Consensus-Based Recommendations on the Definition and Classification of Cholesteatoma

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Development of a consensus on the definitions and classification of cholesteatoma is essential for scientific community to exchange information on clinical studies and compare their outcomes.

The aim of the study is to reach a consensus among members of the European Academy of Otology and Neurotology (EAONO) regarding the definitions and classification related to cholesteatoma.

A set of statements was developed by the authors utilizing the literature on the definition and classification of cholesteatoma. A questionnaire was sent to the members of the EAONO, inviting them to state if they are in agreement with each of the statements and if not, then to provide comments or suggestions for revision. Responses were evaluated and modified using online questionnaire and survey software based on the Delphi technique, a cyclical process of gathering information, summarizing, and re-submitting the revised statements to the same target population until a consensus is reached. Target agreement among the responders was set at a minimum of 80%, and the cycle of revision and re-submission of the statements were repeated until a consensus was reached on a majority of the statements. A steering group has been established to evaluate the results of the survey and worked via the process of cognitive debriefing.

Out of 364 EAONO members, 123 responded to the first consensus cycle, 77 to the second cycle, and 53 to the third cycle. After three cycles, all statements concerning cholesteatoma definitions reached the target of 80% consensus. However, a consensus on the classification of cholesteatoma could not be achieved. The steering group excluded four statements of cholesteatoma definition and established a consensus on cholesteatoma classification.

A consensus on cholesteatoma definitions was reached among the members of the EAONO. The final revision on consensus statements for cholesteatoma definition and classification has been made via the process of cognitive debriefing of the steering group.

KEYWORDS: Cholesteatoma, congenital cholesteatoma, acquired cholesteatoma, definition

INTRODUCTION
The term “cholesteatoma” persists through generations and refers to a disease of an epidermal origin that most commonly occurs in the middle ear cleft. This term may seem to be simple; however, there are various different aspects of cholesteatoma that are defined differently to some extent in the literature. When there is no consensus on definitions, scientific community will not have a common language to exchange information. Comparing the treatment methods and outcomes cannot be accomplished without agreeing on a similar terminology and language.

There are various methods of developing consensus statements. While an expert panel may develop statements based on their expertise, this may not reflect the level and depth of understanding the scientific community at large. One of the methods to reach a consensus is defined as the Delphi technique. It is a cyclical process to send out a set of statements to a target population, synthesize the information obtained from the responses to the questionnaire, and re-send the revised questionnaires until a consensus is reached [1]. The technique is time consuming and it requires a central coordinating mechanism to manage the alteration, transmission, and summarization of questionnaire data. The nominal group technique allows the identification of the questions to be covered in a guideline by a small group of selected experts. A hybrid of two techniques may be used [2].

Authors of this study utilized the Delphi technique to reach a consensus among the EAONO members on the definitions and classification of cholesteatoma. Authors played a role as coordinators in the present consensus process.

This study was presented at the scientific meetings in Antalya 2011, Nice 2012, Nagasaki 2013 and Siena 2014.

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METHODS
An online questionnaire was used to obtain a consensus from the EAONO members [1]. Authors of this study performed a literature search utilizing PubMed, Cochrane Collaboration UpToDate, EMBASE, UK Clinical Research Network Portfolio Database (UKCRN), Research Findings Register (ReFeR), the Guidelines International Network (GIN), DynaMed, and OVID MEDLINE (from 1946 to 2013). The literature was reviewed to identify information relevant to the definitions and classification of cholesteatoma. The literature from the past 10 years was prioritized in the analysis. Selected articles published in previous years by prominent authors on the definition and/or classification of cholesteatoma were also included in the analysis. Search strategy included the following terms and keywords: “cholesteatoma,” “congenital cholesteatoma,” “acquired cholesteatoma,” “cholesteatoma definition,” and “cholesteatoma classification.”

Our consensus technique comprised the following steps: consensus statements of the survey were created based on sources of evidence, searching of database, reviewing and grading of evidence, discussions among the members of the guideline group, and audience of scientific meetings. The first cycle of invitation for participating in the survey was electronically sent to each EAONO member on Oct 30th 2013. The online survey tool Questionpro was used for this purpose (www.questionpro.com). The questionnaire comprised four parts with a total of 37 statements. There were 123 responses in the first cycle; however, everyone did not fill all the four parts of the survey. Therefore, the four parts of the questionnaire was combined in the following cycles. Each EAONO member independently and anonymously indicated whether he/she agrees with each individual statement and recorded their comments. All data generated in step 1 was analyzed. After data compilation, reproduction and revision of the consensus statement, the second version of questionnaire was prepared. After revision of the statements according to responders’ comments, the second cycle of the survey was developed, which comprised 27 statements. Comments and other feedback from EAONO members were also provided during step 2 and step 3. There were 77 responders to the second cycle of questionnaire. The third cycle of questionnaire that also had 27 revised statements was sent to the EAONO members. The participation in the third cycle of consensus survey was completed on 25th Nov, 2014. There were 53 members who responded to the 3rd survey cycle. Upon review of the responses, consensus statements were prepared based on the 80% agreement.

