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The rate and pattern of otic epithelial migration: systematic review

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Abstract

Background. Epithelial migration has been associated with the self-cleansing mechanism of the ear. The rate and pattern of epithelial migration in healthy and pathological ears are reviewed.
Methods. Two authors independently screened articles over one month using the following search terms: epithelial migration, epithelial, tympanic membrane, external auditory canal and mastoidectomy cavity.
Results. Ten studies were included. The fastest rate of epithelial migration was observed in the external auditory canal, with a mean of 144.75 µm per day, whereas the slowest epithelial migration was seen in post-mastoidectomy cavities, with a rate of 20 µm per day. Epithelial migration was present in both studies involving post-mastoidectomy cavities.
Conclusion. Epithelial migration is faster in healthy tympanic membrane than in pathological tympanic membrane. The rate of epithelial migration in the external auditory canal was higher in the pathological group than in the healthy group. Epithelial migration is present in post-mastoidectomy cavities.

Review Article

Dr J Saniasiaya takes responsibility for the integrity of the content of the paper

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Introduction

In 1877,[1] Burnett unravelled the mystery behind epithelial migration of the human eardrum, which was subsequently confirmed by Buck in 1880[2] and Bezold in 1908.[3] Epithelial migration explains the self-cleansing mechanism of the external meatus. Stinson, in 1936, elucidated the epithelial migration of the human tympanic membrane using ink dots.[4] This was followed in 1964 by Alberti, who successfully analysed the pattern and rates of epithelial migration of the human tympanic membrane.[5] Alberti found that the average rate of epithelial migration is 0.07 mm per day, with the umbo being the centre of migration.[5]

Nonetheless, variation in the rate and pattern of epithelial migration exists in various aural conditions. This systematic review aimed to cover the literature available on the rate and pattern of epithelial migration in the healthy and pathological human tympanic membrane and external auditory canal, and to identify the presence of epithelial migration in the post-mastoidectomy cavity.

Methods

A literature search for the period from January 1980 to November 2020 was conducted by searching for English-language articles in the electronic databases PubMed, Scopus (Elsevier, Amsterdam, the Netherlands), Embase (Elsevier) and Google Scholar. Additional relevant articles were obtained by reviewing the references of the screened articles. The following key words were used either individually or in combination to aid in retrieving the articles: epithelium, epithelial migration, tympanic membrane and external auditory canal. Complete details of the search strategy are shown in Figure 1. Duplicate studies were excluded using EndNote™ X10 reference management software.

The search was conducted over a one-month period (November 2020) in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses ('PRISMA') guidelines[6] and the *Cochrane Handbook for Systematic Reviews of Interventions* when appropriate.[7] Original clinical research articles were selected based on our objective and selection criteria. The main eligibility criteria were articles, written in English, which aimed to determine the rate and pattern of human otic epithelial migration. Another inclusion criterion was investigation of the rate and pattern of epithelial migration in humans of all age groups. There were no exclusion criteria concerning study design or duration. Studies that did not report on the rate and pattern of epithelial migration, and studies on the rate and pattern of epithelial migration conducted in animals, were excluded.

Two authors (JS and NP) independently screened the full-text version of each publication, extracted data, and excluded those papers whose content was judged not to be relevant for the purpose of this review. The selected articles were appraised using the Quality Assessment Tool for Case Series Studies from the National Institutes of Health National

