Biomaterials in Rhinology

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Abstract

Introduction. Many different kinds of rhinologic biomaterials, both nonabsorbable and absorbable, have been developed over the years to improve outcomes following endoscopic sinus surgery (ESS) for patients with chronic rhinosinusitis. In particular, these products have been designed to prevent postoperative bleeding, optimize the wound healing process, and reduce inflammation. This review evaluates the most recent evidence on biomaterials used in rhinology, focusing on these outcomes after ESS.

Data Sources. MEDLINE, Scopus, Google Scholar, and Clinicaltrials.gov.

Review Methods. A primary literature search based on the listed databases was performed with combinatorial search terms. Studies were considered for review if they met a set of inclusion and exclusion criteria.

Conclusions. Some products have performed better than others in clinical trials, although significant heterogeneity among studies does not allow for selection of a clearly superior biomaterial. While nonabsorbable biomaterials are still effective in achieving certain outcomes, newer, absorbable substances may be just as effective and avoid the morbidity associated with nasal packing removal. Steroid-eluting biomaterials have shown promising early results in reducing inflammation and promoting wound healing.

Implications for Practice. Certain absorbable biomaterials, such as chitosan gel and fibrin glue, have performed well with respect to postoperative hemostasis and wound healing, although they do not address mucosal inflammation. Steroid delivery systems may play an increasingly important role in reducing disease recurrence after ESS, although more studies are needed to assess long-term outcomes.

Keywords
biomaterials, nasal packing, removable packing, absorbable packing, hemostasis, wound healing, drug-eluting stents, endoscopic sinus surgery, rhinology, chronic rhinosinusitis

Biomaterials have been used in medicine for thousands of years, and over time, their role as a powerful clinical tool has become increasingly important. The National Institutes of Health defines a biomaterial as “any substance (other than a drug) or combination of substances synthetic or natural in origin, which can be used for any period of time, as a whole or part of a system which treats, augments, or replaces tissue, organ, or function of the body.” In the modern era of otolaryngology, biomaterials made their debut in the 1850s with the advent of the tympanostomy tube. As evidenced by our reliance on tracheostomy tubes, metallic plating for facial reconstruction, and cochlear implants, these technologies have since become an integral part of every subspecialty in the field.

In the setting of endoscopic sinus surgery (ESS), the interest in development of biomaterials stems from the desire to decrease postoperative surgical complications and improve patient outcomes. To that end, the initial reason that nasal packing was developed was to prevent postoperative hemorrhage, a common complication after nasal surgery. Nasal packing and hemostatic gels and foams diminish bleeding via either direct physical pressure on the mucosa or enzymatic activation of the clotting cascade. Another potential complication after ESS is the development of synechiae, which can occur in up to 36% of patients. Adhesions can be particularly problematic when they occur between the middle turbinate and lateral nasal wall, which can prevent access for postoperative debridement, impair adequate mucociliary clearance, and reduce the delivery of topical therapies into the sinus cavities. In some cases, postoperative synchiae can result in persistent chronic rhinosinusitis (CRS) symptoms after ESS. Biomaterials have thus been utilized to ensure...
middle turbinate medialization, promote long-term ostial patency, and serve as a physical barrier to adhesion formation. Finally, there has been substantial research and development of implantable spacers capable of delivering continuous, high-potency anti-inflammatory medications directly to the sinus mucosa after ESS in the hopes of preventing disease relapse and reducing the need for systemic therapy.

Hemostasis, adhesion prevention, and topical medication delivery are some of the essential functions provided by nasal biomaterials. This review evaluates the most recent evidence on biomaterials in rhinology.

Materials and Methods
A comprehensive review of the relevant literature from 1990 to June 2015 was carried out in MEDLINE, Scopus, and Google Scholar. Relevant trials registered in Clinicaltrials.gov were reviewed for outcomes and adverse events. The search strategies used the following words or phrases in various combinations: “nasal packing,” “rhinology,” “biomaterials,” “absorbable,” “non-absorbable,” “steroid eluting,” “nasal stents,” “nasal spacers,” “endoscopic sinus surgery,” and “ESS.” Various types of biomaterials were also used as search terms (Table 1). Studies were included if they met a set of inclusion and exclusion criteria. Inclusion criteria consisted of prospective randomized study design (level of evidence 2b), human subjects with CRS undergoing ESS, and use of a rhinologic biomaterial as primary intervention. Exclusion criteria consisted of retrospective or cohort study design, bench or animal research, or primary nasal surgery other than ESS.

Discussion
Among 1628 articles retrieved through primary literature search, 59 publications were deemed relevant based on title and abstract and given full-text analysis (Figure 1). Of these, 21 articles were excluded, leaving 38 articles for inclusion.

Nonabsorbable Nasal Biomaterials
Innovations in nonabsorbable nasal packing have seen tremendous growth since the first description of the rubber nasal pack in 1951. In sinus surgery, most nonabsorbable nasal biomaterials are used to alleviate postoperative hemorrhage via pressure tamponade. They also serve as a physical barrier to adhesion formation. Among the many types of available nonabsorbable packs, this review focuses on some of the more commonly used materials used today, including expandable polyvinyl acetate (PVA) foam tampons (Merocel; Medtronic Xomed, Jacksonville, Florida) and related products, polyethylene terephthalate–coated cotton fleece (Telfa; The Kendall Company, Boston, Massachusetts), and carboxymethylcellulose-coated fabric sponges (Rapid Rhino Riemann; Applied Therapeutics, Obernberg, Germany).

