Biomaterials in the Treatment of Anal Fistula: Hope or Hype?

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Abstract

Keywords

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- bio-LIFT
- stem cells

Anal fistula (AF) presents a chronic problem for patients and colorectal surgeons alike. Surgical treatment may result in impairment of continence and long-term risk of recurrence. Treatment options for AFs vary according to their location and complexity. The ideal approach should result in low recurrence rates and minimal impact on continence. New technical approaches involving biologically derived products such as biological mesh, fibrin glue, fistula plug, and stem cells have been applied in the treatment of AF to improve outcomes and decrease recurrence rates and the risk of fecal incontinence. In this review, we will highlight the current evidence and describe our personal experience with these novel approaches.

CME Objectives: After reading this article, the reader should be able to understand the role of biologic and synthetic materials for treatment of anal fistula.

An anal fistula (AF) is an abnormal communication between the anal glands and the perianal skin. Reliable data on incidence of AF in the general population are not available, but in an epidemiologic study performed in four European countries (England, Germany, Italy, and Spain), the incidence reported was between 12 and 28 per 100,000.¹ The disease presents predominantly in the third and fourth decades of life² and it is more common in men than in women (12.3 vs. 5.6 per 100,000 cases).¹ According to the cryptoglandular hypothesis, intersphincteric gland infection is the initiating event in the formation of AF³ and it usually develops in approximately one-third of patients who presents with a perirectal abscess. In a series⁴ of 170 patients with no history of previous AF followed for an average of 99 months after abscess drainage, a fistula occurred in 37% and recurrent abscess was reported in an additional 10%. A retrospective cohort study⁵ of 148 patients with anorectal abscesses showed again a 37% rate of fistula formation. Patients younger than 40 years had a higher likelihood of developing an AF during a mean follow-up of 38 months. Any recurrent abscess

presenting at the same site should raise the suspicion of a fistula and be treated as such. There are several other causes of atypical/complicated abscess and fistula such as inflammatory bowel disease, fungal infection, mycobacterial infection, neoplasm, and trauma. Fistulas that are secondary to these processes are classified as complex and require the use of nonstandard methods of management.

In 1976, Parks et al⁶ classified AF in four different types according to their passage through the sphincteric planes: intersphincteric, transsphincteric, suprasphincteric, and extrasphincteric (► **Table 1**). The most common presentation is intersphincteric, followed by transsphincteric. The remaining types are relatively uncommon. This is the most widely used classification.⁷ However, a more practical approach is based on whether the internal opening is high or low within the anal canal. Low transsphincteric fistulas involve the lower third of the external anal sphincter mechanism and are generally treated by fistulotomy with a high success rate for cure. High transsphincteric fistulas involving the upper two-thirds of the external sphincter remain a surgical challenge because incontinence may result from the division of muscle involving more than one-third of the sphincter. The basic principles in the treatment of anorectal abscess and AF include eradication of perineal sepsis, complete

Table 1 Anal fistula: Parks' classification

<i>Intersphincteric</i> : The tract forms between the internal and external sphincter muscles and travels through the intersphincteric plane, opening adjacent to the anus
<i>Transsphincteric</i> : The tract forms between the internal and external sphincter muscles, passing from the intersphincteric plane through the external sphincter into the ischioanal fossa
<i>Suprasphincteric</i> : The tract forms between the internal and external sphincter muscles. The fistula travels upward, passing over the puborectal muscle, and then downward again between the puborectal and levator ani muscles, opening adjacent to the anus
<i>Extrasphincteric</i> : The tract forms outside the external sphincter complex, passing from the perianal skin, through the ischioanal fat and levator muscles, into the rectum.

healing of the internal and external openings without recurrence, elimination of drainage, edema, and other symptoms, and preservation of fecal continence.

Patients with an anal abscess usually present with pain, erythema, and fluctuance, making the diagnosis of the different types of fistula challenging. Specifically, a rectal exam often needs to be deferred for an exam under anesthesia due to discomfort. In complex and recurrent situations such as in high transsphincteric fistulas, endorectal ultrasound (ERUS) with injection of hydrogen peroxide through the external openings, CT scans, and MRI can be helpful to define the anatomy and plan treatment.