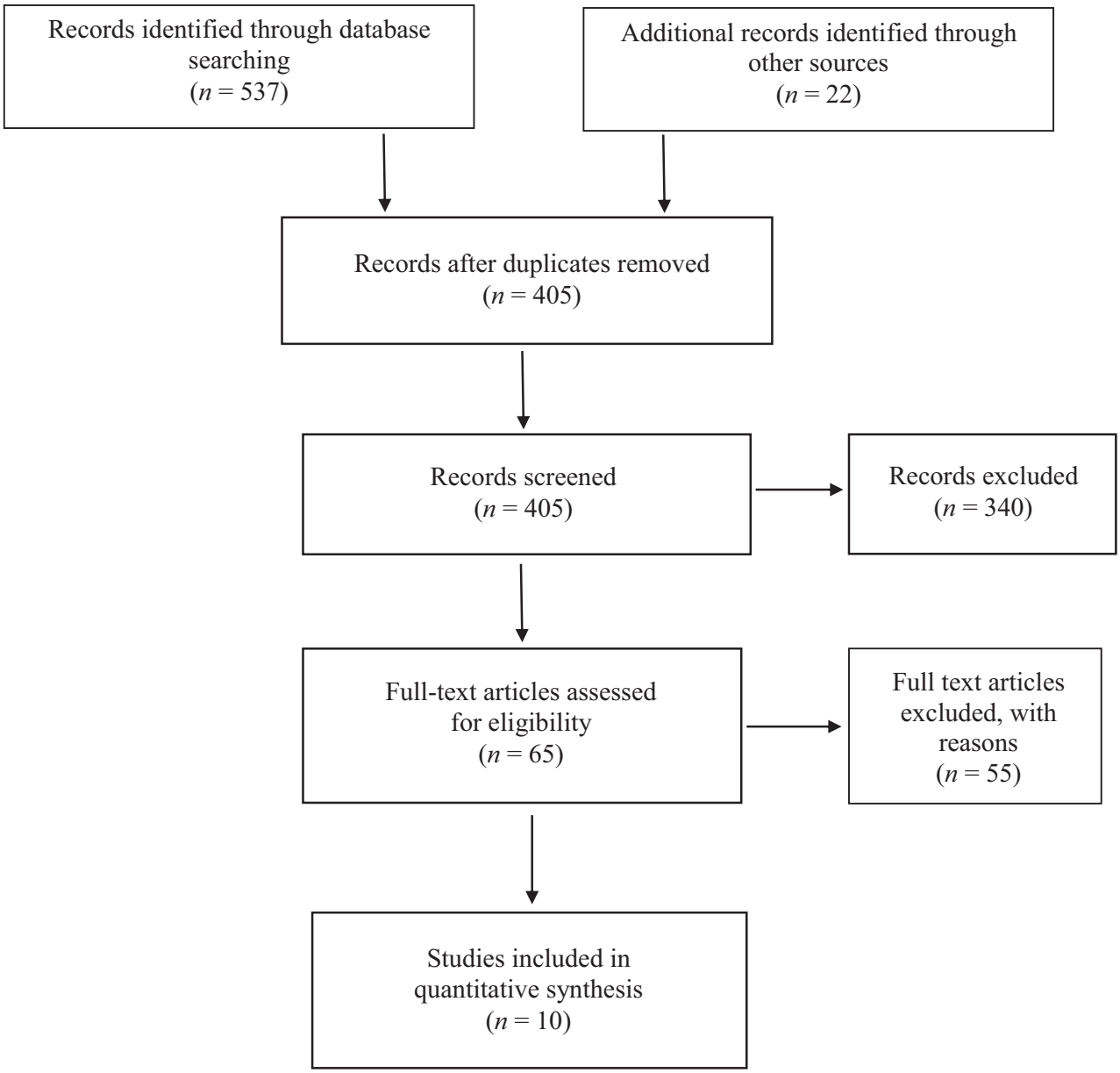

Fig. 1. Flow diagram of Preferred Reporting Items for Systematic Reviews and Meta-Analyses ('PRISMA') for the systematic literature search.

Heart, Lung, and Blood Institute guideline.[8] In order to alleviate the risk of bias, papers of all qualities were included in this systematic review.

Results

A total of 10 studies published between 1983 and 2015 that fulfilled the selection criteria were included in the review.[9–18] All the studies were considered to have class III evidence: six non-randomised prospective case–control studies and four case series. The studies included in this systematic review are summarised in Table 1. A meta-analysis was considered inappropriate because of heterogeneity issues.