The consensus statements were discussed by a steering group during the following meetings: Antalya 2011, Nice 2012, Nagasaki 2013, and Siena 2014. All statements concerning the definition of cholesteatoma reached the target 80% consensus in the third consensus cycle (Table 1). Consensus on the classification of cholesteatoma did not reach the 80% target during all three cycles of the survey. Therefore, the steering group made a final revision on the consensus statements for the definition and classification of cholesteatoma via the process of cognitive debriefing.

RESULTS
Out of 364 EAONO members, 123 responded to the first consensus cycle, 77 to the second cycle and 53 responded to the third cycle. After 3 cycles, all 25 statements concerning cholesteatoma definitions reached the target of 80% consensus (Table 1). However, the steering group excluded the following four statements of cholesteatoma definition: statement #11: acquired cholesteatoma with ear drum perforation develops from an extension of keratinizing squamous epithelium of the tympanic membrane or external ear canal into the middle ear; statement #14: acquired cholesteatoma may be primary or secondary; statement #21: precholesteatoma is a stage of retraction pocket with/without invisible depth or partially visible depth, with/without bony erosion, with early signs of loss of self-cleaning ability without apparent accumulation of keratin debris; and statement #24: recurrent cholesteatoma occurs after complete surgical removal as a result of a new pathological process of the tympanic membrane or the dysfunction of the regulation of middle ear pressure. The 12th and 22nd statements were rewritten as follows: statement #12: retraction pocket can develop into acquired cholesteatoma when the retraction pocket loses its self-cleaning ability and starts the accumulation of keratin debris and statement #22: cholesteatoma recidivism includes both residual or recurrent cholesteatoma. It is essential to differentiate them. The revised set of statements on cholesteatoma definition provided by a steering group is shown on Table 2.

A consensus on the classification of cholesteatoma could not be achieved. After the third cycle of the survey, only a consensus of 75% was achieved, and the statements #26 and #27 were excluded. Therefore, the steering group developed a statement on cholesteatoma classification (Figure 1). Cholesteatoma is divided into the following types: congenital and acquired. Acquired cholesteatoma is then differentiated into attic, sinus, and tensa. All of these types are surgically treated, which may cause residual or recurrent cholesteatoma. Acquired aural cholesteatoma may extend into the middle or posterior cranial fossa. Petrous apex cholesteatoma was also included in the classification with the following five subtypes according to its relationship with the labyrinth: supralabyrinthine, infralabyrinthine, massive labyrinthine, infralabyrinthine-apical and apical.

DISCUSSION
In particular, cholesteatoma guidelines are directed to the European otolaryngologists and otologists with the overall aim to support them during decision-making process in patient care and research development. Development of the guidelines for the definitions or classification cannot be based on research evidence. Research is not conducted to compare the definitions or classifications. Instead, research is conducted after the definitions and classifications are accepted. Therefore, there was a need to utilize the published opinions and preferred definitions and classifications in the literature to start forming the statements for developing the questionnaires [2]. We performed a review of the literature for the definitions and classifications related to cholesteatoma. A systematic method of literature search was employed in the preparation of an initial draft of the statements. For the construction of statements related to the definitions and classifications, more recent publications and the publications of prominent authors that are frequently referenced were utilized.

Because of the nature of the material, the grade of the quality of evidence or strength of recommendations could not be precisely established, according to Shekelle et al. [3]. Prospective, randomized clinical studies were not available on the definitions and classification. To select the relevant literature, inclusion and exclusion crite-
1. Acquired cholesteatoma is a subcategory of chronic otitis media. 80%

2. Cholesteatoma is a mass formed by the keratinizing squamous epithelium in the middle ear and/or mastoid, subepithelial connective tissue and by the progressive accumulation of keratin debris with/without surrounding inflammatory reaction. 95%

3. Acquired cholesteatoma is characterized by clinical symptoms that are the result of growth with/without the destruction of adjacent structures:
   - ± tympanic membrane perforation
   - ± otorrhea
   - ± hearing deterioration
   and/or CT/MRI findings (soft tissue masses, focal areas of bony erosion of the middle ear, and mastoid).

