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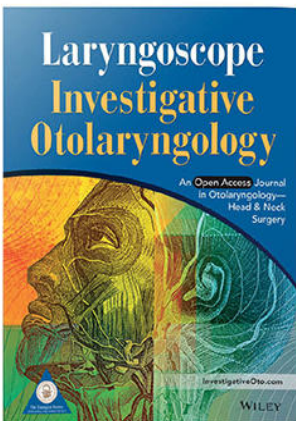


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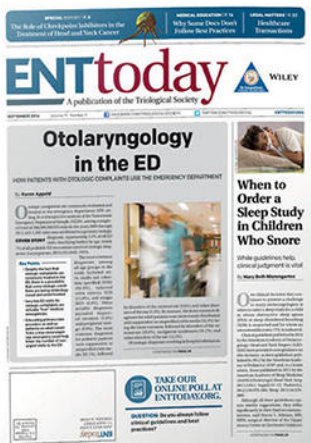
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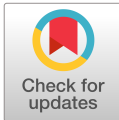
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WILEY



# A Systematic Review of Nonautologous Graft Materials Used in Human Tympanoplasty

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**Objectives:** Nonautologous graft materials may solve several dilemmas in tympanoplasty by obviating the need for graft harvest, facilitating consistent wound healing, and permitting graft placement in the clinical setting. Prior studies of nonautologous grafts in humans have shown variable outcomes. In this systematic review, we aim to 1) summarize clinical outcomes and 2) discuss limitations in the literature regarding nonautologous grafts for tympanoplasty in humans.

**Methods:** A literature review was performed using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations. The study size, etiology and duration of perforation, type of nonautologous graft, and postoperative closure rate were assessed.

**Results:** The PRISMA approach yielded 61 articles, including 3,247 ears that met inclusion criteria. Studies evaluated nonautologous grafts including paper patch, gelatin sponge, growth factors, porcine small-intestinal submucosa, among others. Traumatic perforations (62.3%) were most commonly studied, whereas postinfectious perforations (31.9%) and other etiologies (5.8%) comprised a minority of cases. Acute perforations of <8 weeks duration constituted just over half of all treated ears. Overall closure rate was 82.1%, with significantly higher closure rates in acute (89.9%) versus chronic perforations (64.9%,  $P < .01$ ), regardless of material. A median postoperative air-bone gap of 5.6 dB was found in the 23% of studies reporting this metric.

**Conclusions:** The majority of publications reviewing nonautologous materials in tympanoplasty evaluate acute or traumatic perforations, and few rigorously report hearing outcomes. Given available data, porcine submucosa and basic fibroblast growth factor may hold promise for chronic perforation closure. Future studies should report closure rates and hearing outcomes in perforations >8 weeks duration.

**Key Words:** Tympanoplasty, synthetic graft, tympanic membrane.

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## INTRODUCTION

Modern methods of tympanic membrane (TM) reconstruction utilize techniques that are relatively unchanged from those first described by Sheehy over 50 years ago.<sup>1,2</sup> In transcanal or postauricular tympanoplasty, autologous grafts, such as vein, fascia, perichondrium, or cartilage, may be utilized to repair the damaged TM.

Unfortunately, tympanoplasty with autologous grafts has variable outcomes, with several recent large-scale case series reporting failure rates of up to 20%.<sup>3–5</sup> Hearing outcomes after standard tympanoplasty are also variable. In four large reviews, persistent conductive hearing loss >10 dB was found in 56% to 60% of postoperative patients.<sup>4–7</sup> Although poor outcomes may be due to surgical technique, ongoing chronic otitis media, persistent eustachian tube dysfunction, and/or ossicular abnormalities, it is important to consider how graft materials contribute to healing and hearing outcomes.

Autologous materials may not be ideal for TM reconstruction for several reasons. First, grafts require an incisional harvest from the patient and may not be available in revision surgery. Second, the structural properties of autologous materials: mass and thickness, may not be optimized for sound conduction or prevention of TM retraction. Third, some autologous graft materials have been found to possess structural defects that may give rise to weakness, retraction, and reperforation. For example, the crater-like defects have been found in the collagen matrix of temporalis fascia grafts on electron microscopy.<sup>1</sup> Finally, healing after tympanoplasty with autologous grafts may be prolonged. As such, many groups have assessed nonautologous graft alternatives for

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Additional supporting information may be found in the online version of this article.

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TM reconstruction. A commercially available option may eliminate current problems with autologous grafts and play an increasingly important role in the era of trans-canal endoscopic ear surgery.

A variety of nonautologous grafts have been previously evaluated in human tympanoplasty; however, no single graft material has radically changed the otologist's preference for autologous materials. This reluctance to change surgical practice may be due to variability in the size, design, and quality of published research studies. Human trials evaluating novel graft materials in tympanoplasty are often retrospective, frequently have small sample sizes, and do not always contain standardized outcome measures. Comparison across studies can be challenging due to heterogeneous patient populations and inclusion of acute perforations, which may close spontaneously without intervention. Finally, outcomes from investigations of nonautologous grafts for acute TM perforations may not translate to use in chronic perforations.