Traditional surgical treatment options include fistulotomy, fistulectomy, and cutting seton. These surgical modalities are associated with prolonged postoperative pain and wound healing, but more importantly a relatively high fecal incontinence rate.^{8–10} In fact, cutting setons are associated with healing rates of approximately 80 to 100% but fecal incontinence has been reported in as many as 60% of patients.^{11–13} Fistulotomy also produces healing rates between 75 and 100%¹³ but impairs continence in up to 60% of patients, especially those with a complex fistula.^{14–16} In the past 30 years, two sphincter-sparing techniques, such as ligation of the intersphincteric fistula tract (LIFT), and transanal advancement flap repair (TAFR) have been proposed. Flap repair has a success rate of approximately 57 to 90%.¹⁴ However, the reported rate of fecal incontinence after this procedure has unexpectedly been as high as 40% in preliminary studies.^{11,17,18} More recent studies have showed a more reasonable incontinence rate between 0 and 23%.^{19–22}

LIFT, which was first described in 2007,²³ has not been associated with fecal incontinence in published series and healing rates with this technique range between 57 and 94%.^{23–28} Given the less than ideal results with traditional approaches, new biosynthetic tools such as biologic mesh, fibrin glue, fistula plugs, and stem cells have been proposed to treat AF to decrease incontinence rates and increase healing with limited morbidity.

Fibrin Glue

Initially introduced by Hjortrup et al²⁹ in 1991 to treat AF, fibrin glue is a minimally invasive option in the armamentarium of the colorectal surgeon. It is a mixture of fibrinogen, thrombin, and calcium ions, which when combined form a soluble clot, as fibrinogen is cleaved into fibrin. This soluble

clot is transformed into an insoluble, stable clot as the thrombin and calcium activate factor XIII. The glue is infused into the fistulous tract with the idea that collagen formation within the tract would stimulate healing. It also stimulates the migration and proliferation of fibroblasts and pluripotent endothelial cells to heal the fistula. Between days 7 and 14, plasmin that is present in the surrounding tissue lyses the fibrin clot as the tract is replaced by synthesized collagen.³⁰ Various biologic glues have been evaluated within the last decades to assess their ability to seal the fistula tract after curettage.^{31,32} Autologous cryoprecipitate,³³ reconstituted bovine thrombin,³⁴ and recently donor plasma³⁵ have been used to seal the fistula tract. BioGlue Surgical Adhesive (CryoLife, Inc., Kennesaw, GA) is composed of purified bovine serum albumin and glutaraldehyde and provided a four time stronger bond than fibrin glue, remaining intact for up to 2 years. However, there has not been a preparation that has been shown to have better healing rates or fewer complications.³⁶

The procedure is simple and reproducible with minimal learning curve, in contrast to traditional procedures. Both openings of the tract are identified and the tract is mechanically curetted and irrigated with normal saline or hydrogen peroxide. The double-barreled syringe, containing the two components of the glue, depending on the preparation used, is inserted through the external opening until the tip is seen at the internal opening. The syringe is depressed, which mixes the two components as they are injected into the canal while withdrawing the syringe. The tract is filled completely until a blob of glue is seen at the external opening. The glue is allowed to set for 30 to 60 seconds to form its stable clot. Different investigators have advocated suturing the internal or external opening around the bead of glue,³⁷ although others have demonstrated no statistically significant benefits.^{38,39} Data on preoperative bowel preparation and the use of perioperative antibiotics are widely variable with none shown to confer a benefit.^{38,40} The authors' experience with this technique has been variable. It appears that the presence of persistent sepsis significantly impairs success rates. The authors therefore advocate placement of a loose seton before proceeding with fibrin glue injection. The etiology of the fistula (i.e., primary vs. secondary to Crohn disease, cancer, radiation, etc.) also is a significant factor in outcome. Overall, the technique is quite simple and morbidity minimal.