The total number of patients in each study ranged from 12 to 81. A total of 415 ears were included in this review, of which 257 were healthy ears and 158 were pathological ears. Amongst the included pathological ears, the ear conditions encompassed various ear pathologies, including post-mastoidectomies, post-myringoplasty, atelectatic tympanic membrane, keratosis obturans, post-irradiated ear, atrophy, clouding and calcification. One study investigated the rate and pattern of epithelial migration amongst children.[9] Six studies analysed epithelial migration of the tympanic membrane,[9,11–14,16] two studies included epithelial migration of the tympanic membrane and external auditory canal,[10,18] two studies analysed epithelial migration of post-mastoidectomy cavities,[13,15] and only one study included epithelial migration of the external auditory canal.[17] In one study, the control was the healthy contralateral ear.[16]

The fastest epithelial migration rate was observed in the external auditory canal, with a mean of 144.75 μm per day amongst irradiated nasopharyngeal carcinoma patients,[18] whereas the slowest epithelial migration rate was seen in the post-mastoidectomy cavity, at 20 μm per day (Table 2).[13]

The differences in rate and pattern of epithelial migration in healthy and pathological ears vary between the tympanic membrane and the external auditory canal. The rate of epithelial migration was determined by calculating the mean of the total sum of epithelial migration in each group, such as healthy

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Table 1. Summary of included studies

Study (year)	Study type	Total patients (gender) (*n*)	Age range (mean) (years)	Total ears (*n*)	Part of ear studied	Total healthy ears (*n*)	Total pathological ears (*n*)
O'Donoghue[9] (1983)	Case series	31 (14M, 17F)	3–12 (7.5)	61	TM	61	Nil
Makino & Amatsu[10] (1986)	Prospective case–control	N/A	N/A	56	TM, EAC	24	15 TM, 17 EAC
Michaels & Soucek[11] (1990)	Case series	12 (4M, 8F)	21–63	24	TM	24	Nil
Moriarty *et al.*[12] (1991)	Case series	15	N/A	15	TM	15	Nil
Bonding & Charabi[13] (1994)	Prospective case–control	N/A	Healthy = 22–51; pathological = 19–81	32	TM, mastoid cavity	15	17
Deong *et al.*[14] (2006)	Prospective case–control	23 (6M, 17F)	16–62	46	TM	23	23
Ong *et al.*[15] (2007)	Case series	18 (10M, 8F)	17–66	18	Mastoid cavity	18	Nil
Tang *et al.*[16] (2009)	Prospective case–control	80 (21M, 19F)	11–71	80	TM	40	40
Revadi *et al.*[17] (2011)	Prospective case–control	17	20–32	17	EAC	15	2
Santhi *et al.*[18] (2015)	Prospective case–control	81	Healthy = 37–70; pathological = 37–74	81	TM, EAC	55	20

M = male; F = female; TM = tympanic membrane; EAC = external auditory canal; N/A = data not available

Table 2. Summary of epithelial migration rate findings in included studies

		Epithelial migration rate (μm/day)	
Study (year)	Pathology type	Healthy ear	Pathological ear
O'Donoghue[9] (1983)	Healthy ear	131	Nil
Makino & Amatsu[10] (1986)	TM: atrophy, clouding, calcification EAC: cholesteatoma	TM: 140 EAC: 142	TM: 105 EAC: 112
Michaels & Soucek[11] (1990)	Healthy ear	90	N/A
Moriarty *et al.*[12] (1991)	Healthy ear (contralateral history of cholesteatoma)	40–110	N/A
Bonding & Charabi[13] (1994)	History of mastoid surgery (canal wall down)	100	20–450
Deong *et al.*[14] (2006)	Post-myringoplasty TM	91.7	93.4
Ong *et al.*[15] (2007)	Post-mastoidectomy cavity	Nil	100
Tang *et al.*[16] (2009)	Atelectatic TM	64.7	62.6
Revadi *et al.*[17] (2011)	Keratosis obturans	94.33	114
Santhi *et al.*[18] (2015)	Post-radiation TM + EAC	TM: 64.68 EAC: 94.33	TM: 51.35 EAC: 144.75

TM = tympanic membrane; EAC = external auditory canal; N/A = data not available

ears and pathological ears. The mean epithelial migration rate in a healthy tympanic membrane is 94.51 μm per day, whereas the mean epithelial migration rate in the healthy external auditory canal is 110.22 μm per day. The most common pattern of epithelial migration is the posterior-superior pattern, which was found in the healthy tympanic membrane (66.7 per cent), whereas the other two patterns of epithelial migration reported were anterior-inferior[10] and superior (Table 3).[12] For the external auditory canal, the healthy ear canal group revealed a linear pattern of epithelial migration in both studies.[17,18]