To date, a systematic review of outcomes using nonautologous graft materials in human tympanoplasty has not been undertaken. Pooled data on relevant surgical outcomes, including rates of perforation closure and hearing improvement, should allow a more comprehensive analysis of the impact of graft material on tympanoplasty success. Such a study will identify knowledge gaps to direct future clinical trials. In this systematic review, we aimed to summarize clinical outcomes and discuss limitations in the literature regarding the use of nonautologous grafts for human tympanoplasty. For this review, our definition of nonautologous excludes any graft material using nonrecombinant human components, such as cadaveric material, homograft TM, and human fibrinogen-based collagen fleece. Herein, we review pooled nonautologous graft material tympanoplasty outcomes across studies and locate knowledge gaps for future research.

## METHODS

### *Literature Review*

A comprehensive review of the literature was performed to identify articles related to the application of nonautologous grafts for TM perforation repair in human subjects. The Preferred Reporting Items for Systemic Reviews and Meta-Analyses (PRISMA) methodology was utilized.<sup>8</sup> Specifics of the search strategy and terminology can be found in Supporting Information, Appendix 1. Inclusion criteria for published studies were: 1) use of nonautologous graft material for tympanoplasty, 2) inclusion of human subjects, 3) reporting of perforation closure rate, and 4) a sample size of at least  $n = 5$ . Exclusion criteria were: 1) absence of clear methodology, 2) studies evaluating tympanostomy tube removal with simultaneous myringoplasty, 3) studies evaluating topical medications without scaffold, 4) procedures that included an ossiculoplasty, 5) non-peer-reviewed articles, 6) case reports and 7) non-English language full text. No articles were excluded on the basis of study design or quality alone.

### *Data Analysis*

Perforation closure rate (percent tympanoplasty success) was defined as the number of ears with complete closure of TM perforation at the time of study completion divided by the total

number of ears treated. These data were available for every study and constituted the raw data for pooled analysis. When pooling data, closure rates from each study were weighted by the size of the study's treatment group, thereby allowing a normalized analysis of overall closure rates for each graft material and a comparison of the effect preoperative characteristics have on tympanoplasty success.

Patient demographic information, number of ears treated, and perforation etiology were reported, when available. The initial TM perforation size was graded using the system described by Saliba<sup>9</sup>: (grade 1:  $\leq 25\%$ ; grade 2:  $26\% - 50\%$ ; grade 3:  $51\% - 75\%$ /subtotal; grade 4: total drum loss), when sufficient information was available. Otherwise, TM perforation size was reported according to the original authors' description. To standardize the nomenclature used across studies, duration of TM perforation was designated as acute ( $\leq 8$  weeks duration prior to surgery) and chronic ( $> 8$  weeks duration prior to surgery) for each study. When insufficient information was available for this standardized designation, the duration reported by the original study was used instead. The duration of TM healing was reported when available and is defined as length of time between intervention and documented closure of the perforation. The number of procedures/attempts for perforation closure was also listed. Hearing improvement (postoperative minus preoperative) using reported pure-tone averages for air conduction and/or air-bone gap (ABG) was noted for patients who underwent pre- and postoperative audiometry. Comparisons between groups (e.g., closure rate in acute vs. chronic perforations) were performed using  $\chi^2$  analyses. Unpaired  $t$  tests were used for comparison of healing times and hearing outcomes, when data were available. Statistical significance for both tests was set at  $P < .05$ . A meta-analysis could not be performed due to the marked heterogeneity and quality disparities among the studies.

### *Level of Evidence/Quality Assessment*

All articles were subject to quality assessment using two rating systems. First, articles were categorized into four levels based on the Oxford Center for Evidence-Based Medicine (EBM) levels of evidence guidelines<sup>10</sup>: level 1: systematic reviews of randomized trials, level 2: high-quality randomized or observational trials that describe a significant effect, level 3: individual nonrandomized controlled cohort studies, and level 4: case-series, case-control studies, or poor-quality prognostic cohort studies. Second, the quality of nonrandomized trials was assessed using the Methodological Index for Non-Randomized Studies (MINORS) rating system.<sup>11</sup>

## RESULTS

### *Study Selection and Quality Assessment*

A literature search performed on May 30, 2020 revealed 690 articles published between January 1955 and May 2020. Review of reference lists of the publications provided eight additional studies, for a total of 698 articles. Of these, 637 were eliminated based on exclusion criteria. Leaving 61 publications for our systematic review of nonautologous graft material for TM repair and regeneration (Fig. 1). A total of 10 different types of graft material were identified: paper patch, silk fibroin patch, Steri-Strip tape, gelatin (Gelfoam/Gelfilm), hyaluronic acid (EpiFilm/EpiDisc), growth factors (including basic fibroblast growth factor and epidermal growth factor), bacterial cellulose, protease-solubilized collagen (atelocollagen), small-intestinal submucosa (SIS), and