Early studies reported excellent results with a success rate ranged from 68 to 85%.^{31,41,42} These results have not been replicated and did not seem to be durable with subsequent reviews and follow-up studies reporting success rates as low as less than 55%.^{43–45} In randomized studies,^{34,46,47} healing rates range from 21 to 69% because of the complexity of the disease and the viability in surgical technique (► **Table 2**). Sentovich⁴⁸ reported a success rate of 69% with a follow-up of 22 months. An important issue with the studies is the length of follow-up. It appears that most failures occur within 6 months.⁴⁰ While some investigators advocate as long as 2 years for follow-up, and that may be correct when dealing with Crohn disease patients,³⁰ the minimum should be no less than 6 months.^{38,42,48}

de la Portilla et al⁴⁹ used BioGlue to seal the fistulous tract after curettage in 14 patients. They found a healing rate of 50% with a mean follow-up of 14 months. In striking contrast, Abbas and Tejrani⁵⁰ reported acute anal sepsis in four of their six patients treated with BioGlue and therefore they concluded that BioGlue should not be used to treat cryptoglandular AF.

Reasons for failure of the glue have been postulated by many authors, with dislodgement being the most common. For this reason, some surgeons would advise their patients not to take sitz baths and to avoid vigorous exercise and excessive straining (some are given stool softeners or put on a liquid diet).³⁸ There are no data to support such a practice. Recurrence of AF after fibrin glue application has been attributed to inadequate preparation of the curetting and

irrigation³⁰ and the natural course of secondary disease. Another cause of failure is recurrent sepsis, as has been the authors' experience, and it is reported to be as high as 5%.⁴⁰ This is believed to be caused by incomplete tract filling with glue, thus representing a technical error,³⁴ or, once again, by incomplete tract preparation before injection of the glue.^{34,42} To theoretically decrease septic complications, antibiotics have been mixed with the glue,⁴³ and other authors irrigate the tract with antibiotics before glue injection.⁵¹ The authors have no experience with this approach. Debate persists regarding the length of the tract and its impact on success of fibrin glue. Patrly et al⁵¹ and Lindsey et al³⁴ had better results with longer tracts, attributing this to the risk of glue leakage from shorter tracts (< 3.5 cm). On the contrary, Sentovich,^{42,48} Cintron et al,³⁶ and Maralcan et al⁵² had greater success with shorter tracts. To date, there is no consensus on this issue and therefore tract length is not an inclusion/exclusion criterion. On the other hand, it is clear that better results are obtained with glue in primary AF. Sixty-three percent of failure was noted in recurrent, surgically treated AF, even more likely among the high transsphincteric AFs ($p < 0.05$).⁵³ Similar results with recurrent AFs were reported by Loungrath et al⁵⁴ (62%) and by Park et al⁴¹ (50%) in their trials. Several explanations have been proposed including the difficulty in finding the original tract, the presence of side branches, dense fibrosis, and adhesions that may prevent healing and facilitate dislodgment of the clot.

Recently, Alexander et al⁵⁵ conducted a pilot study to assess whether obliteration of the fistula tract with BioGlue may improve healing rates of TAFR. This procedure includes cleaning and debridement of the fistula tract, mobilization of a well-vascularized rectal mucosal or anodermal flap, instillation of the glue into the tract, and the coverage of the internal opening with or without closure of the tract before coverage. In his consecutive series of eight patients undergoing TAFR with concomitant instillation of BioGlue, fistula healing was observed in only one of these patients. The failures were due primarily to septic complications. Other authors have used fibrin glue as an adjunct to flap repair with similar results.

Mizrahi et al⁵⁶ were the first to report the outcome of this combined therapy. They observed fistula healing in only 6 of their 12 patients (50%). A few years later, Ellis et al⁴⁶ conducted a randomized controlled study among 35 patients of whom 17 underwent concomitant instillation of fibrin glue. The healing rate in this group was 41.1 versus 83.3% in the group undergoing TAFR alone. Recently, van Koperen et al¹⁸ conducted a retrospective study to assess the additional value of fibrin glue in combination with flap repair. A series of 26 patients underwent a flap repair with concomitant instillation of fibrin glue. The failure rate in this series was 46%, which was much higher than the failure rate of 17% among the patients who underwent flap repair alone. The results of these studies are comparable to the outcome of Alexander's pilot study, indicating that neither the instillation of fibrin glue nor the use of BioGlue is beneficial for patients who undergo a flap repair.