For the pathological ears, the mean rate of epithelial migration in the pathological tympanic membrane was 78.09 μm per day, and the mean epithelial migration in the pathological external auditory canal was 123.6 μm per day. Epithelial migration was present in both studies involving post-mastoidectomy cavities.[13,15] In parallel, amongst the pathological tympanic membranes, the most common pattern of epithelial migration was the posterior-superior pattern (50 per cent), followed by the posterior-inferior[18] and inferior patterns.[10] For the external auditory canal, the pathological group showed linear,[17] superior, linear and whorled,[18] and inferior[10] patterns of epithelial migration. Interestingly, in the post-mastoidectomy group, the patterns of epithelial migration were inferior-lateral[15] and centrifugal.[13]

Discussion

The skin of the tympanic membrane and external auditory canal, unlike the other parts of the surface of the body, which undergo constant frictional force, does not undergo desquamation. Epithelial migration is a unique 'modus operandi' that functions to prevent the excessive stratum corneum from piling up within the tympanic membrane and external auditory canal. Epithelial migration is the ability of surface

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Table 3. Summary of epithelial migration direction findings in included studies

Study (year)	Pathology type	Epithelial migration direction	
		Healthy ear	Pathological ear
O'Donoghue[9] (1983)	Healthy ear	Posterior-superior (72%)	Nil
Makino & Amatsu[10] (1986)	TM: atrophy, clouding, calcification EAC: cholesteatoma	Anterior-inferior	TM: inferior EAC: inferior
Michaels & Soucek[11] (1990)	Healthy ear	Posterior-superior	N/A
Moriarty *et al.*[12] (1991)	Healthy ear (contralateral history of cholesteatoma)	Superiorly	N/A
Bonding & Charabi[13] (1994)	History of mastoid surgery (canal wall down)	Centrifugal	Centrifugal
Deong *et al.*[14] (2006)	Post-myringoplasty TM	Posterior-superior	Posterior-superior
Ong *et al.*[15] (2007)	Post-mastoidectomy cavity	Nil	Inferior-lateral
Tang *et al.*[16] (2009)	Atelectatic TM	Posterior-superior	Posterior-superior
Revadi *et al.*[17] (2011)	Keratosis obturans	Linear	Linear
Santhi *et al.*[18] (2015)	Post-radiation TM + EAC	Posterior-superior	Posterior-superior

TM = tympanic membrane; EAC = external auditory canal; N/A = data not available

layers of the tympanic membrane and external auditory canal epithelium to migrate. Apart from the human tympanic membrane, myriad studies on animals have revealed that animals possess a similar unique property of epithelial migration. The distinctive characteristic of epithelial migration is attributed to the distribution of F-actin microfilament bundles in the basal layer of the tympanic membrane. Yet, the extraordinary migratory properties of the tympanic membrane and auditory canal were disregarded until skin grafting of the tympanic membrane and mastoid cavities gained popularity. The initial utilisation of non-migratory post-auricular skin led to a serious consequence: the continual accumulation of keratin and debris, causing iatrogenic cholesteatoma.

Aural epithelial migration can be characterised on the basis of the two modes of cellular mechanism: passive and active. During the passive mechanism, cells are passively displaced following the pressure elicited by the adjacent cells, which results from the generation of new cells by mitosis. The active mechanism is based on the intrinsic locomotor capability possessed by individual cells via the action of the contractile proteins. Epithelial migration of the tympanic membrane has been postulated to be secondary to the passive mechanism,[19] although some authors have proposed epithelial migration to occur secondary to the active mechanism.[20] On the other hand, epithelial migration in the external auditory canal has been associated with an active mechanism whereby migration takes place in the deeper layers of the epithelium.[19]