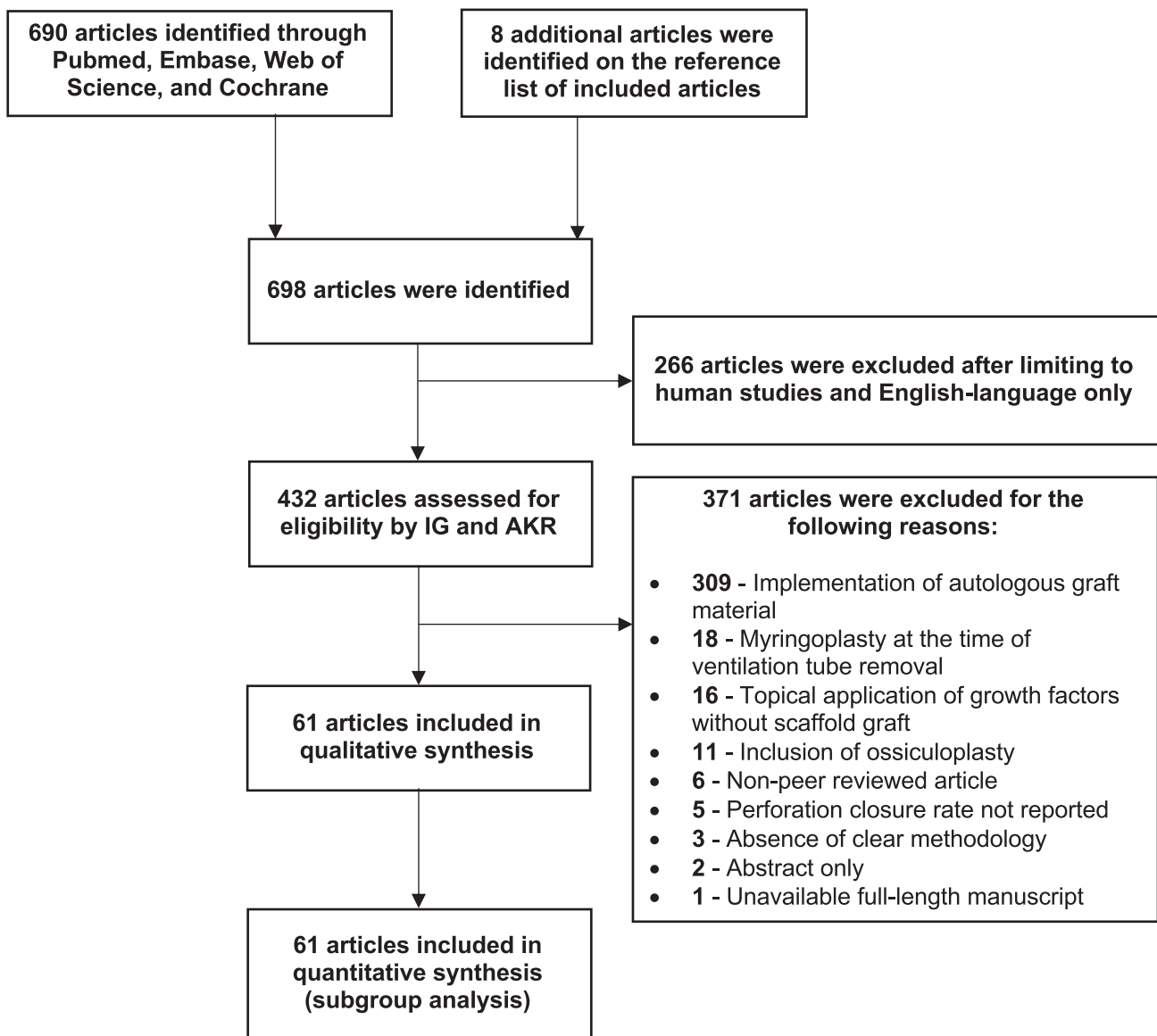


Fig. 1. Flowchart for article selection in the systematic review. AKR = Aaron K. Remenschneider (author); IG = Iman Ghanad (author).

silicone foil (Silastic). Three studies contained information about two nonautologous graft materials from different categories.<sup>12–14</sup> Study-specific data tables are found in Supporting Information, Appendices 2–6.

Of the 61 publications included, 20 (33%) were randomized control trials (RCTs) with an EBM level of evidence of 2. The remaining studies were either EBM level 3 (33%) or level 4 (34%). The mean score of the 41 non-randomized studies assessed using the MINORS system was  $13 \pm 4$  (range, 3–20). Forty percent of all RCTs were investigations of paper patch grafting. Study quality for each graft material is summarized in Table I.

### **Summative Outcomes of Nonautologous Graft Materials**

Outcomes from 3,247 tympanoplasties were reported in the 61 articles that met inclusion criteria. Traumatic

perforations (62.3%) were most commonly studied, whereas postinfectious perforations (31.9%) and other etiologies (5.8%) comprised a minority of cases. A summary of preoperative perforation characteristics is provided in Table II. Duration of perforation was reported in 82% of cases; of these, just over half were classified as acute perforations. Overall closure rate was 82.1%, with significantly higher closure rates in acute (89.9%) versus chronic perforations (64.9%,  $P < .01$ ) (Table III). A median postoperative ABG of 5.6 dB was found in the 23% of studies reporting this metric. Speech reception threshold was rarely reported.