There have been numerous trials comparing the efficacy of various nonabsorbable biomaterials in ESS (Table 2). Investigators have studied various sleeves and coatings on PVA foam. Four trials have looked at sheathing PVA in a latex or vinyl glove finger. Kim and colleagues found that when PVA was inserted into a latex glove finger, the sheath caused significantly less pain and bleeding on pack removal and improved endoscopic scores during follow-up when compared with plain PVA. Similar findings were produced by Akbari et al, although the authors failed to indicate the type of glove material that was used. Melis and colleagues studied the efficacy of various PVA coatings, such as oxidized cellulose (Merocel Hemox; Medtronic Xomed) and polyethylene film (Merocel 2000; Medtronic Xomed). For comfort during removal, the polyethylene coating performed best, followed by oxidized cellulose and then plain PVA. For hemostasis following removal, the oxidized cellulose coating was most effective, followed by polyethylene film and then standard PVA. All differences reported were statistically significant.

Cruise et al showed that polyethylene terephthalate–coated cotton fleece effectively reduces bleeding, crusting, and adhesion formation after ESS but causes significantly more pain on removal when compared with a carboxymethylcellulose-coated fabric sponge. This brings up a major drawback of nonabsorbable packs, which is that they must be removed following their insertion, an event that can cause significant pain and can also

Table 1. List of Specific Biomaterials Used as Search Terms.

<table>
<thead>
<tr>
<th>Biomaterial Search Terms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyvinyl acetate</td>
</tr>
<tr>
<td>Vaseline gauze</td>
</tr>
<tr>
<td>Gelatin film</td>
</tr>
<tr>
<td>Gelatin foam</td>
</tr>
<tr>
<td>Hemospheres</td>
</tr>
<tr>
<td>Collagen</td>
</tr>
<tr>
<td>Hyaluronic acid</td>
</tr>
<tr>
<td>Fibrin glue</td>
</tr>
<tr>
<td>Cellulose</td>
</tr>
<tr>
<td>Carboxymethylcellulose</td>
</tr>
<tr>
<td>Microporous polysaccharide</td>
</tr>
<tr>
<td>Chitosan</td>
</tr>
<tr>
<td>Polyurethane foam</td>
</tr>
</tbody>
</table>

Figure 1. Flowchart illustrating literature search and screening process. ESS, endoscopic sinus surgery.
induce mucosal shearing and bleeding. The mucosal trauma caused by nonabsorbable packs can be significant, with animal models exhibiting areas of demucosalization of up to 70% in the region of the pack.\textsuperscript{10} Other complications—including posterior dislodgement and aspiration, eustachian tube dysfunction, obstructive sleep apnea, foreign body reactions, and toxic shock syndrome\textsuperscript{11}—have spurred the innovation and implementation of absorbable biomaterials for nasal packing.
Absorbable Biomaterials

Absorbable biomaterials were first described in the otolaryngologic literature in 1969 with a report on oxidized regenerated plant cellulose for control of hemorrhage. Since then, a staggering number of different classes of absorbable substances have been developed. This review classifies and addresses these substances as follows:

- **Extracellular matrix–based materials**: gelatin film, gelatin foam, flowable gelatin matrix with thrombin, hyaluronic acid (HA) gels and foams
- **Coagulation cascade precipitants**: fibrin glue
- **Natural and synthetic biopolymers**: oxidized cellulose, carboxymethylcellulose, microporous polysaccharide hemospheres (MPH), chitosan, polyurethane foam (PUF), thermosensitive polyethylene glycol poloxamer
- **Steroid delivery compounds**: PVA, carboxymethylcellulose, PUF, poly(lactide-co-glycolide) stent

**Extracellular Matrix–Based Biomaterials**

Biomaterials belonging to this category are derived from either collagen or HA and are usually formulated as a porous sponge, foam, or gel (Table 3).

**Collagen-Based Materials**. The expansile qualities of collagen-based substances are exploited when exposed to blood, which results in tamponade of hemorrhage. These materials also achieve hemostasis through activation of the coagulation cascade via the intrinsic pathway. This is augmented in certain commercial products that incorporate thrombin into the collagen matrix. They also serve as a temporary spacer, which prevents adhesion formation. The collagen in these materials usually takes the form of gelatin and is often derived from purified porcine or bovine tissue. Complete liquefaction is generally seen in 3 to 5 days after being placed in the nasal cavity.

A number of different gelatin products have been studied in the setting of ESS. Tom et al examined the utility of middle meatal stenting with gelatin film13 (Gelfilm; Pharmacia and Upjohn Company, Kalamazoo, Michigan). The authors found no significant difference in adhesion formation between middle meati that were stented versus those that were left unstented, arguing against the wound healing efficacy of this product.

Multiple proprietary gelatin sponge or foam formulations are commercially available (Gelfoam, Pharmacia and Upjohn Company; Spongostan, Ferrosan, Copenhagen, Denmark; Cutanplast, Mascia Brunelli SpA, Milan, Italy). All of these products are porous, water-insoluble hemostatic agents, although the density and porosity differ among them. Wee et al evaluated gelatin foam against an intrapatient unpacked control and found no differences in subjective symptoms, endoscopic findings, or bleeding events between the 2 arms. In comparison with PVA, gelatin foam caused significantly less discomfort while in situ and less bleeding on pack removal, although there was no difference in Lund-Mackay scores at any time point. Two proprietary formulations of gelatin foam have also been compared and were found to provide equivalent wound healing and hemostatic benefits, although differences were noted in patient comfort.