Table 2 Results of fibrin glue studies

Author	Year	No. of subjects	Success rate (%)	Follow-up interval (mo)
Cintron et al ³¹	1999	26	81	3.5
Cintron et al ³⁶	2000	79	61	18
Patrly et al ⁵¹	2000	69	74	28
Park et al ⁴¹	2000	29	68	6
Sentovich ⁴²	2001	20	85	10
Lindsey et al ³⁴	2002	42	63	4
Sentovich ⁴⁸	2003	48	69	22
Loungrath et al ⁵⁴	2004	39	31	26
Zmora et al ⁴³	2005	60	53	6
Gisbertz et al ³⁷	2005	27	33	7
Singer et al ⁴⁷	2005	75	21 ^a	27
Maralcan et al ⁵²	2006	36	83	12
Ellis and Clark ⁴⁶	2006	28	54	22
Dietz ³⁹	2006	39	31	23
Witte et al ⁵⁷	2007	34	55	7
Adams et al ⁴⁰	2008	36	61	3
de Parades et al ³⁸	2010	30	50	12

^aOnly the group that received intra-adhesive antibiotics.

In summary, the use of glue has minimal impact on continence,³⁹ morbidity is minimal, and in the case of failure glue does not preclude subsequent treatments, such as repeat glue injection and conventional fistula treatments.⁵⁷ Despite its limited success rates reported, glue offers a less invasive option for first-line fistula treatment.

Fistula Plug

The concept of a plug was first introduced in 2006 by Robb et al⁵⁸ and Johnson et al⁵⁹ with the idea that securing the plug into the primary opening of a fistula tract could close the tract more reliably than previous procedures, without compromising continence because the sphincters were not incised or divided. The Surgisis (COOK Biotech, West Lafayette, IN) is a plug made of lyophilized porcine small intestinal submucosa, which has an inherent resistance of infection, generates no foreign body or giant cell reaction, and is repopulated by host cell tissue within 3 months.⁶⁰ Its conical shape allows for added mechanical stability as high pressures within the anal canal maintain the plug in its proper position, avoiding dislodgement during straining.

The critical steps of the procedure are as follows: the plug must be rehydrated first (►Fig. 1), usually in a 0.9% normal saline solution, before insertion; it must be inserted in the internal opening and then pulled through the tract until light resistance is met (►Fig. 2); and it must be sutured securely in the primary opening. Various suture types have been used for securing the plug. Suturing the plug in place supposedly reduces the incidence of dislodgement and consequently failure rate. Trimming excess plug from the external opening at the skin level and irrigating the tract with hydrogen peroxide before insertion are options during the procedure. The external opening must be partially open at the end of the procedure as this is the path that allows drainage and prevents a closed-space infection.⁶¹ The concept of the loose seton maturing the tract, making the wall more fibrotic, which results in increased healing, has been proposed by

Fig. 1 This image shows the porcine fistula plug undergoing hydration. Note that a Vicryl suture has been placed through one of the distal perforations before hydration. Contrary to initial recommendations, the plug need not undergo prolonged hydration, and may simply be submerged under saline solution for 30–60 seconds.

Fig. 2 This image shows the plug being pulled through the internal opening using the previously placed Vicryl suture.

several investigators^{62,63} and is recommended by a recent consensus.⁶⁴ It has also been shown to minimize sepsis and facilitate fistula closure when used in conjunction with other procedures, such as an advancement flap.⁶⁵ However, O'Connor et al⁶⁶ and Champagne et al⁶⁷ found no correlation between seton placement and increasing healing rates. They stated that the presence of the seton resulted in a technically easier insertion of the plug because it helped define the anatomy of the primary and secondary opening and helped "pull" the plug through the tract. Use of a fistula brush to gently debride granulation tissue from the tract has also been found to be helpful by some (►Fig. 3). The use of mechanical bowel preparation, the use of preoperative antibiotics, and patient positioning are dictated by surgeon's preferences and vary significantly.⁶⁵ In the authors' experience, this is the preferred approach to patients that are not candidates for fistulotomy or advancement flap. The procedure is relatively straightforward, it is associated with minimal complications, and it does not prevent subsequent intervention and more aggressive treatment.