### **Patching Materials: Paper Patch**

Twenty-two studies reported outcomes of paper patches for repair of TM perforations.<sup>13–34</sup> Several different types of paper were utilized, including rice paper,

TABLE I.  
Summary of Study Quality.

	Total No. of Studies	No. of Ears	EBM Level of Evidence*			MINORS Score†		
			Level 2	Level 3	Level 4	No. of Studies Scored	Mean Score	Score Range
Paper patch	22	859	8	3	11	14	12	3–19
Silk fibroin	2	46	0	1	1	2	19	
Steri-Strip	3	158	1	1	1	2	7	
Gelatin	10	511	6	2	2	4	13	5–20
Hyaluronic acid	3	88	0	3	0	3	14	9–19
Growth factors	16	1,079	4	9	3	12	15	10–16
Bacterial cellulose	3	76	2	0	1	1	16	
Atelocollagen	1	19	0	1	0	1	10	
Porcine SIS	2	222	1	0	1	1	12	
Silicone foil	2	189	0	0	2	2	15	
<b>All materials</b>	<b>61‡</b>	<b>3,247</b>	<b>20‡</b>	<b>20</b>	<b>21‡</b>	<b>41‡</b>	<b>13</b>	<b>3–20</b>

\*Study quality assessed using Oxford Center for Evidence-Based Medicine levels of evidence = 1–4<sup>10</sup>.

†Nonrandomized control trials also received a quality score based on MINORS criteria<sup>11</sup>.

‡Does not reflect summation of column, as three studies were double counted as they evaluated two nonautologous grafts from different categories. EBM = evidenced-based medicine; MINORS = methodological index for nonrandomized studies; SIS = small-intestinal submucosa.

TABLE II.  
Perforation Characteristics.

	No. of Studies	No. of Ears	Perforation Types Treated (When Indicated by Study)						
			Acute	Chronic	Trauma	Postinfectious	Vent Tube	Revision	Others
Paper patch	22	859	356 (51%)	342 (49%)	472 (58.1%)	313 (38.5%)	14 (1.7%)	8 (1%)	6 (0.7%)
Silk fibroin	2	46	26 (56.5%)	20 (43.5%)	—	—	—	—	—
Steri-Strip	3	158	138 (100%)	—	148 (93.7%)	—	10 (6.3%)	—	—
Gelatin	10	511	300 (94.6%)	17 (5.4%)	379 (81.3%)	76 (16.3%)	11 (2.4%)	—	—
Hyaluronic acid	3	88	88 (94.6%)	5 (5.4%)	88 (100%)	—	—	—	—
Growth factors	16	1,079	435 (47.7%)	477 (52.3%)	597 (57.7%)	316 (30.6%)	49 (4.7%)	63 (6.1%)	9 (0.9%)
Bacterial cellulose	3	76	—	76 (100%)	—	60 (100%)	—	—	—
Atelocollagen	1	19	—	—	11 (57.9%)	—	3 (15.8%)	5 (26.3%)	—
Porcine SIS	2	222	—	222 (100%)	15 (6.8%)	207 (93.2%)	—	—	—
Silicone foil	2	189	189 (100%)	—	189 (100%)	—	—	—	—
<b>All materials</b>	<b>61*</b>	<b>3,247</b>	<b>1,532 (56.9%)</b>	<b>1,159 (43.1%)</b>	<b>1,899 (62.3%)</b>	<b>972 (31.9%)</b>	<b>87 (2.8%)</b>	<b>76 (2.5%)</b>	<b>15 (0.5%)</b>

\*Does not reflect summation of column. Three studies were double counted, as they evaluated two nonautologous grafts from different categories. Not all studies indicated perforation type; therefore, the total number of ears may be higher than the sum of perforation types. SIS = small-intestinal submucosa.

cigarette paper, and paper patch (not otherwise specified). Pooled data resulted in a total of 859 adult and pediatric cases, in which 72.2% of the perforations were grade 2 or below. The predominant etiology of TM perforations in these studies was traumatic (58.1%), with the remainder caused by otitis media (38.5%), previous ventilation tube placement (1.7%), or other causes (1.7%). The mean (weighted average) closure rate across studies (n = 859) using paper patch was 71.1%, with a range of 10% to 100% (Table III). The mean closure rate of acute perforations (90.6%) was significantly higher than that of chronic perforations (47.0%,  $P < .0001$ ).