Bovine-derived, granulated gelatin matrix admixed with thrombin has been developed as a flowable compound (FloSeal; Baxter International, Deerfield, Illinois) for injection into sinus cavities. This gelatin-thrombin admixture was initially evaluated by Gall et al17 and has been repeatedly shown to be an effective hemostatic agent in ESS. When compared with unpacked control, the flowable gelatin-thrombin admixture significantly reduced the postoperative bleeding time and the amount of pain while in situ. No difference in crusting or adhesions was noted at 1 and 3 months. Flowable gelatin-thrombin admixture has also exhibited comparable hemostatic capabilities to a plant-based polysaccharide (HemoStase; Cryolife Inc, Kennesaw, Georgia).

Gelatin sponges can be infused with a solution containing thrombin immediately prior to their insertion for enhanced hemostatic effect. Chandra et al compared this preparation with flowable gelatin-thrombin admixture. While the hemostatic capabilities of the 2 compounds were equivalent, the nasal cavities injected with flowable gelatin-thrombin admixture had significantly more granulation tissue and adhesions. However, the evaluators were not blinded to treatment.

As a class, collagen-based biomaterials appear to be effective hemostatic agents in the setting of ESS. While collagen and thrombin are coagulation cascade precipitants and theoretically proinflammatory, the studies presented here do not demonstrate an increased propensity for adverse wound healing outcomes with the use of these materials.

**HA Biomaterials**. Several HA-based products are available for use in ESS and are formulated as a gel, mesh, or foam. Hybrid foams composed of HA and collagen also exist. HA compounds are postulated to increase the rate of reepithelialization and prevent adhesion formation.

A nasal pack composed of esterified HA (MeroGel; Medtronic Xomed) has performed inconsistently with respect to inhibition of synechia formation. Wormald et al reported no significant difference in synechia formation between this HA pack and unpacked control. When Miller and colleagues compared HA with PVA, they observed no significant differences in adhesion formation. Franklin and Wright found a similar result when this HA pack was compared with “standard” nonabsorbable nasal packing. For Berlucchi et al, esterified HA packing performed better than PVA, with significantly fewer adhesions noted at all time points. An absorbable nasal packing containing 80% HA and 20% collagen (MeroPack; Medtronic Xomed) was evaluated in a pediatric population. The authors found that the HA-collagen hybrid pack was effective in controlling postoperative hemorrhage as compared with unpacked control, although no difference was seen in adhesion formation between the treatment arms.
Fewer studies have evaluated the efficacy of a chemically cross-linked, water-insoluble HA polymer gel (Sepragel Sinus; Genzyme Biosurgery, Cambridge, Massachusetts). In a small study containing 10 patients, this injectable HA gel was randomized to either right or left nasal cavities after ESS, with endoscopic evaluations at 1-week intervals following surgery.26 The

