Eventually, children with tympanic membrane retractions were more likely to be treated with BET-only than children with COME (Table 1B, C), as were children with lower hearing thresholds (Fig. 1). Children with type A tympanograms before BET were more likely to be treated with BET-only, while children with type B tympanograms were more likely to be treated with concomitant procedures. After treatment however, their results were comparable regarding tympanic membrane appearance, hearing thresholds, and tympanogram type (Tables 1 and 2, Fig. 1). Considering children with COME only, the current 15% rate of revision VTs within the follow-up interval due to recurrent disease was half than the previously reported revision rate of approx. 30% for isolated VT insertions (32). Mandel et al. (49) identified ETD as a prime predictor for their 40% recurrence rate for COME after short-term VTs became nonfunctional. In another study, Mandel et al. (45) reported on 6-year-old children with past recurrent acute otitis media still exhibiting residual ET opening inefficiency while without active middle ear disease. They conclude that otitis media ''is not passing the ET without a trace'' but rather causally associated with impaired ET function. Indeed, Christov and Gluth (50) observed advanced mucosal disease at the tympanal ET orifice in 61% of adult human temporal bone specimens where patients had suffered from COME during lifetime. These observations in synopsis with the results of the current study suggest that BET offered to children earlier on, i.e., when dilatory ET impairment has not progressed for too long, could be even more successful in improving dilatory ET function and its related ear diseases.

CONCLUSION

BET indeed seems to be a promising treatment option for ear diseases due to dilatory ETD in children. In the current study, it was feasible, safe, and an effective second-line treatment in children 4 years and older. Significant treatment effects could be observed by microscopic otoscopy, in hearing threshold assessment and tympanometry. This study thereby provides detailed pilot data for design and planning of prospective pilot studies in children. This prospective confirmation of BET effectiveness, along with the comparison to current gold standard therapy, like VTs, or even natural resolution, is imperatively needed before BET could become a routine treatment for dilatory ETD-related diseases, especially COME, in children.

Acknowledgments: Ralf Schoepfer, University College London, Division of Biosciences, Department of Neuroscience, Physiology and Pharmacology, UK, reviewed the manuscript and provided language advice.

REFERENCES

1. Bluestone CD, Klein JO. *Otitis Media in Infants & Children.*, 4th ed: DC Decker Inc; 2007. pp. 41–72.
2. Gultekin E, Develioglu ON, Yener M, Ozdemir I, Kulekci M. Prevalence and risk factors for persistent otitis media with effusion in primary school children in Istanbul, Turkey. *Auris Nasus Larynx* 2010;37:145–9.
3. Kamtsiuris P, Atzpodien K, Ellert U, Schlack R, Schlaud M. Prevalence of somatic diseases in German children and adolescents. Results of the German Health Interview and Examination Survey for Children and Adolescents (KiGGS) [in German]. *Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz* 2007;50:686–700.
4. Martines F, Bentivegna D, Maira E, Sciacca V, Martines E. Risk factors for otitis media with effusion: Case-control study in Sicilian schoolchildren. *Int J Pediatr Otorhinolaryngol* 2011; 75:754–9.
5. Simpson SA, Lewis R, van der Voort J, Butler CC. Oral or topical nasal steroids for hearing loss associated with otitis media with effusion in children. *Cochrane Database Syst Rev* 2011;CD001935.
6. Venekamp RP, Burton MJ, van Dongen TM, van der Heijden GJ, van Zon A, Schilder AG. Antibiotics for otitis media with effusion in children. *Cochrane Database Syst Rev* 2016;CD009163.
7. MRC Multicentre Otitis Media Study Group. Adjuvant adenoidectomy in persistent bilateral otitis media with effusion: Hearing and revision surgery outcomes through 2 years in the TARGET randomised trial. *Clin Otolaryngol* 2012;37:107–16.