Paper patch myringoplasty in adult patients was primarily performed in an office setting under local anesthesia. A single study by Lindeman et al.<sup>31</sup> performed myringoplasty using paper patch in pediatric patients under general anesthesia. Ten publications<sup>13,15–19,24–27</sup> mentioned additional edge trimming in the procedure methodology. When sorted by perforation etiology, we found lower closure rates for perforations caused exclusively by otitis media (three articles,<sup>20,26,29</sup> range, 10.0%–52.2%) versus trauma (11 articles,<sup>14–16,21–23,25,31–34</sup> range, 80.0%–95.2%). Weighted averages showed that closure rates were lower for perforations secondary to otitis



TABLE III.  
Closure Rates.

	No. of Studies	No. of Ears	Closure Rate						
			Overall	Acute	Chronic	Acute vs. Chronic	Trauma	Postinfectious	Trauma vs. Postinfectious
Paper patch	22	859	71.1%	90.6%	47.0%	$P < .0001^*$	93.8%	47.7%	$P < .001^*$
Silk fibroin	2	46	82.6%	92.3%	70.0%	$P = .47$	—	—	—
Steri-Strip	3	158	96.8%	96.8%	—	—	—	—	—
Gelatin	10	511	86.1%	88.7%	82.4%	$P = .43$	—	—	—
Hyaluronic acid	3	88	89.8%	95.2%	0%	$P < .001^*$	—	—	—
Growth factors	16	1,079	84.5%	98.1%	72.3%	$P < .001^*$	—	—	—
Bacterial cellulose	3	76	88.2%	—	88.2%	—	—	—	—
Atelocollagen	1	19	42.1%	—	42.1%	—	—	—	—
Porcine SIS	2	222	96.4%	—	96.4%	—	—	—	—
Silicone foil	2	189	64.6%	64.6%	—	—	—	—	—
<b>All materials</b>	<b>61<sup>†</sup></b>	<b>3,247</b>	<b>82.1%</b>	<b>89.9%</b>	<b>64.9%</b>	<b><math>P &lt; .01^*</math></b>	—	—	—

Statistics were performed using a  $\chi^2$  test.

\*Statistically significant ( $P < .05$ ).

<sup>†</sup>Does not reflect summation of column. Three studies were double counted, as they evaluated two nonautologous grafts from different categories. Not all studies indicated closure rates stratified by chronicity or etiology of the perforation.

SIS = small-intestinal submucosa.

media (47.7%) compared to trauma (93.8%,  $P < .001$ ). Seven analyzed the effect of perforation characteristics on closure, and six found a negative correlation between perforation size and closure rate.<sup>17,19,21,24,26,32</sup> Six articles reporting audiometric ABG outcomes in healed TMs repaired with a paper patch found a mean postoperative ABG of 7.5 dB (range, 1–15 dB).<sup>15,16,20-22,26</sup>

Several studies compared outcomes from paper-patch grafting to various control groups, including autologous perichondrium, adipose tissue (fat plug), platelet-rich fibrin membranes, and spontaneous TM healing.<sup>14,15,17,21,25,31-34</sup> Dursun et al.<sup>17</sup> demonstrated that tympanoplasty with perichondrium or adipose tissue showed a relatively higher average closure rate and improved ABG (87.7%,  $5.4 \pm 0.8$  dB, respectively) when compared to paper-patch grafting (66.7%,  $8.4 \pm 2.2$  dB, respectively); however, the small sample size of 15 patients may have contributed to the inability to reach statistical significance. In two studies, the use of platelet-derived growth factors with paper patching produced equivalent closure rates and hearing outcomes as compared to paper patch alone.<sup>15,29</sup> Furthermore, eight studies found higher closure rates in patients treated with paper patch (91.6%) than patients being observed for spontaneous closure (78.8%,  $P < .001$ ).<sup>14,21,23,25,31-34</sup> Reported outcomes of spontaneous closure consistently showed a longer duration for complete TM healing but similar postoperative audiometric outcomes when compared to paper-patch grafting.<sup>14,21,25</sup>

### Patching Materials: Silk Fibroin

Silk fibroin, a natural polymer with long-term degradation characteristics (up to 16 months), has also been studied for TM repair in humans.<sup>13,35</sup> Two studies

reviewed outcomes in acute and chronic perforations (Table II). From the 46 cases included, overall closure rates using silk fibroin was found to be 82.6% (Table III). A prospective study by Lee et al.<sup>35</sup> of patients with chronic perforations demonstrated that silk fibroin graft material, in comparison to standard perichondrium myringoplasty, produced similar closure rates (70.0% vs. 80.0%, respectively,  $P = .07$ ) and healing times ( $12.0 \pm 9.3$  vs.  $9.7 \pm 6.0$  weeks, respectively,  $P = .77$ ). However, the rate of complications, postoperative otorrhea, and surgical time were significantly lower in the silk fibroin group ( $P < .02$  for each). Hearing improvement was not significant. Another article by the same authors reported results for acute traumatic perforations, and found a slightly higher closure rate in the silk fibroin treatment group (92.3%) versus the paper-patch group (84.6%), although spontaneous closure rates were not assessed.<sup>13</sup>