### Table 3. Extracellular Matrix–Based Materials.

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Size, n</th>
<th>Comparison Method</th>
<th>Outcomes Measured</th>
<th>Efficacy Comparisons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tom (1997)13</td>
<td>51</td>
<td>Intrapatient</td>
<td>Wound healing: adhesions, granulation tissue, sinus ostial patency</td>
<td>= No pack for wound healing</td>
</tr>
<tr>
<td>Gelatin film</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wee (2012)14</td>
<td>21</td>
<td>Intrapatient</td>
<td>Comfort: symptom index</td>
<td>= No pack for wound healing, comfort</td>
</tr>
<tr>
<td>Gelatin (foam/sponge)</td>
<td></td>
<td></td>
<td>Wound healing: crust, granulation tissue, edema</td>
<td></td>
</tr>
<tr>
<td>Cho (2013)15</td>
<td>100</td>
<td>Intrapatient</td>
<td>Comfort: VAS</td>
<td>&gt; PVA for hemostasis on pack removal and for comfort while in situ; = for wound healing</td>
</tr>
<tr>
<td>Hemostasis: custom scale</td>
<td></td>
<td></td>
<td>Wound healing: Lund-Kennedy</td>
<td></td>
</tr>
<tr>
<td>Cho (2015)16,b</td>
<td>100</td>
<td>Intrapatient</td>
<td>Comfort: symptom index</td>
<td>= Gelatin foam (Spongostan) for wound healing and hemostasis; &gt; for comfort</td>
</tr>
<tr>
<td>Hemostasis: custom scale</td>
<td></td>
<td></td>
<td>Wound healing: Lund-Kennedy</td>
<td></td>
</tr>
<tr>
<td>Flowable gelatin-thrombin admixture</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jameson (2006)18</td>
<td>45</td>
<td>Intrapatient</td>
<td>Comfort: pain relative to contralateral side</td>
<td>&gt; No pack for hemostasis and comfort; = for wound healing</td>
</tr>
<tr>
<td>Hemostasis: postoperative bleed time</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wound healing: crusting and scarring</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beyea (2011)19</td>
<td>18</td>
<td>Interpatient</td>
<td>Hemostasis: intraoperative blood loss amount</td>
<td>= MPH for hemostasis</td>
</tr>
<tr>
<td>Chandra (2003)20</td>
<td>20</td>
<td>Intrapatient</td>
<td>Hemostasis: need for additional packing</td>
<td>&lt; Gelatin foam with thrombin for wound healing; = for hemostasis</td>
</tr>
<tr>
<td>Wound healing: granulation tissue, adhesions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyaluronic acid</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wormald (2006)21</td>
<td>42</td>
<td>Intrapatient</td>
<td>Wound healing: adhesions, edema</td>
<td>= No pack for wound healing</td>
</tr>
<tr>
<td>Miller (2003)22</td>
<td>37</td>
<td>Intrapatient</td>
<td>Wound healing: adhesions, edema</td>
<td>= PVA for wound healing</td>
</tr>
<tr>
<td>Franklin (2007)23</td>
<td>35</td>
<td>Intrapatient</td>
<td>Wound healing: Lund-Mackay</td>
<td>= PVA for wound healing</td>
</tr>
<tr>
<td>Berlucchi (2009)24</td>
<td>66,c</td>
<td>Not stated</td>
<td>Wound healing: adhesions</td>
<td>&gt; PVA for wound healing</td>
</tr>
<tr>
<td>Song (2013)48</td>
<td>66</td>
<td>Intrapatient</td>
<td>Wound healing: adhesions, edema</td>
<td>= Thermosensitive PEG poloxamer for wound healing</td>
</tr>
<tr>
<td>Hu (2008)25,d</td>
<td>60</td>
<td>Intrapatient</td>
<td>Hemostasis: incidence of postoperative hemorrhage Wound healing: adhesions, granulation tissue, sinus ostial patency</td>
<td>&gt; No pack for hemostasis; = for wound healing</td>
</tr>
<tr>
<td>Kimmelman (2001)26</td>
<td>10</td>
<td>Intrapatient</td>
<td>Comfort: VAS</td>
<td>&gt; No pack for wound healing and comfort</td>
</tr>
<tr>
<td>Frienkiel (2002)27</td>
<td>20</td>
<td>Intrapatient</td>
<td>Hemostasis: custom scale, volume of blood loss</td>
<td>= No pack for hemostasis</td>
</tr>
<tr>
<td>Shi (2013)28</td>
<td>54</td>
<td>Intrapatient</td>
<td>Wound healing: reepithelialization, adhesion, crusts, edema</td>
<td>&gt; No pack for wound healing</td>
</tr>
</tbody>
</table>

Abbreviations: HA, hyaluronic acid; MPH, microporous polysaccharide hemospheres; PEG, polyethylene glycol; PVA, polyvinyl acetate; VAS, visual analog scale.

*Equal sign (=) denotes no statistical significance (P > .05) in performance between the biomaterial and the comparison; greater-than sign (>) indicates that the biomaterial performed significantly better (P < .05) than the comparison; and lesser-than sign (<) indicates that the biomaterial performed significantly worse (P < .05) than the comparison.

*Cutanplast.

*Treatments were randomized to 88 nasal cavities in 66 patients.

*HA-collagen hybrid.
authors reported significantly fewer adhesions, less middle
meatal stenosis, and less edema and granulation tissue in the HA
gel treatment arm after week 2 when compared with unpacked
control. The hemostatic properties of HA gel were investigated
by Frenkiel et al, who found no significant difference in total
blood loss between HA gel and unpacked control.27

A single study evaluated the efficacy of a cross-linked
hyaluronan hydrogel (PureRegen Gel Sinus; BioRegen
Biomedical, Changzhou, China). Compared with unpacked
control, this material demonstrated improved wound healing
as determined via endoscopic score.28

Cross-linked HA gel and hyaluronan hydrogel appear to
conferr good benefit in terms of wound healing, although the
evidence consists of a single study for each product. While the
esterified HA nasal pack has been more extensively trialed,
there is disagreement among studies with regard to its wound
healing properties. More studies are needed to evaluate the
hemostatic abilities of these compounds.

**Coagulation Cascade Precipitants**

This class includes agents that primarily participate in some
aspect of the coagulation cascade. Fibrin sealants are the sole
member of this category in wide use today (Table 4).

Fibrin glue (Evicel; Omrix Biopharmaceuticals, Ramat Gan,
Israel) is a surgical sealant composed of purified human-origin
cryoproteins and thrombin that induces clot formation at the site
of bleeding. Because this product is composed of pooled human
blood products, there is a very small risk of virus transmission.
Fibrin glue has been shown to be an effective hemostatic agent
when used post-ESS, with a postoperative bleeding incidence of
3%.29 It performed better than PVA in that it avoided many of the
complications and pitfalls associated with nonabsorbable pack-
ing. Although concerns about the proinflammatory properties
of this biomaterial have been raised,30 studies have shown this
product to be slightly better than PVA in preventing adhesions.31
The evidence seems to support fibrin glue as an effective hemostatic
and antiadhesion agent, although this product has not been trialed
against negative control.

**Natural and Synthetic Absorbable Biopolymers**

This class of biomaterials includes plant-sourced products,
such as oxidized cellulose and carboxymethylcellulose
(CMC), MPH, crustacean-derived polymers (eg, chitosan),
and purely synthetic materials (eg, polyurethane and polyeth-
ylene glycol). Effects on hemostasis and wound healing have
been variably studied for this group of products (Table 5).