4. The term "chronic otitis media with or without cholesteatoma" is appropriate. 84%

5. Cholesteatoma consists of the following: matrix (keratinizing squamous epithelium), perimatrix (varying thickness of subepithelial connective tissue), and keratin debris. 97%

6. Pathophysiology of cholesteatoma is not completely understood. 91%

7. Recurrent infections and inflammatory reaction at the subepithelial connective tissue of cholesteatoma contribute to the bone resorption in the adjacent area. 88%

8. Cholesteatoma is diagnosed by detailed otological history and by physical examination with otoscopy and/or otomicroscopy with or without imaging. 86%

9. Cholesteatoma is classified into the following two general categories: congenital and acquired. 95%

10. Acquired cholesteatoma is associated with either a perforation or a retraction pocket of the tympanic membrane or implantation from trauma or iatrogenic causes. 93%

11. Acquired cholesteatoma with ear drum perforation develops from the extension of keratinizing squamous epithelium of the tympanic membrane or external ear canal into the middle ear and/or mastoid. 90%

12. Acquired cholesteatoma with retraction pocket originates from the external layer of the tympanic membrane retraction pocket when the retraction pocket loses its ability of self-cleaning and starts accumulating keratin debris. 97%

13. Acquired cholesteatoma is not present at birth. 93%

14. Acquired cholesteatomas may be primary or secondary. 95%

15. Primary acquired cholesteatoma develops from the retraction pocket of the pars flaccida, pars tensa, or both and is a sequela of the dysfunction of the regulation of middle ear pressure. 86%

16. Secondary acquired cholesteatoma may develop secondary to the tympanic membrane perforation as a result of acute or chronic otitis media and ear trauma, or it may be iatrogenic. 93%

17. Congenital cholesteatoma is an expanding cystic mass with keratinizing squamous epithelium located medially to the intact tympanic membrane, assumed to be present at birth but usually diagnosed during infancy or in early childhood in patients with no prior history of otorrhea, perforation, or previous ear surgery. 95%

18. A history of previous bouts of otitis media or an effusion does not exclude a congenital cholesteatoma. 97%

19. Congenital cholesteatoma is usually located at the anterosuperior quadrant of the middle ear. However, it may be located at the posterosuperior quadrant or at other intracranial locations. 93%

20. The clinical presentation of congenital cholesteatoma is determined by the location and extent of the lesion. It may be characterized by the following:
   - ± abnormal otoscopic examination (white mass medial to the intact tympanic membrane)
   - ± rare conductive hearing loss when enlarged to fill the middle ear or erosion of the ossicles
   - ± pain (extremely rare)
   and/or CT/MRI findings (usually as a round soft tissue mass at the anterosuperior quadrant, rarely with bony erosion).

21. Precholesteatoma is a stage of retraction pocket with/without invisible depth or partially visible depth, with/without bony erosion, with early signs of loss of self-cleaning ability without apparent accumulation of keratin debris. 91%

22. Cholesteatoma recidivism may be either from residual or recurrent cholesteatoma. 95%

23. Residual cholesteatoma results from incomplete surgical removal of the epidermal matrix of cholesteatoma. 97%

24. Recurrent cholesteatoma occurs after complete surgical removal as a result of a new pathological process of the tympanic membrane or the dysfunction of the regulation of middle ear pressure. 91%
The definition of cholesteatoma described herein is based upon a systematic analysis of the peer-reviewed literature supplemented by a consensus from an expert panel. Initial searches executed to identify relevant guidelines concerning cholesteatoma did not reveal any in the popular databases. There was only one published guideline document proposed by an expert panel of the French Society of Otolaryngology Head and Neck Surgery in 2010 titled “Imaging of cholesteatoma: clinical practice guidelines.”

A number of limitations affected the process of achieving a consensus on the definitions regarding cholesteatoma among the members of the EAONO. One limitation was the number of responders and the other was the variability in opinions among the responders.
There was a relatively low number of responders in each cycle. This is not unusual for these types of questionnaires that targeted the members of a society. A recent study to reach a consensus among the EAONO members regarding retraction pockets had fewer number of responders [6, 7]. Potential reasons for the low and decreasing number of responders may include the following: lack of time to spare for responding to the questionnaire because of professional, personal or family commitments; fatigue from a large number of surveys that are sent by various societies; lack of enthusiasm regarding the development of a consensus on the definitions of cholesteatoma; and the proportion of members having low-academic interests. It is also possible that the database of the e-mail addresses of the members that the society has is not completely accurate or the e-mails inviting the members to respond is blocked by spam filters.