### Patching Materials: Steri-Strip

Steri-Strip and micropore tape patches are similar to paper patches but contain an adhesive element to discourage lateral displacement of the graft. Three studies, including 158 cases, assessed outcomes in acute traumatic perforations and found closure rates of 96.8% (Table III).<sup>14,36,37</sup> Hearing outcomes were similar to paper patching; however, perforation characteristics varied widely, with the majority of perforations classified as acute and grade 1 in the micropore study and grade 2 or higher in the Steri-Strip study.<sup>14,37</sup>

### Gelatin: Gelatin Sponge

Multiple publications evaluated the use of gelatin-containing material, which included the terms gelatin

sponge, gelatin film, and Gelfoam/Gelfilm (Pfizer, New York, NY).<sup>12,38–46</sup> The sole study on gelatin film was excluded, as the tympanoplasty procedure included ossiculoplasty.<sup>47</sup> This resulted in a total of 511 adult and pediatric cases, in which 21.1% of perforations were grade 1, whereas the remaining 78.9% of perforations were grade 2 or higher. The etiology of perforations in these cases was predominantly traumatic (81.3%) with the remainder caused by infection (16.3%), or removal of a ventilation tube (2.4%) (Table II). The mean (weighted average) closure rate across studies (n = 511) was 86.1% for tympanoplasty performed with gelatin sponge (Table III). Chronic perforations were evaluated in only one study and represented the minority of cases (5.4%).

Myringoplasty with gelatin sponge was performed in all publications, with adults under local anesthesia and children under general anesthesia. Perforation edges were removed to promote closure of the TM in 37.6% of cases. A prospective study by Niklasson and Tano of 18 ears undergoing gelatin-sponge patching following surgical edge approximation, found lower closure rates in pediatric cases (70%) compared to adult cases (100%), but no significant improvement in postoperative hearing for all patients.<sup>43</sup> Although this study did not control for surgical perforation edge approximation, another study by Lou et al. found that edge approximation prolonged healing time when compared to gelatin sponge patching without prior edge approximation.<sup>48</sup>

### **Hyaluronic Acid (EpiFilm/EpiDisc)**

Three publications reported the use of esterified hyaluronic acid film (EpiFilm/EpiDisc; Medtronic, Dublin, Ireland) as a graft material in a total of 88 adult and pediatric patients (Table II).<sup>49–51</sup> Across all studies (n = 88) the mean (weighted average) closure rate was 89.8% for hyaluronic acid film (Table III). TM repair was performed by a transcanal technique with local anesthesia. Chronic TM perforations were only included in one study of five patients; however, the researchers prematurely terminated the study due to the 0% closure rate.<sup>50</sup> In the other two studies, all perforations were a result of acute trauma, and approximately 73% were grade 1.<sup>49,51</sup> The largest of those studies, which included 74 ears patched with hyaluronic acid film, reported a closure rate of 94.8% and significant ABG closure of 3.4 dB. In comparison, those who were observed for spontaneous healing showed slightly decreased closure rates (85.6%) but a similarly significant ABG closure of 5.0 dB.<sup>51</sup>

### **Growth Factors**

Sixteen publications, with a total of 1,079 ears, analyzed the efficacy of growth factors with for TM regeneration.<sup>12,48,52–65</sup> Studies employed basic fibroblast growth factor (bFGF) or epidermal growth factor (EGF). A close distribution of acute (47.7%) and chronic (52.3%) perforations were included; however, the majority of cases were of a traumatic etiology (57.7%), whereas only 30.6% were postinfectious (Table II). The mean (weighted average) closure rate across studies for treatments utilizing growth

factors (n = 1,079 ears) was 84.5% (Table III). Surgical repairs were performed by a transcanal approach, with the majority using local anesthesia in adults and one study using general anesthesia in pediatric patients. Studies showed a higher average closure rate among acute perforations (98.1%) compared to chronic perforations (72.3%,  $P < .001$ ). When reported, untreated TMs closed spontaneously in 11% to 94.3% of cases, with acute perforations demonstrating higher rates of spontaneous closure.

When looking specifically at studies using bFGF, perforations were typically grade 2 in size, and etiologies, when reported, included trauma (49.3%), otitis media (37.3%), tympanoplasty failure (7.9%), removal of a ventilation tube (4.7%), and other (0.8%). Closure rates for traumatic perforations appeared higher (range, 97%–99%) than for infectious perforations (range, 66%–81%), but due to insufficient raw data, subgroup pooled analysis was not performed. The average improvement in pure-tone audiometric values in patients treated with bFGF was 14.9 dB. Posttreatment complications included otorrhea, epithelial pearl formation, granulation formation, and myringitis.

Comparison groups in bFGF studies consisted of various treatment approaches, including spontaneous healing, atelocollagen membrane coated in saline (as opposed to bFGF), and direct application of bFGF without a scaffold. Patients followed for spontaneous healing and those treated with saline-coated atelocollagen, as control groups, exhibited lower closure rates and lesser hearing improvement (50.1% vs. 40% and 12.4 dB vs. 4.1 dB, respectively) compared to bFGF impregnated scaffolds.<sup>48,53–55</sup> There was no observed difference between closure rates in pediatric versus adult patients treated with bFGF.<sup>48,52</sup> Of particular note is a recent double-blinded RCT comparing saline- versus bFGF-impregnated gelatin sponge in chronic TM perforations.<sup>65</sup> Contradicting previously published results, the authors observed no significant difference in closure rates for saline placebo: 71.4% versus bFGF: 57.5% ( $P = .36$ ). Hearing improvement between the two groups was also no different.