Fig. 3 The newest generation fistula plug kit contains a flexible soft brush that can be used to gently debride granulation tissue from the tract. It may also be used to guide the Vicryl suture through the tract after brushing.

Healing rates for the collagen plug, including two randomized trials,^{68,69} have ranged between 20 and 92% (► **Table 3**). A review article from Garg et al⁷⁰ examined the literature up to 2009. They consider the data too heterogeneous to allow weighted comparisons, and reported a range of success between 24 and 92%, with a follow-up of 3.5 to 12 months. In complex AFs, success rates were 35 to 87%. The overall tract closure rate ranged from 61 to 90%. In patients with recurrent fistula, the success rate ranged from 13 to 71%, while in those with Crohn disease it was 29 to 86%. The definition of success, healing, and tract closure widely differs between studies, thus making a systematic review practically impossible.

Two randomized controlled trials compared TAFR to fistula plug in patients with complex AF. Van Koperen et al⁶⁹ found no statistically significant differences between groups at 11 months in 60 patients, but reported high recurrence rates, with only 29% healing with the fistula plug and 48% healing with TAFR. The trial performed by Ortiz et al⁶⁸ in 31 patients with complex AFs was halted due to poor performance with the fistula plug, with only 20% of patients healing at 1 year versus 87.5% in the TAFR group.

The issue of cost of the bioprosthesis material also ought to be considered. Adamina et al⁷¹ performed a cost analysis comparing bioprosthesis plug to TAFR. Based solely on commercial costs, one plug represented an additional \$1,021 in costs per fistula treated. However, the total cost was lower for fistula plug than TAFR mainly because of the shorter hospitalization period.

One of the main causes of treatment failure is plug migration or extrusion,^{11,72} as in the case of fibrin glue, which has been reported to occur in 4 to 41% of patients.⁷⁰ Plug dislodgment has also been noted in the studies looking at other "biological" fistula plugs (made from human or porcine cellular dermal matrix) that have been published, with the reported rates between 21⁷³ and 11%.⁷⁴

Table 3 Results of collagen fistula plug studies

Author	Year	No. of subjects	Success rate (%)	Follow-up interval (mo)
Johnson et al ⁵⁹	2006	25	87	3
Champagne et al ⁶⁷	2006	46	83	12
O'Connor et al ⁶⁶	2006	20	80	10
Ellis ⁹²	2007	13	92	6
Ky et al ⁷	2008	45	55	6.5
Christoforidis et al ⁶²	2008	47	43	6.5
Safar et al ⁷⁵	2009	36	14	4.2
Ortiz et al ⁶⁸	2009	15	20	12
El-Gazzaz et al ⁶³	2010	33	25	7.4
van Koperen et al ⁶⁹	2011	31	29	11

Steps proposed to prevent dislodgement include adequately securing the plug to the primary opening, ensuring it is not dangling,⁶¹ and instructing the patient to avoid strenuous activity for at least 2 weeks.^{64,66,67} Champagne et al⁶⁷ noticed plug dislodgement as the primary cause of failure in their study, prompting them to use a 2–0 absorbable suture for anchoring to provide a stronger securing suture. Avoidance of securing the plug at the external opening has been suggested because it would cause tension on the suture at the internal opening, leading to dislodgement. Another cause of dislodgement is enlarging the fistula tract, which has been done by curetting or overdebridement of the tract. Multiple fistula tracts are often associated with a higher failure rate caused by the persistence of one or more tracts, usually those not treated by the plug at the time of the initial procedure.⁶⁶ These tracts are candidates for plug insertion at a later date. The importance of ensuring that the secondary opening remains open as a site for drainage must be overemphasized because this prevents the formation of abscesses, which is not only a cause of failure but also a cause of significant morbidity and potential mortality in these patients due to perineal sepsis.⁷⁵ Many of the available published studies were performed using the original version of the biologic fistula plug, which has undergone two modifications. We do not have data available on use of the most recent modification of the device (► **Fig. 4**). Technique varies widely in the published literature, which may account for widely variable success rates. The manufacturer suggests raising a small flap of rectal mucosa near the internal opening, securing of the head of the plug to the underlying musculature at four points, and coverage of the plug head with the mucosal flap.