Oxidized cellulose, a vegetable-derived product, and its
various formulations have been widely used as hemostatic
agents for decades. These products promote hemostasis by
precipitating platelet aggregation. Despite their widespread
use, there is a paucity of literature documenting their effec-
tiveness in rhinology. A powdered formulation of oxidized
cellulose (Bloodcare; Anser Medical, Saffron Walden, UK)
was recently been evaluated by Al-Shaikh and colleagues.32
The investigators showed that oxidized cellulose powder is
more effective than PVA in preventing postoperative hemor-
rhage and leads to roughly the same incidence of crusting and
adhesion formation.

Carboxymethylcellulose is a plant-sourced polysaccharide
biomaterial that is a potent activator of the coagulation cascade
and is available as a mesh, foam, or gel. Randomized controlled
trials have failed to demonstrate the efficacy of the gel or mesh
formulations with respect to hemostasis33 or wound healing34
when compared with unpacked control. CMC foam performed
similarly to PVA sheathed in a latex glove finger for hemostasis
and wound healing.35 CMC has also been coated with silver
(Aquacel-Ag; Convatec Japan, Tokyo, Japan), and it produces
similar results for hemostasis and patient comfort when com-
pared with chitin-coated gauze36 (Beschtin-F; Unitika Ltd,
Tokyo, Japan), a popular nasal pack in Japan.

MPH (Medafor Inc, Minneapolis, Minnesota) is a hemo-
static nasal packing material produced from potato starch.
MPH has been shown to significantly reduce bleeding on
postoperative day 1 when compared with negative control as
determined via graded endoscopic score.37 Additionally, its
use resulted in an incidence of adhesion formation equivalent
to that of the unpacked control.38 MPH effected a similar
degree of blood loss as compared with flowable gelatin-
thrombin admixture.19

Chitosan is a biopolymer synthesized via deacetylation of
chitin, a major component of crustacean exoskeletons. In
addition to its bacteriostatic properties, it is believed to poten-
tiate the coagulation cascade and is commercially available
in gel and aerosolized formulations. When compared with a
negative control, chitosan gel significantly reduced the time to postoperative hemostasis and achieved significantly fewer adhesions at all follow-up time points.\cite{39} Chitosan gel has also been shown to significantly reduce sinus ostial stenosis after ESS.\cite{40} In this study, maxillary, frontal, and sphenoid ostia treated with chitosan gel were measured at various time points.

### Table 5. Natural and Synthetic Biopolymers\(^a\)

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Size, n</th>
<th>Comparison Method</th>
<th>Outcomes Measured</th>
<th>Efficacy Comparisons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxidized cellulose powder</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Al-Shaikh (2014)\cite{32}</td>
<td>50</td>
<td>Intrapatient</td>
<td>Comfort: VAS&lt;br&gt;Hemostasis: bleeding score&lt;br&gt;Wound healing: adhesions</td>
<td>&gt; PVA for hemostasis; = for wound healing</td>
</tr>
<tr>
<td>Kastl (2009)\cite{33}</td>
<td>41</td>
<td>Intrapatient</td>
<td>Hemostasis: intraoperative Boezaart scale, postoperative bleeding score</td>
<td>= No pack for hemostasis</td>
</tr>
<tr>
<td>Kastl (2009)\cite{34}</td>
<td>26</td>
<td>Intrapatient</td>
<td>Wound healing: adhesions, crusting</td>
<td>= No pack for wound healing</td>
</tr>
<tr>
<td>Szczygelski (2010)\cite{35}</td>
<td>60</td>
<td>Interpatient</td>
<td>Comfort: VAS&lt;br&gt;Hemostasis: postoperative bleeding requiring repacking&lt;br&gt;Wound healing: adhesions</td>
<td>= PVA sheathed in latex glove finger for wound healing and hemostasis; &gt; for comfort</td>
</tr>
<tr>
<td>Carboxymethylcellulose</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Akiyama (2014)\cite{36}</td>
<td>44</td>
<td>Interpatient</td>
<td>Comfort: VAS&lt;br&gt;Hemostasis: postoperative bleeding requiring repacking</td>
<td>= Chitin-coated gauze for comfort and hemostasis</td>
</tr>
<tr>
<td>Antisdel (2009)\cite{37}</td>
<td>40</td>
<td>Intrapatient</td>
<td>Comfort: VAS&lt;br&gt;Hemostasis: bleeding score on postoperative day 1</td>
<td>&gt; No pack for hemostasis; = for comfort</td>
</tr>
<tr>
<td>Antisdel (2011)\cite{38}</td>
<td>40</td>
<td>Intrapatient</td>
<td>Wound healing: adhesions, edema&lt;br&gt;Hemostasis: intraoperative blood loss amount</td>
<td>= No pack for wound healing</td>
</tr>
<tr>
<td>Beyea (2011)\cite{39}</td>
<td>18</td>
<td>Interpatient</td>
<td></td>
<td>= Flowable gelatin-thrombin admixture for hemostasis</td>
</tr>
<tr>
<td>Valentine (2010)\cite{39}</td>
<td>40</td>
<td>Intrapatient</td>
<td>Chitosan gel&lt;br&gt;Hemostasis: Boezaart bleeding scale&lt;br&gt;Wound healing: edema, crusts, granulation, adhesions</td>
<td>&gt; No pack for wound healing and hemostasis; = for comfort</td>
</tr>
<tr>
<td>Ngoc Ha (2013)\cite{40}</td>
<td>26</td>
<td>Intrapatient</td>
<td>Wound healing: sinus ostial patency</td>
<td>&gt; No pack for wound healing</td>
</tr>
<tr>
<td>Microporous polysaccharide hemospheres</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antisdel (2009)\cite{37}</td>
<td>40</td>
<td>Intrapatient</td>
<td>Comfort: VAS&lt;br&gt;Hemostasis: bleeding score on postoperative day 1</td>
<td>&gt; No pack for hemostasis; = for comfort</td>
</tr>
<tr>
<td>Antisdel (2011)\cite{38}</td>
<td>40</td>
<td>Intrapatient</td>
<td>Wound healing: adhesions, edema&lt;br&gt;Hemostasis: intraoperative blood loss amount</td>
<td>= No pack for wound healing</td>
</tr>
<tr>
<td>Beyea (2011)\cite{39}</td>
<td>18</td>
<td>Interpatient</td>
<td></td>
<td>= Flowable gelatin-thrombin admixture for hemostasis</td>
</tr>
<tr>
<td>Polyurethane foam</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shoman (2009)\cite{41}</td>
<td>30</td>
<td>Intrapatient</td>
<td>Comfort: VAS&lt;br&gt;Hemostasis: bleeding scale&lt;br&gt;Wound healing: presence of adhesions, mucosal edema</td>
<td>= PVA sheathed in vinyl glove finger for hemostasis, wound healing, comfort</td>
</tr>
<tr>
<td>Verim (2014)\cite{42}</td>
<td>56</td>
<td>Intrapatient</td>
<td>Wound healing: Lund-Kennedy Comfort: VAS&lt;br&gt;</td>
<td>= PVA for wound healing; &gt; for comfort</td>
</tr>
<tr>
<td>Thermosensitive PEG poloxamer</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Song (2013)\cite{43}</td>
<td>54</td>
<td>Intrapatient</td>
<td>Wound healing: reepithelialization, = Hyaluronic acid for wound healing adhesion, crusts, edema</td>
<td>= Hyaluronic acid for wound healing</td>
</tr>
</tbody>
</table>