Two studies reviewed a total of 215 patients treated with EGF appended to scaffold materials. All perforations were grade 1, with only eight (4%) the sequelae of infection and the remaining (96%) due to trauma. Ramsay et al.<sup>57</sup> observed a 0% closure rate with the application of EGF on paper patch for chronically perforated TMs caused by infection. In contrast, Lou et al.<sup>56</sup> reported a near complete closure rate of 98.2% with EGF on gelatin sponge for acute, traumatic TM perforations.

### **Others: Bacterial Cellulose, Protease-Solubilized Collagen, SIS, Silicone Foil**

Three studies reported a total of 76 pediatric and adult cases of chronic TM perforations repaired with bacterial cellulose grafts (Table II).<sup>66–68</sup> The mean (weighted average) closure rate across studies (n = 76) was 88.2%. The authors noted a significant decrease in operative

time for cellulose grafts versus autologous fascia grafts.<sup>66,68</sup>

Atelocollagen (protease-solubilized collagen) on a silicone-scaffold sheet was used in one study that reported 19 cases of medium- and large-sized perforations caused by trauma (57.9%), ventilation tubes (15.8%), or previously failed tympanoplasty (26.3%). The authors found this material to require multiple interventions to obtain perforation closure. After a single application, only 42.1% of perforations closed, but upon multiple revisions, closure was achieved in 73.7% of patients.<sup>69</sup> No hearing outcomes or posttreatment complications of atelocollagen were reported, nor were there adequate data to compare outcomes in acute versus chronic perforations.

Two studies reported the use of porcine SIS (Bio-design; Cook Medical, Bloomington, IN) as a graft material in 222 adult and pediatric cases.<sup>70,71</sup> The largest of these two studies compared SIS to temporalis fascia for tympanoplasty in a randomized controlled trial of 432 ears of pediatric patients with chronic perforations caused by otitis media and trauma.<sup>70</sup> The majority of perforations (75%) in this study were grade 1 or 2 in both groups, and all patients underwent formal underlay myringoplasty under general anesthesia. All perforations were reported as chronic, and 94.2% were postinfectious. Results demonstrated comparably high closure rates between the 217 perforations in the SIS group (96.3%) and the 215 perforations in the temporalis fascia control group (94.8%). Specific audiometric outcomes for the SIS group were not reported, but the authors noted that there were no statistically significant differences between the SIS and temporalis fascia groups. A recent study of five patients undergoing in-office repair of a TM perforation using SIS demonstrated 80% closure rate after the initial attempt, with 100% success after a single revision procedure in one patient. The ABG was significantly improved following tympanoplasty.<sup>71</sup>

Two studies reported a total of 189 pediatric and adult cases of acute, traumatic TM perforations splinted with a silicone foil (Silastic).<sup>72,73</sup> Although the mean (weighted average) closure rate across studies ( $n = 189$ ) was 64.6%, there was substantial variation between the two studies (range, 51.6%–91.8%). Both groups noted worse rates of perforation closure when repair occurred beyond a 3-day window from the time of otologic trauma.

## DISCUSSION

The aim of this systematic review was to summarize clinical outcomes and discuss limitations in the literature regarding the use of nonautologous grafts for tympanoplasty in humans. Although we found 61 distinct studies on the topic, the inclusion criteria, perforation size and chronicity, surgical techniques, and postoperative outcome reporting were highly heterogeneous. Across all studies, closure rates were found to be 82.1%, but acute perforations demonstrated significantly higher closure rates than chronic perforations (89.9% vs. 64.9%,  $P < .01$ ). Spontaneous closure rates for acute perforations ranged from 40% to 100%.<sup>23,31,49,55</sup> Thus, the duration of perforation was found to be a significant independent

variable determining tympanoplasty outcomes, regardless of the material utilized.

Several studies using specific materials reported highly favorable closure rates but studied a plurality of patients with acute perforations. Specifically, acute perforations comprised 94.6% of the study population treated with gelatin sponge (Gelfoam) and 94.6% of the study population treated with hyaluronic acid film (EpiFilm/EpiDisc). Overall closure rates were found to be 86.1% and 89.8%, respectively. It is difficult to interpret whether the high rates of closure were associated with spontaneous healing or the material utilized. Further study of these materials is necessary to form conclusions about their success rates in traditional tympanoplasty candidates with chronic perforations.