8. Kay DJ, Nelson M, Rosenfeld RM. Meta-analysis of tympanostomy tube sequelae. *Otolaryngol Head Neck Surg* 2001;124:374–80.
9. Ockermann T, Reineke U, Upile T, Ebmeyer J, Sudhoff HH. Balloon dilatation eustachian tuboplasty: A clinical study. *Laryngoscope* 2010;120:1411–6.
10. Poe DS, Silvola J, Pyykko I. Balloon dilation of the cartilaginous eustachian tube. *Otolaryngol Head Neck Surg* 2011;144:563–9.
11. Poe D, Anand V, Dean M, et al. Balloon dilation of the eustachian tube for dilatory dysfunction: A randomized controlled trial. *Laryngoscope* 2018;128:1200–6.
12. Anand V, Poe D, Dean M, et al. Balloon dilation of the eustachian tube: 12-month follow-up of the randomized controlled trial treatment group. *Otolaryngol Head Neck Surg* 2019;160:687–94.
13. Meyer TA, O'Malley EM, Schlosser RJ, et al. A randomized controlled trial of balloon dilation as a treatment for persistent eustachian tube dysfunction with 1-year follow-up. *Otol Neurotol* 2018;39:894–902.
14. Catalano PJ, Jonnalagadda S, Yu VM. Balloon catheter dilatation of Eustachian tube: A preliminary study. *Otol Neurotol* 2012;33:1549–52.
15. Dalchow CV, Loewenthal M, Kappo N, Jenckel F, Loerincz BB, Knecht R. First results of Endonasal dilatation of the Eustachian tube (EET) in patients with chronic obstructive tube dysfunction. *Eur Arch Otorhinolaryngol* 2016;273:607–13.
16. Liang M, Xiong H, Cai Y, et al. Effect of the combination of balloon Eustachian tuboplasty and tympanic paracentesis on intractable chronic otitis media with effusion. *Am J Otolaryngol* 2016;37:442–6.
17. McCoul ED, Anand VK. Eustachian tube balloon dilation surgery. *Int Forum Allergy Rhinol* 2012;2:191–8.
18. Schroder S, Reineke U, Lehmann M, Ebmeyer J, Sudhoff H. Chronic obstructive eustachian tube dysfunction in adults: Long-term results of balloon eustachian tuboplasty [in German]. *HNO* 2013;61:142–51.
19. Silvola J, Kivekas I, Poe DS. Balloon dilation of the cartilaginous portion of the eustachian tube. *Otolaryngol Head Neck Surg* 2014;151:125–30.
20. Tisch M, Maier S, Maier H. Eustachian tube dilation using the Bielefeld balloon catheter: Clinical experience with 320 interventions [in German]. *HNO* 2013;61:483–7.
21. Wanscher JH, Svane-Knudsen V. Promising results after balloon dilatation of the Eustachian tube for obstructive dysfunction. *Dan Med J* 2014;61:A4818.
22. Williams B, Taylor BA, Clifton N, Bance M. Balloon dilation of the Eustachian tube: A tympanometric outcomes analysis. *J Otolaryngol Head Neck Surg* 2016;45:13.
23. Xiong H, Liang M, Zhang Z, et al. Efficacy of balloon dilation in the treatment of symptomatic Eustachian tube dysfunction: One year follow-up study. *Am J Otolaryngol* 2016;37:99–102.
24. Jenckel F, Kappo N, Gliese A, et al. Endonasal dilatation of the Eustachian tube (EET) in children: Feasibility and the role of tubomanometry (Esteve) in outcomes measurement. *Eur Arch Otorhinolaryngol* 2016;272:3677–83.
25. Leichtle A, Hollfelder D, Wollenberg B, Bruchhage KL. Balloon eustachian tuboplasty in children. *Eur Arch Otorhinolaryngol* 2017;274:2411–9.
26. Maier S, Tisch M, Maier H. Balloon dilation of the Eustachian tube in pediatric chronic obstructive Eustachian tube dysfunction patients [in German]. *HNO* 2015;63:686–8. 690–684, 696–687.
27. Tisch M, Maier S, Hecht P, Maier H. Bilateral Eustachian tube dilation in infants: An alternative treatment for persistent middle ear functional dysfunction [in German]. *HNO* 2013;61:492–3.
28. Tisch M, Maier H, Sudhoff H. Balloon dilatation of the Eustachian tube: Clinical experience in the management of 126 children. *Acta Otorhinolaryngol Ital* 2017;37:509–12.
29. Schilder AG, Bhutta MF, Butler CC, et al. Eustachian tube dysfunction: Consensus statement on definition, types, clinical presentation and diagnosis. *Clin Otolaryngol* 2015;40:407–11.