Abbreviations: PEG, polyethylene glycol; PVA, polyvinyl acetate; VAS, visual analog scale.

\(^a\)Equal sign (=) denotes no statistical significance (\(P > .05\)) in performance between the biomaterial and the comparison; greater-than sign (>) indicates that the biomaterial performed significantly better (\(P < .05\)) than the comparison; and lesser-than sign (<) indicates that the biomaterial performed significantly worse (\(P < .05\)) than the comparison.
postoperatively and compared with preoperative dimensions. Chitosan gel significantly improved the degree of patency for all ostia when compared with unpacked control.

There are currently 2 purely synthetic absorbable biomaterials on the market: PUF (Nasopore; Stryker, Hamilton, Canada) and polyethylene glycol thermosensitive poloxamer (TPX; Samyang Co, Seoul, South Korea). Nasopore is a freeze-dried PUF with hydrophilic properties that allow it to function as a meatal spacer while permitting fragmentation. It has performed inconsistently with respect to postoperative hemostasis and synechia prevention. Two trials exist comparing PUF and PVA. Shoman et al showed that there was no significant difference between PUF and vinyl glove–sheathed PVA in terms of mucosal healing nor with regard to pain and bleeding on pack removal.41 However, given that the PUF pack was suctioned out at 1 week postoperatively, the product was arguably not used as intended. Verim et al showed no difference between PUF and PVA, indicating that mucosal healing and reepithelialization, although PUF caused significantly less pain and nasal obstruction.42 PUF has not been trialed against negative control.

A TPX composed of polyethylene glycol has been studied as an antiadhesions agent given its hydrophilic, biodegradable properties. In a trial by Song et al,43 all patients received PVA following ESS, and subsequent to its removal at 24 hours, each nasal cavity was then randomized to receive either TPX or a cross-linked HA pack. The authors found no significant difference between TPX and HA with respect to adhesion formation. No studies have been carried out to date assessing the hemostatic abilities of this product.

Plant-based biopolymers, such as CMC, MPH, and oxidized cellulose, function primarily as hemostatic agents. The evidence supports this function for MPH and powered oxidized cellulose but is less robust for CMC gel and mesh in ESS. Chitosan gel appears to be an effective hemostatic agent, with evidence supporting its antiadhesion properties as well. Conclusions regarding the hemostatic and antiadhesion abilities of PUF as compared with PVA are mixed, while initial studies on TPX have supported its antiadhesion properties and demonstrate close similarities to HA.

**Steroid Delivery Compounds**

While the above biomaterials may function to prevent postoperative hemorrhage and improve wound healing via structural support of the middle meatus after ESS, none of these products ameliorate underlying mucosal inflammation. CRS is a disease primarily of inflammation.44 ESS serves as effective therapy for patients who fail medical therapy by aerating the sinus cavities; removing polyps, mucus, and other debris; and restoring mucociliary clearance. While oral and topical steroids remain critical components of the medical management of CRS, each has its limitations.