It is noteworthy that aural epithelial migration can be affected by myriad pathological conditions, such as otitis externa, trauma, cholesteatoma and keratosis obturans, as well as the ageing process. Inflammatory processes may affect the distinct arrangement of F-actin microfilament bundles residing in the basal layer, resulting in disrupted or delayed epithelial migration. Similarly, disruption of the blood supply resulting from various pathological conditions affects the rate of epithelial migration.[10]

The original study on epithelial migration of the tympanic membrane was pioneered in 1936 by Stinson, who undertook an incidental observation of the migration of a piece of reed, which was initially embedded in the tympanic membrane and slowly carried out from the eardrum to the posterior auditory canal and finally to the exterior.[4] Stinson, armed with this revelation, had a breakthrough by observing the migration of spots of Indian ink in various tympanic membranes. Five laws of 'epithelial escalation' were expounded: (1) the epidermis migrates on its natural plane from the anterior to the posterior margin of the membrane and along the canal wall to the exterior; (2) the epidermis over the pars flaccida fans out over the canal wall; (3) the epithelium over the short process proliferates in whorls to the superior part of the canal; (4) the progress is most rapid in the inferior posterior quadrant; and (5) the epithelium does not proliferate from the canal to the drumhead. Magnoni postulated that the epithelial migration movement is radial and disagreed with Stinson's finding.[21] Similarly, Magnoni discovered that the epithelium does not migrate from the auditory canal to the tympanic membrane.[21]

Litton estimated the rate of epithelial migration to be 0.05 mm per day and stated that a dot placed at the umbo migrates radially outward.[22] Alberti, on the other hand, estimated a rate of 0.07 mm per day and observed centrifugal migration in a centrally perforated tympanic membrane.[5] In parallel to this, both Litton and Alberti found a difference in the rate of epithelial migration, and the rate was proportional to the thickness of the epithelial layer. Additionally, the rate of epithelial migration was reported to reduce with increasing distance from the umbo.[14] Alberti discovered the umbo to be the centre of epithelial migration based on a study performed by placing ink dots on the tympanic membrane.[5] It is noteworthy that two migratory patterns were described: a radial pattern (80 per cent) and a straight pattern (20 per cent).[5]

Interestingly, Link, in 1952, found that ink dots placed on the tympanic membrane move in the same direction as the vascular channels,[23] and postulated that the lymph movement propelled the epithelium outward. This was followed by a study by Makino and Amatsu, who investigated epithelial migration on the tympanic membrane and found the blood vessels that supply the epidermal layer of the tympanic membrane to be responsible for its epithelial migration as well as its metabolism.[10]

From this review, we found that the mean rate of epithelial migration in the healthy tympanic membrane is 94.51 µm per day, whereas in the pathological tympanic membrane the rate of epithelial migration reduces to 78.09 µm per day. The slower rate of epithelial migration in the pathological tympanic membrane can be explained by poor blood supply, which leads to slower metabolism and a concurrently sluggish epithelial migration rate.[10]

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As for the epithelial migration rate in the external auditory canal, a mean rate of 110.22 µm per day was observed in the healthy ear canal, and a faster rate was seen in the pathological ear canal, with a mean rate of 123.6 µm per day. Interestingly, most patients from the pathological external auditory canal group had received prior radiotherapy; high-dose radiation led to a robust differential squamous cell epithelial growth, thus increasing the rate of epithelial migration in the external auditory canal.[18] The rate of epithelial migration was noted to be reduced with advancing age.[14] A faster rate of epithelial migration was observed amongst children,[9] which could be secondary to the vast blood supply of the tympanic membrane.

Numerous patterns of epithelial migration have been described by various authors. Classically, the anterior-inferior direction of epithelial migration was associated with adults[5] and the posterior-superior direction with children.[9] The most common pattern of epithelial migration in this review is the posterior-superior direction, found in the healthy tympanic membrane (66.7 per cent), followed by the anterior-inferior[10] and superior patterns of epithelial migration.[12] As for the pattern of epithelial migration direction in the pathological tympanic membrane, the posterior-superior direction is the most common pattern (50 per cent), followed by the posterior-inferior (25 per cent)[18] and inferior (25 per cent) patterns.[10] The linear pattern was the most common pattern observed in the healthy external auditory canal (66.7 per cent).[17,18] In the pathological external auditory canal, despite the linear direction being seen in both studies,[17,18] Santhi *et al.*[18] reported superior and whorled patterns, in addition to the linear direction, in their group of patients,[18] and an inferior direction was noted by Makino and Amatsu.[10] In the post-mastoidectomy group, the patterns of epithelial migration in the cavity were inferior-lateral[15] and centrifugal.[13]

