Medical Policy Manual Surgery, Policy No. 175

Plugs for Enteric and Anorectal Fistula Repair

Effective: June 1, 2018

Next Review: May 2019
Last Review: May 2018

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Fistula plugs are anchored in the fistulae (abnormal openings, usually in the intestine or anus) to provide scaffolding for new tissue growth, aiming to promote healing and fistula closure. The plug is absorbed into the body in 6-8 weeks.

MEDICAL POLICY CRITERIA

Biosynthetic fistula plugs, including plugs made of porcine small intestine submucosa or of synthetic material, are considered **investigational** for repair of enteric and anal fistulas.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

CROSS REFERENCES

None

BACKGROUND

ENTERIC FISTULA

Enteric fistulas are an abnormal passage between the gastrointestinal (GI) tract and other abdominal organs, the chest, or skin. Eighty-five percent of enteric fistulas occur following surgery; 20 to 30 percent are in patients with Chron disease; other causes include infectious diseases, malignancy, radiation therapy, and ulcer.[1] Symptoms associated with fistulas vary depending on anatomical location, and may be accompanied by infection; one fourth of mortality from fistulas occurs as a result of infection and related sepsis. Internal or external enteric fistula are classified based upon whether they drain externally to the skin or internally to the gastrointestinal tract or other organ (e.g., bladder, vagina), and with respect to which segment(s) of bowel is involved.[2] Anorectal fistula are detailed in a separate section, below.

Successful treatment of enteric fistulae includes control and maintenance of drainage, appropriate treatment of infection and avoidance of sepsis, and adequate nutrition. Fistula involved with the GI tract often resolve with no surgical intervention; with appropriate initial treatment approximately one-third of enteric fistulas heal spontaneously, however, most exposed fistulas (enteroatmospheric) will not.[1] External fistulas require management of fluid output, which may include bag drainage, pharmacologic therapy, and negative pressure wound therapy. Deep, exposed fistula may require immediate surgery to cover exposed bowel sections, and patients with any enteric fistula who have not responded to five to six weeks of nonoperative treatment are likely to require surgery. Surgical techniques may include resecting the segment of bowel containing the fistula, then reestablishing GI continuity. In addition to closing the fistula opening, the goal of surgical management of enteric fistula is to close the abdominal wall, which may include flap techniques. Complete resection may not be possible in patients with short bowel syndrome, whereas patients with Chron disease require complete fistula resection in addition to adjacent diseased bowel to prevent future recurrence.

ANAL FISTULA

An anal fistula is an abnormal communication between the interior of the anal canal or rectum and the skin surface. Rarer forms may communicate with the vagina or other pelvic structures, including the bowel. Most fistulas begin as anorectal abscesses, which are thought to arise from infection in the glands around the anal canal. When the abscess opens spontaneously into the anal canal (or has been opened surgically), a fistula may occur. Studies have reported that 26 to 37 percent of cases of perianal abscesses eventually form anal fistulas.[3]

The most widely used classification of anal fistulas is the Parks' classification system, which defines anal fistulas by their position relative to the anal sphincter as trans-sphincteric, intersphincteric, suprasphincteric, or extrasphincteric. More simply, anal fistulas are described as low (present distally and not extending up to the anorectal sling) or high (extending up to or beyond the ano-rectal sling). The repair of high fistulas can be associated with incontinence. Diagnosis may involve fistula probe, anoscopy, fistulography, ultrasound, or magnetic resonance imaging (MRI).