Oral steroids are commonly used by otolaryngologists for acute sinusitis exacerbations45 but are poorly suited for long-term therapy due to their systemic side effects, such as metabolic derangements, psychiatric destabilization, and negative effects on bone health.46 Topical steroids currently play a vital role in maintenance therapy for patients with CRS, due to their ease of use and tolerability. However, these medications may not be effective for patients with inflammation localized to the frontal or sphenoid sinuses, anatomic regions that are difficult to reach with sprays and irrigations. In addition, patients who have issues with compliance are not ideally suited for long-term daily medication treatment. Furthermore, the duration and concentration of steroid in the nasal mucosa are variable and unknown.47 For these reasons, a significant effort has been directed toward the development of a drug-eluting biomaterial that could be inserted post-ESS. The theoretical advantages of such a drug delivery system include a controlled, sustained release of medication to the affected mucosa, as well as adhesion prevention and maintenance of ostial patency.

A variety of different biomaterials, both nonabsorbable and absorbable, have been investigated as possible drug delivery systems (Table 6). Chang and colleagues experimented with PVA soaked in budesonide, gentamicin, or Manuka honey, each of which was compared with dry PVA.48 The packs were inserted post-ESS and removed on day 7 following surgery. Assessed outcomes included tissue inflammation as determined by histology, endoscopic score of mucosal healing, and pain on pack removal. All 3 soaked interventions did not reach significant difference in any of these outcomes, although budesonide-soaked Merocel trended toward decreased inflammation and decreased pain on removal.

CMC foam (Stammberger Sinu-Foam; Arthrocare, Austin, Texas) has also been studied as a steroid delivery system.49 In this trial, CMC was impregnated with dexamethasone and inserted after ESS. Mucosal healing was evaluated endoscopically at various time points with a Lund-Kennedy score. The authors found no significant difference in endoscopic scores between steroid-soaked CMC and saline-soaked CMC, thus arguing against the ability of this system to reduce inflammation.

Similar experiments have also been carried out with PUF. Côté and Wright compared triamcinolone-soaked PUF with saline control inserted after ESS.50 As determined via endoscopic scores, nasal cavities receiving triamcinolone-soaked PUF had significantly improved wound healing at 7 days, 14 days, 3 months, and 6 months when compared with the saline control, suggesting that steroid-soaked PUF may be effective at reducing local inflammation after ESS.

An expandable polylactide-co-glycolide polymer impregnated with mometasone furoate (Propel; Intersect ENT, Palo Alto, California) has been studied as a steroid-releasing implant. Each implant contains 370 μg of steroid medication, 90% of which is released by day 13; 85% of the implant is reabsorbed by day 30. Two prospective trials investigated the efficacy of this steroid-releasing implant, the first of which was conducted by Murr et al.51 In this multicenter study, patients undergoing bilateral ESS had 1 nasal cavity randomized to receive the steroid-containing implant. The contralateral cavity received an implant without steroid. The cavities that received the steroid implant had significant reductions in inflammation, frequency of polyp formation, and incidence of adhesions when compared with nasal cavities that received the untreated implant. The authors reported no detectable
systemic steroid exposure. In a similar study design, Marple et al focused on how the steroid-releasing implant affected postoperative interventions. Compared with the intrapatient negative control cavity, the authors showed a significant relative reduction in overall postoperative interventions, as well as a significant decrease in incidence of frank polyposis.

Preliminary evidence suggests improved wound healing and reduced inflammation when steroid-releasing implants are used post-ESS. Various steroid-soaked biodegradable foam applications appear less efficacious in reducing inflammation but might represent a less expensive alternative. Further investigations need to be performed before this new technology can be considered for widespread use, addressing such issues as long-term results, cost-effectiveness, and relative efficacy when compared with other commonly used nasal biomaterials and postoperative regimens.

**Implications for Practice**

As evidenced by this review, numerous commercially available sinonasal biomaterials have been evaluated in the setting of sinus surgery (Figures 2 and 3). These products have been variably studied to characterize their ability to perform critical functions—namely, postoperative hemostasis, postoperative adhesion prevention, and most recently, postoperative control of inflammation. While this review included only controlled randomized studies (level 2b) conducted in humans, certain difficulties were encountered that hampered our ability to evaluate these products objectively. Differing metrics and methods of measuring outcomes made comparing relative efficacy among studies unwieldy and impaired an evaluation based on descriptive statistics or meta-analysis. Further confounding this issue was the comparison that the investigators chose to evaluate a product against—that is, whether to compare a certain biomaterial with a different one or with unpacked control. It is interesting to note that PV A appears to be the most popular “standard” to which other biomaterials are compared, and yet, there are no published studies evaluating PV A against an unpacked control.

This review was not designed with the goal of selecting a superior biomaterial for ESS, nor is this likely possible given the heterogeneity among available studies. However, it is still possible to identify trends and derive meaningful conclusions from the evidence presented here. While certain nonabsorbable biomaterials (eg, PVA) have long been used for packing post-ESS due to their good hemostatic abilities, it is clear that the need to remove the pack postoperatively is a major drawback that most patients and surgeons would like to avoid given the pain and potential risk of bleeding. This—paired with

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**Table 6. Steroid Delivery Compounds.**