Bioabsorbable Synthetic Fistula Plug

The bioabsorbable synthetic fistula plug (GORE BIO-A Fistula Plug, W.L. Gore & Associates, Flagstaff, AZ) is made of a polymer-based prosthetic material (polyglycolic acid/trimethylene carbonate; PGA/TMC) that is gradually absorbed by the body. The material constituting the plug has a three-dimensional, nonwoven matrix of open, interconnected pores

Fig. 4 This image shows the newest generation porcine plug.

that serve as a scaffold for tissue regeneration. After implantation, PGA/TMC undergoes hydrolytic and enzymatic degradation, leaving no synthetic material behind. The polymer scaffold is replaced by a layer of new tissue that reinforces the repair.⁷⁶ The synthetic plug device consists of a PGA/TMC disk to which several narrow PGA/TMC tubes are attached. At the time of insertion, the plug can be tailored to fit and fill the specific fistula both by trimming the diameter of the disk and by removing one or more of the tubes. The synthetic plug does not require rehydration before use.

Heydari et al,⁷⁶ in their retrospective study on cryptoglandular, transsphincteric, and intersphincteric AF treated by bioabsorbable synthetic fistula plug, reported an overall healing rate at 12 months of 69.3% confirmed by ERUS. Among patients that healed, 24.2% had healed by 3 months, 63.6% by 6 months, and 12.1% by 12 months. Moreover, no patient noted worsening of continence or other major adverse effects. Any postoperative perineal pain was short term and generally minimal.

Currently, GORE BIO-A has not yet been investigated in a randomized trial, but Buchberg et al⁷⁷ conducted a small, retrospective study that compared this device to the Cook AFP (anal fistula plug, COOK Biotech). Twelve of the patients received a total of 16 porcine plugs, and 10 were given a total of 11 synthetic plugs. The treated fistulas were either cryptoglandular ($n = 10$), traumatic ($n = 5$), or associated with HIV infection ($n = 1$). The mean follow-up time was approximately 3 months in the porcine-plug group and 2 months in the synthetic-plug group. Treatment success was achieved in 12.5% of patients in the porcine-plug group and 54.5% of those in the synthetic-plug group. The porcine plug that was used was the original first generation device without a disk to secure to the internal opening. Two of the treatment failures in the porcine-plug group were due to plug dislodgment; there were no dislodgments in the synthetic-plug group. Overall, 70% of the patients treated for a cryptoglandular fistula healed. No patient reported new onset of incontinence. The researchers did not assess or report postoperative pain. Buchberg et al⁷⁷ commented that the disk-and-tubes design of the synthetic plug optimizes its fixation at the internal opening and prevents plug migration. They also noted that the complexity of their patient population (75% of patients had 1–3 previous treatment failures) probably contributed to the low success rate in both groups.

Another published investigation of GORE BIO-A was a pilot study by de la Portilla et al⁷⁸ in 19 patients with cryptoglandular high ($n = 10$) or low ($n = 9$) transsphincteric AFs. During the 12-month follow-up period in this trial, three patients (16%) noted healing. No cases of plug migration or anal stenosis occurred. One patient had onset of fecal (urge) incontinence. The researchers speculated that their low success rate may have been associated with the lack of preoperative seton drainage in their series.