We also find that published studies on the use of nonautologous graft materials include more patients with traumatic perforations compared to infectious etiologies. The proportion of reviewed studies evaluating tympanoplasty outcomes in traumatic perforations was 62.3%, whereas only 31.9% of studies evaluated outcomes for perforations related to chronic otitis media. This disparity is relevant, given that many of the benefits of nonautologous graft materials (i.e., availability in revision cases) apply disproportionately to infectious causes of perforation, in which the rate of surgical failure, using traditional techniques, is often high.<sup>17,20,29</sup> The only material with enough data to permit a direct comparison of closure rate between postinfectious and traumatic perforations was the paper patch, which demonstrated clear differences in outcome (47.7% vs. 93.8%,  $P < .001$ , respectively). Unfortunately, lack of adequate raw data prevented comparison of closure rates by etiology for perforations repaired using other graft materials; however, rates generally appeared lower for postinfectious perforations compared to trauma. Thus, reservations in the adoption of nonautologous grafts for tympanoplasty in chronic otitis media may in part be due to scant available data and inferior outcomes reported by small studies.

Hearing outcomes in patients undergoing myringoplasty using nonautologous graft materials frequently demonstrated persistent conductive hearing loss.<sup>15,20,21,26,29,51</sup> Many studies did not include audiometric outcomes, or only reported the mean improvement in ABG. Future clinical studies must rigorously report both pre- and postoperative thresholds. This may allow surgeons to choose grafts based on expected hearing outcomes, in addition to closure rates.

A major consideration identified by this review is that there remains a need for high-quality clinical studies evaluating novel biomaterials to successfully and consistently repair chronic, high-grade perforations that arise from traumatic or infectious etiologies. Most studies focused on acute, traumatic, low-grade perforations, thereby limiting external validity of these results. The exception is the relatively high quality studies on bFGF and EGF that reviewed both acute and traumatic perforations, as well as a relatively high percent of postinfectious perforations (30.6%). Closure rates for chronic perforations range from 57.5% to 100% with some more recent studies from a single group demonstrating higher rates of



success, perhaps due to improved surgical/application technique.<sup>53,58–61</sup> A single study using SIS demonstrated successful TM repair in cases of chronic infectious and traumatic perforations; however, these results are from a single surgeon and have not yet been reproduced on a large scale.<sup>70</sup> It is also notable that a limited number of groups are responsible for a plurality of published reports on the use of nonautologous grafts in tympanoplasty. These groups include Lou (Yiwu Central Hospital, China), Lou (Xinxiang Medical University, China), and Hakuba (Ehime University School of Medicine, Japan). Whereas this clearly represents a dedicated effort to elucidate optimal materials for TM repair, it also raises questions about overlapping patient populations and reproducibility of results. Recently, an RCT using bFGF was performed in the United States<sup>65</sup> in an effort to duplicate previously reported outcomes.<sup>53,58–61</sup> The US authors found no difference in closure rates or hearing outcomes when compared to placebo, raising significant questions about the reproducibility of the earlier results. This example reiterates the need for additional clinical trials spanning a diverse range of institutions.

Although this review presents a comprehensive comparison of nonautologous graft materials, it is limited by several factors. First, the quality of the reviewed publications was inconsistent. However, only a subset of studies were RCTs and selection bias for included cases may alter closure rates and hearing outcomes. Second, as previously mentioned, several authors published multiple studies, which may have resulted in duplication of patient cohorts. A plurality of these potential duplicates is found in investigations of tympanoplasty using gelatin and/or growth factors. Based on the number of publications with the same corresponding author, we conservatively estimate that, at most, 324 out of 3,247 cases (10%) may represent duplicates. Additionally, perforation size, duration, and etiology were inconsistently reported across studies. Many studies lacked necessary information for subgroup analyses according to perforation size and etiology. This limitation also serves as a source of error in our subgroup analysis of outcomes according to perforation duration. Furthermore, in some cases, comparisons were made across studies with variable inclusion criteria. It was also difficult to evaluate hearing outcomes across studies, as many articles did not report audiometric data. Finally, it is important to note that pooled closure rates were not calculated via meta-analysis methodology. Although simple statistical comparisons of the subgroups were made, these should only be considered hypothesis generating.

Despite limitations, we find that nonautologous graft materials including paper patch, hyaluronic acid film, gelfoam, and bFGF are highly successful at closing acute perforations; however, there is some evidence to suggest these perforations may have healed without intervention given adequate time. Chronic and postinfectious perforations clearly demonstrate lower closure rates than acute and traumatic perforations. Notably, closure rates using bFGF and porcine SIS in chronic perforations were 73.5% and 96.4%, but their role in patients with chronic otitis media or for use in revision surgery is less clear. High-quality RCTs are needed to compare perforation closure

rates and audiometric outcomes between autologous and nonautologous materials.

## CONCLUSION

Closure rates for acute and traumatic perforations are approximately 90%, regardless of the material used. This is significantly higher than the closure rates seen in chronic perforations (64.9%). Available data suggest porcine submucosa and bFGF have the highest success at chronic perforation closure; however, little data exist on healing times and expected closure rates of postinfectious perforations. Future studies of nonautologous graft materials in tympanoplasty should focus on chronic perforations from postinfectious etiologies and rigorously report hearing outcomes.

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