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Size, n</th>
<th>Comparison Method</th>
<th>Outcomes Measured</th>
<th>Efficacy Comparisons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chang (2011)</td>
<td>48</td>
<td>Intrapatient</td>
<td>Comfort: VAS on pack removal</td>
<td>= Unmedicated PVA for comfort, wound healing, and anti-inflammation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Wound healing: endoscopic scores</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Anti-inflammation: mucosal biopsy</td>
<td></td>
</tr>
<tr>
<td>Rudmik (2012)</td>
<td>36</td>
<td>Interpatient</td>
<td>Wound healing: Lund-Kennedy</td>
<td>= Unmedicated CMC for wound healing</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Côté (2010)</td>
<td>19</td>
<td>Intrapatient</td>
<td>Wound healing: Lund-Kennedy and POSE scores</td>
<td>&gt; Unmedicated polyurethane foam at 1 wk, 2 wk, 3 mo, 6 mo postoperatively</td>
</tr>
<tr>
<td>Murr (2011)</td>
<td>38</td>
<td>Intrapatient</td>
<td>Anti-inflammation: VAS of inflammation; polypoid change</td>
<td>&gt; Unmedicated implant for anti-inflammation and wound healing</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Wound healing: middle turbinate position, adhesions</td>
<td></td>
</tr>
<tr>
<td>Marple (2012)</td>
<td>105</td>
<td>Intrapatient</td>
<td>Anti-inflammation: VAS of inflammation; polypoid change</td>
<td>&gt; Unmedicated implant for anti-inflammation, wound healing, and need for postoperative interventions</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Wound healing: middle turbinate position, adhesions</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Need for postoperative interventions</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CMC, carboxymethylcellulose; POSE, perioperative sinus endoscopic; PVA, polyvinyl acetate; VAS, visual analog scale.

*Equal sign (=) denotes no statistical significance (P > .05) in the measured outcomes between the biomaterial and the comparison; greater-than sign (>) indicates that the biomaterial yielded a significantly better (P < .05) outcome than the comparison; and lesser-than sign (<) indicates that the biomaterial produced significantly worse outcomes (P < .05) than the comparison.*
other previously discussed complications, such as aspiration and toxic shock syndrome—has amplified the need for an absorbable biomaterial that can effectively achieve intraoperative and postoperative hemostasis while also promoting optimal wound healing conditions.

Currently available absorbable biomaterials have attained these goals to varying degrees. Collagen-based biomaterials seem to be generally effective in achieving hemostasis, especially when mixed with a coagulation cascade participant, such as thrombin. However, the evidence supporting the wound healing capabilities of these compounds is weak, and questions remain whether components such as thrombin act in a proinflammatory fashion to stimulate granulation tissue and synechiae formation. Conversely, HA biomaterials seem to promote wound healing as a class, yet their hemostatic abilities have not been well demonstrated. Fibrin glue shows promising results in early trials, although drawbacks unique to this product (eg, risk for viral transmission) have limited its popularity somewhat. Among the natural and synthetic biopolymers, chitosan gel appears to stand out as a material that exhibits both hemostatic and wound healing properties.

It is interesting to note the number of studies that found no statistical difference in hemostasis or wound healing between packing (removable or absorbable biomaterials) and no packing after ESS. There seem to be 2 possible explanations for this trend—either that most nasal biomaterials are ineffective at preventing these complications or that as a routine practice, packing post-ESS may be unnecessary for most patients. Indeed, the habitual use of nasal packing for postoperative hemostasis has been called into question by a number of studies. Eliashar et al found that 92% of patients did not require any nasal packing whatsoever for hemostasis post-ESS.53 In contrast, postoperative synechia formation is one of the most common minor complications of ESS and can have potentially negative effects on surgical outcomes. While certain biomaterials may work to promote reepithelialization or act as barriers for adhesion prevention, there is simply no replacement for meticulous surgical technique.

Finally, surgery does not address the underlying pathophysiology of CRS, which is one of persistent inflammation. Addressing this issue is a relatively new trend in rhinologic biomaterial development. Steroid-releasing implants have shown promising results so far, with reduced rates of adhesion formation and decreased requirements for postoperative interventions. However, it is still too early to predict the long-term benefits that these stents may have on disease course or how they compare to other forms of nasal packing.

Biomaterials continue to play a vital role in rhinology, as they have for the past 60 years. Ideally, a rhinologic biomaterial would decrease postoperative bleeding, improve healing, and decrease inflammation after ESS. A large number of biomaterials with differing properties have been studied to varying degrees. Certain products do seem to be more effective than others in reducing postoperative complications and producing better outcomes, although the heterogeneity among studies does not allow for selection of a superior biomaterial for ESS. While nonabsorbable biomaterials are still effective in providing certain important functions, newer, absorbable substances may be just as effective and avoid the morbidity associated with packing removal. Given that CRS is a disease characterized primarily by inflammation, drug-eluting systems may play an increasingly important role in preventing disease recurrence and improving outcomes. However, more studies are needed on this newer technology before it can be considered for widespread use. As evidenced by the growing number of products released over the past decade, there will likely be many more exciting developments to come in this continually expanding field.

**Author Contributions**

Conner J. Massey, data analysis, drafting, final approval, accountability for all aspects of the work; Jeffrey D. Suh, data analysis,
drafting, final approval, accountability for all aspects of the work; Belachew Tessema, data analysis, drafting, final approval, accountability for all aspects of the work; Stacey T. Gray, data analysis, drafting, final approval, accountability for all aspects of the work; Ameet Singh, data analysis, drafting, final approval, accountability for all aspects of the work.

Disclosures

Competing interests: Belachew Tessema, speaker for Intersect ENT; Ameet Singh, primary investigator for Intersect study for products not currently on the market. Financial support provided to Dr. Singh’s institution—not to Dr. Singh.

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References