Table 2. Statements on cholesteatoma definition established by the steering group via the process of cognitive debriefing

- **Statement**

  1. Acquired cholesteatoma is a subcategory of chronic otitis media.
  2. Cholesteatoma is a mass formed by the keratinizing squamous epithelium in the middle ear and/or mastoid, subepithelial connective tissue and by the progressive accumulation of keratin debris with/without surrounding inflammatory reaction.
  3. Acquired cholesteatoma is characterized by clinical symptoms that are the result of growth with/without the destruction of adjacent structures:
     - ± tympanic membrane perforation
     - ± otorrhea
     - ± hearing deterioration
     and/or CT/MRI findings (soft tissue masses, focal areas of bony erosion of the middle ear, and mastoid).
  4. The term “chronic otitis media with or without cholesteatoma” is appropriate.
  5. Cholesteatoma consists of the following: matrix (keratinizing squamous epithelium), perimatrix (varying thickness of subepithelial connective tissue), and keratin debris.
  6. Pathophysiology of cholesteatoma is not completely understood.
  7. Recurrent infections and inflammatory reaction at the subepithelial connective tissue of cholesteatoma contribute to the bone resorption in the adjacent area.
  8. Cholesteatoma is diagnosed by detailed otological history and by physical examination with otoscopy and/or otomicroscopy with or without imaging.
  9. Cholesteatoma is classified into the following two general categories: congenital and acquired.
  10. Acquired cholesteatoma is associated with either a perforation or a retraction pocket of the tympanic membrane or implantation from trauma or iatrogenic causes.
  11. Retraction pocket can develop into acquired cholesteatoma when the retraction pocket loses its ability of self-cleaning and starts accumulating keratin debris.
  12. Acquired cholesteatoma is not present at birth.
  13. Acquired cholesteatoma might develop from the retraction pocket of the pars flaccida, pars tensa, or both and could be a sequela of the dysfunction of the regulation of middle ear pressure.
  14. Acquired cholesteatoma may also develops secondary to the tympanic membrane perforation as a result of acute or chronic otitis media and ear trauma, or it may be iatrogenic.
  15. Congenital cholesteatoma is an expanding cystic mass with keratinizing squamous epithelium located medially to the intact tympanic membrane, assumed to be present at birth but usually diagnosed during infancy or in early childhood in patients with no prior history of otorrhea, perforation, or previous ear surgery.
  16. A history of previous bouts of otitis media or an effusion does not exclude a congenital cholesteatoma.
  17. Congenital cholesteatoma is usually located at the anterosuperior quadrant of the middle ear. However, it may be located at other locations.
  18. The clinical presentation of congenital cholesteatoma is determined by the location and extent of the lesion. It may be characterized by the following:
     - ± abnormal otoscopic examination (white mass medial to the intact tympanic membrane)
     - ± rare conductive hearing loss when enlarged to fill the middle ear or erosion of the ossicles
     - ± pain (extremely rare)
     and/or CT/MRI findings (usually as a round soft tissue mass at the anterosuperior quadrant, rarely with bony erosion).
  19. Cholesteatoma recidivism includes both residual or recurrent cholesteatoma. It is essential to differentiate them.
  21. Recurrent cholesteatoma originates from the reformation of retraction pocket after complete surgical removal of the previous cholesteatoma.
  22. Following is classification of cholesteatoma proposed by the authors based on systemic search of evidence: Cholesteatoma is classified as congenital or acquired. Although not mutually exclusive, acquired cholesteatoma is subclassified as attic, sinus, or pars tensa cholesteatoma. Post-surgical cholesteatoma may be residual or recurrent, although not mutually exclusive.

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The other limitation in achieving a consensus among the responders may be related to the discrepancy among responders’ education, different schools of training, personal opinions based on individual experience and potentially different and even possibly conflicting textbooks that each member had utilized in their training or after the training during their professional practice, the regional differences in the degree of access to the newly published books and articles and limited attendance of these members to conferences on the topic.

On the other hand, despite these limitations, authors believe that the guidelines group has achieved the goal of developing a consensus among a considerable number of active members of the EAONO.

CONCLUSIONS

A consensus on the definitions but not on the classification of cholesteatoma is reached among the members of the EAONO. A revision of the consensus statements for cholesteatoma definition and classification has been made via the process of cognitive debriefing of the steering group.

Peer-review: Externally peer-reviewed.

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Author contributions: E.O.: Created a survey according literature review, evaluation of the surveys during three cycles. N.Ö.: Participation in three cycles of survey, evaluation of survey results, a consultant during the whole study.

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REFERENCES
5. Horn KL. Intracranial extension of acquired aural cholesteatoma. Laryngoscope 2000; 110: 761-72. [CrossRef]