Ratto et al⁷⁹ published a retrospective study of 11 patients with a complex AF who underwent insertion of bioabsorbable synthetic plugs. Fistulas were high anterior transsphincteric in five patients and high posterior transsphincteric in six patients. All patients had a loose seton placement before plug

Table 4 Results of synthetic plug studies

Author	Year	No. of subjects	Success rate (%)	Follow-up interval (mo)
Buchberg et al ⁷⁷	2010	10	54	2
de la Portilla et al ⁷⁸	2011	19	16	12
Ratto et al ⁷⁹	2012	11	73	5
Ommer et al ¹³	2012	40	57	12
Heydari et al ⁷⁶	2013	48	69	12

insertion. The median follow-up period was 5 months. No patient reported any fecal incontinence. There was no case of early plug dislodgment. Treatment success was noted for 8 (72.7%) of 11 patients at the last follow-up appointment. The authors concluded that implanting a Gore Bio-A Fistula Plug is a simple, minimally invasive, safe, and potentially effective procedure to treat complex AF. Patient selection and preparation with seton drainage are critical factors for success.

Recently, Ommer et al¹³ published their experience with bioabsorbable synthetic plugs in the treatment of high AFs. Forty patients underwent closure of a high transsphincteric ($n = 28$) or a suprasphincteric ($n = 12$) fistula with Gore Bio-A Fistula Plug. Four patients had Crohn disease. Preoperatively, 33 patients were completely continent; 7 patients reported minor incontinence. One patient developed an abscess postoperatively requiring drainage. In two patients, the plug had fallen out within the first 2 weeks postoperatively. Six months after surgery, complete healing of the fistula had occurred in 20 patients (50.0%). Three additional fistulas healed after 7, 9, and 12 months. The overall healing rate was 57.5% (23/40). The healing rate was closely correlated to the number of previous interventions. In patients who have had only drainage of the abscess, success rate was 63.6% (14/22), whereas in patients after one or more flap fistula reconstructions the healing rate decreased to 50% (9/18). No patient reported any impairment of preoperative continence function. The authors concluded that plug placement should be considered a safe therapeutic option in high AFs, especially with a fistula tract longer than 4 cm, and previous surgery seems to have a negative impact on success rate (→ **Table 4**).

LIFT and Bio-LIFT

First described by Rojanasakul et al,²³ the LIFT procedure specifically addresses the transsphincteric fistula tract with the potential for complete regression or at the very least conversion from transsphincteric to an intersphincteric fistula amenable to fistulotomy. The technique is performed by identifying the fistula tract within the intersphincteric plane. This tract is then ligated and the internal opening is sutured closed, while the distal tract is curetted. With a median follow-up of 26 months, Liu et al⁸⁰ reported a primary healing rate of 62%, with the majority of failures occurring within the

first 6 months. Those that did fail tended to have longer tracts, which they report as a way to guide treatment. Several studies^{23–26,28} on the LIFT procedure reported no new onset incontinence. LIFT healing rate ranges from 57 to 90% in cryptoglandular disease, even in recurrent fistula.^{25,26,28} In patients undergoing primary LIFT, the healing rate is reported to be as high as 90%.⁸¹ Although the procedure holds promise, it has not undergone rigorous evaluation with long-term follow-up. When looking at the failures and recurrences after LIFT, persistence of the internal opening resulting in drainage and failure of healing of the wound in the intersphincteric incision was noted to be one of the main reasons.²⁷ This pattern of failure (poor wound healing and a persistence of fistulous disease despite intervention) is likely to be higher in patients with Crohn disease than in the general population; however, data on LIFT in Crohn disease are lacking. For this very reason, the authors have not utilized LIFT for Crohn patients, but rather have reserved this procedure for recurrent disease after failure of less invasive approaches with good results.

LIFT can be further reinforced by adding a bioprosthetic material in the intersphincteric plane to buttress the closure of the intersphincteric tract, also known as Bio-LIFT, originally described by Ellis et al.⁸² With Bio-LIFT, the bioprosthetic must overlap the closure of the fistula tract by at least 1 to 2 cm in all directions requiring more extensive dissection in the intersphincteric space. Ellis⁸² reports a success rate of 94% with Bio-LIFT in his series of 31 patients, with a 1-year follow-up. Success was defined as absence of drainage with no residual fistula tract.^{83,84} Finally, a new LIFT-plug approach for AF was described by Han et al⁸⁵ in 2012. They reported a success rate of 95.2% over a median follow-up period of 14 months, similar to the success rate of studies on the Bio-LIFT and better than those with LIFT alone. A larger randomized, multicenter prospective trial comparing Bio-LIFT with LIFT alone is in progress (NCT01478139). The authors have no experience with these two techniques.