30. Smith ME, Takwoingi Y, Deeks J, et al. Eustachian tube dysfunction: A diagnostic accuracy study and proposed diagnostic pathway. *PLoS One* 2018;13:e0206946.
31. Smith ME, Tysome JR. Tests of Eustachian tube function: A review. *Clin Otolaryngol* 2015;40:300–11.
32. 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 Syst Rev* 2010;CD001801.
33. Yoshinoka S, Naito K, Fujii N, Katada K, Takeuchi K. Age change in the Eustachian tube three-dimensionally measures by multislice CT [in Japanese]. *Nihon Jibiinkoka Gakkai Kaiho* 2008;111:523–32.
34. Hong J, Chen K, Lyu H, et al. Age-related changes in the morphological relationship between the supratubal recess and the Eustachian tube. *Auris Nasus Larynx* 2018;45:88–95.
35. Toll EC, Browning M, Shukla R, Rainsbury JW. Cartilaginous Eustachian tube length and carotid canal dehiscence in children: A radiological study. *Eur Arch Otorhinolaryngol* 2018;275:2675–82.
36. Burova OV, Bogomil'sky MR, Polunin MM, Soldatsky YL. Balloon dilatation of the cartilaginous portion of the Eustachian tube in the children presenting with relapsing exudative otitis media [in Russian]. *Vestn Otorinolaringol* 2016;81:59–60.
37. Skevas T, Dalchow CV, Euteneuer S, Sudhoff H, Lehnerdt G. Cervicofacial and mediastinal emphysema after balloon eustachian tuboplasty (BET): A retrospective multicenter analysis. *Eur Arch Otorhinolaryngol* 2018;275:81–7.
38. Luukkainen V, Kivekäs I, Hammarén-Malmi S, et al. Balloon Eustachian tuboplasty under local anesthesia: Is it feasible? *Laryngoscope* 2017;127:1021–5.
39. Alper CM, Teixeira MS, Richert BC, Swarts JD. Presentation and eustachian tube function test results in children evaluated at a specialty clinic. *Laryngoscope* 2019;129:1218–28.
40. Kivekas I, Chao WC, Faquin W, et al. Histopathology of balloon-dilation Eustachian tuboplasty. *Laryngoscope* 2015;125:436–41.
41. Malik JE, Swarts JD, Ghadiali SN. Multi-scale finite element modeling of Eustachian tube function: Influence of mucosal adhesion. *Int J Numer Method Biomed Eng* 2016;32:.
42. Mandel EM, Doyle WJ, Winther B, Alper CM. The incidence, prevalence and burden of OM in unselected children aged 1-8 years followed by weekly otoscopy through the ''common cold'' season. *Int J Pediatr Otorhinolaryngol* 2008;72:491–9.
43. McCoul ED1, Anand VK, Christos PJ. Validating the clinical assessment of eustachian tube dysfunction: The Eustachian Tube Dysfunction Questionnaire (ETDQ-7). *Laryngoscope* 2012;122:1137–41.
44. Schröder S, Lehmann M, Sauzet O, Ebmeyer J, Sudhoff H. A novel diagnostic tool for chronic obstructive eustachian tube dysfunction—the eustachian tube score. *Laryngoscope* 2015;125:703–8.
45. Mandel EM, Casselbrant ML, Richert BC, Teixeira MS, Swarts JD, Doyle WJ. Eustachian tube function in 6-year-old children with and without a history of middle ear disease. *Otolaryngol Head Neck Surg* 2016;154:502–7.
46. Alper C, Olszewska E. Assessment and management of retraction pockets. *Otolaryngol Pol* 2017;71:1–21.
47. Rosenfeld RM, Shin JJ, Schwartz SR, et al. Clinical practice guideline: Otitis media with effusion executive summary (update). *Otolaryngol Head Neck Surg* 2016;154:201–14.
48. Rovers MM, Black N, Browning GG, Maw R, Zielhuis GA, Haggard MP. Grommets in otitis media with effusion: An individual patient data meta-analysis. *Arch Dis Child* 2005;90:480–5.
49. Mandel EM, Swarts JD, Casselbrant ML, et al. Eustachian tube function as a predictor of the recurrence of middle ear effusion in children. *Laryngoscope* 2013;123:2285–90.
50. Christov F, Gluth MB. Histopathology of the mucosa of Eustachian tube orifice at the middle ear in chronic otitis media with effusion: Possible insight into tuboplasty failure. *Ann Otol Rhinol Laryngol* 2018;127:817–22.