The fastest epithelial migration was observed in the external auditory canal, with a mean of 144.75 µm per day amongst irradiated nasopharyngeal carcinoma patients.[18] A post-radiation increase in squamous cell differentiation in the external auditory canal contributed to an increased rate of epithelial migration amongst these patients. Surprisingly, the rate of epithelial migration in the tympanic membrane of the post-radiation group was found to be low, which was suggested to be secondary to poor blood supply in the post-radiated tympanic membrane.[18] We postulate that the varying rate of epithelial migration between external auditory canal and tympanic membrane could be caused by a variation of radiation-induced toxicity between the tympanic membrane and the external auditory canal.

In our review, the slowest epithelial migration rate was seen in the post-mastoidectomy cavity, at 20 µm per day.[13] However, Bonding and Charabi highlighted that large inter-subject variations were found in their study.[13] The self-cleansing property is especially pertinent in the post-mastoidectomy group. The pattern of epithelial migration in the post-mastoidectomy cavities is not uniform because of the randomly organised blood vessels of the epithelial lining. Ong *et al.* found an epithelial migration rate of 0.10 mm per day in their post-mastoidectomy cavities, which is faster than the average migration rate in healthy ears.[15] Accumulation of wax could be attributed to a varying epithelial migration rate and patterns in other parts of cavities that do not move outward. Additionally, the pattern and rate of epithelial migration in post-mastoidectomy cavities will differ between cavities obliterated with a muscle flap and those without obliteration. Bonding and Charabi concluded that the accumulation of debris is related to the surgical technique used and the contour of the cavity.[13] Mastoidectomy cavities habitually regain their self-cleansing property once epithelial migration is re-established. As for the size of the cavity, Bonding and Charabi reported that normal epithelial migration is established regardless of the cavity size.[13]

Failure or abnormality of epithelial migration has been associated with numerous aural pathologies, including otitis externa, keratosis obturans, cholesteatomas and retraction pockets. There are various explanations for the variation in epithelial migration rates in different conditions. In keratosis obturans, chronic inflammation within the subepithelial tissue causes hyperplasia of the epithelium, resulting in the build-up of squamous material in the auditory canal, hindering the epithelial migration.[24] Parallel to that, a deficiency in the unidentified enzyme responsible for the separation of the superficial layers of keratin and damage to the migratory basal epithelial cells has been linked to a delay in the rate of epithelial migration. The ageing epithelium has been postulated to lose its ability to migrate. Additionally, hypoxic conditions resulting from the poor blood supply to meatal skin also leads to a slower epithelial migration rate.

Meanwhile, an atelectatic retraction pocket of the tympanic membrane has been regarded as unstable because of its dynamic epithelial migration characteristics.[16] Interestingly, retraction of the tympanic membrane fluctuates during sleep over weeks and months. Nonetheless, Tang *et al.* found no difference in epithelial migration rate between the atelectatic ear and contralateral healthy tympanic membrane in the same patient.[16]

Limitations

Several notable limitations are present in this systematic review. Based on the search strategy, this systematic review includes some studies published years ago. Most of the included studies comprise small samples, the data analysed may not represent the true numbers, and generalisation of findings should be attempted cautiously. All the analyses demonstrated a substantial degree of heterogeneity. Only one study included children, who may not be representative. Thus, it was challenging to reach the conclusion provided. Hence, the results should be interpreted cautiously, and further comparative studies are warranted. Future studies should include a larger population hailing from various socio-demographic groups, and the pathology as well as the long-term ramifications of epithelial migration need to be assessed.

Conclusion

Epithelial migration is present in both healthy and pathological groups. The rate of epithelial migration is higher in the healthy tympanic membrane than in the pathological group. Epithelial migration is present in post-mastoidectomy cavities.

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