Stem Cells

Three international groups are actively working with expanded adipose-derived stem cells (eADSC) for the treatment of AF. Autologous eADSC can be easily obtained with liposuction with minimal adverse effects on the patient, and the use of donor eADSC is currently being investigated. The use of eADSC seems to suppress inflammation and promote healing.⁸⁶ The technique is described as follows: (1) identification of the internal opening; (2) accurate curettage of the tract especially at the level of the intersphincteric tract; (3) closure of the internal opening and sealing of the fistulous tract with fibrin glue; and (4) injection of cell suspension through a long fine needle into the tract walls with half of the total cells being placed in the intersphincteric tract and those adjacent to the internal opening, and the other half being placed in the tract walls in the direction of the external opening. In a multicenter randomized controlled trial, Garcia-Olmo et al⁸⁷ have explored the use of eADSC isolated

from lipoaspirated fat, to treat complex cryptoglandular, rectovaginal, and Crohn AFs. Initially promising results of 71% clinical healing, compared with 16% in the control group (fibrin glue only), were reported. Unfortunately, at 1 year the healing rate had decreased to 62.5 and to 33% at 3 years.⁸⁸ Ciccocioppo et al⁸⁹ injected autologous bone marrow-derived mesenchymal stromal cell (MSC) solutions into intractable Crohn AFs. This was performed in an outpatient setting with minimal mechanical tract preparation. The MSC solution was injected into the lumen and walls of the fistula, on a median of four occasions per patient at 4-week intervals. At 1-year follow-up, there was clinical and MRI evidence of complete fistula healing in 70% of patients, with the remainder experiencing a significant clinical improvement. No adverse events or disturbance of continence was reported.

Another treatment similar to the stem cell therapy is the use of collagen paste. An English group⁹⁰ has published a small pilot study demonstrating the efficacy of fibroblasts in the treatment of AFs. This study was performed on a porcine AF model after excision of all the granulation tissue lining the fistula track. The internal opening was then closed with a mucosal advancement flap. An injectable form of Permacol (Tissue Science Laboratories, Covington, GA), a type of porcine acellular collagen matrix, was modified by centrifugation to form a paste. Cultured autologous fibroblasts were added to the paste, which was then injected into the track via the external opening, completely filling the track. This treatment was compared with the paste alone, the paste plus the advancement flap, the paste plus the fibroblasts, and finally the paste plus the fibroblasts and the advancement flap. The results were interesting; 29/29 tracks treated with collagen paste, with or without cells, showed complete histological healing.⁹⁰ The filling of the fistula tract and concomitant connection between the reamed tract walls demonstrated well vascularized tissue completely filling the entire track from wall to wall along with complete integration with the host tissue and lack of inflammatory changes. Although this is an animal study, the results seem promising and may not require the addition of an advancement flap or autologous fibroblasts. Pilot studies in humans are currently ongoing.

Conclusion

Treatment of AF is challenging. Options abound with variable results. Biologic alternatives typically should be considered low-risk options with variable success rates. While they do provide hope as we develop newer material, initial results are not necessarily associated with significant long-term advantages over traditional surgical treatment. The major benefit of the sphincter-preserving techniques described is the minimal impact on continence, although we do not have reliable, long-term quantitative and qualitative data available from large trials.⁹¹ Promising stem cell technology, micro-environmental adjustments, and technological advances together with better understanding of this disease and a standardization of the technique may ultimately come together to create the best

results yet. We must continue to critically evaluate newer techniques until reproducible results are achieved to reach the ultimate goals of low recurrence, increased quality of life, and preservation of continence.

Conflict of Interest

The authors declare no conflict of interest.

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