Treatment for anal fistula is aimed at repairing the fistula without compromising continence. Surgical treatments include fistulotomy/fistulectomy, endorectal/anal sliding flaps, ligation of the intersphincteric fistula tract (LIFT) technique, seton drain, and fibrin glue. Fistulotomy involves division of the tissue over the fistula and laying open of the fistula tract. Although fistulotomies are widely used for low fistulas, lay-open fistulotomies in high fistulas carries the risk of incontinence. A seton is a thread placed through the fistula tract for the purpose of draining fistula material and preventing the development of a perianal infection. Draining setons can control sepsis, but few patients heal after removal of the seton, and the procedure

is poorly tolerated long-term. A “cutting seton” refers to the process of regular tightening of the seton to encourage gradual cutting of the sphincteric muscle with subsequent inflammation and fibrosis. Cutting setons can cause continence disturbances. Endorectal advancement flaps involve the advancement of a full or partial thickness flap of the proximal rectal wall over the internal (rectal) opening of the fistula tract. The LIFT technique involves identifying the intersphincteric plane and then dividing the fistula tract; its use has been reported in two studies, but long-term follow-up is unavailable.[4,5] Fibrin glue is a combination of fibrinogen, thrombin, and calcium in a matrix, which is injected into the fistula track. The glue induces clot formation within the tract, which is then closed through overgrowth of new tissue.

FISTULA PLUGS

Fistula plugs are designed to provide a structure that acts as a scaffold for new tissue growth. The scaffold, which can be derived from animal (e.g., porcine) tissue or a synthetic copolymer fiber, is degraded by hydrolytic or enzymatic pathways as healing progresses. The plug is pulled through the fistula tract and secured at the fistula’s proximal opening; the fistula tract is left open at the distal opening to allow drainage. A fistula plug derived from autologous cartilage tissue has been investigated in a small (n=10) pilot study.[6]

REGULATORY STATUS

The following table includes examples of fistula plugs that have received U.S. Food and Drug Administration (FDA) 510(k) approval.

Device name (FDA no.), FDA product code	Company	Date approved
SIS Fistula Plug (K050337), FTM	Cook Biotech Inc.	3/9/2005
Surgisis RVP Recto-Vaginal Fistula Plug (K062729), FTM	Cook Biotech Inc.	10/10/2006
Surgisis Biodesign Enterocutaneous Fistula Plug (K082682), FTM	Cook Biotech Inc.	2/27/2009
GORE® BIO-A® Fistula Plug (K083266), FTL	W.L. Gore & Associates, Inc.	3/27/2009
Biodesign Enterocutaneous Fistula Plug (K150668), FTM	Cook Biotech Inc.	12/09/2015

EVIDENCE SUMMARY

ENTERIC FISTULA

Initial treatment for enteric fistulas includes nutritional therapy, treatment of infection, and for external fistulas, controlling drainage. When fistulas do not close following initial measures, surgical treatment becomes necessary. The surgical procedure will vary based on the fistula classification, and depending on the indication, a gold-standard procedure might not exist. The majority of the evidence for the use of biosynthetic fistula plugs focuses on anal fistulae, which is detailed in the next section. Other publications on the use of fistula plugs as a treatment for enterocutaneous fistulae (non anal/rectal) are limited to a small number of nonrandomized studies.

Nonrandomized Studies

In 2014, Darrien and Kasem published a case series on seven patients with gastrocutaneous fistulas, unfit for surgical repair, who underwent repair with a Surgisis® (Cook Biotech Inc.) fistula plug between November 2008 and January 2010.[7] All patients had fistulae which failed

to heal following previous conservative management, and showed no radiological or clinical evidence of tissue disease at the site of the fistula, ongoing sepsis, or distal obstruction. Four patients had non-healing gastrostomies; the other fistulae were a result of anastomotic leak following oesophagectomy and distal gastrectomy. Five patients underwent direct repair under local anesthesia; fistula output ceased at a median of day twelve, and none of the five cases have had fistula recurrence at 30-59 months follow-up. Two patients underwent endoscopic repair; fistula output ceased immediately, and neither of the two cases had fistula recurrence at 30-59 months follow-up. While this case series demonstrates successful fistula closure, durable to at least two years follow-up, this is a highly selective group of patients with no comparative group.

Other studies are limited to case reports in duodenocutaneous fistula treated with a Biodesign enterocutaneous fistula plug (Cook Biotech Inc.)[8]; multiple complex gastro-bronchial fistulae[9]; enteroatmospheric fistulae treated with silicone fistula plug in conjunction with negative pressure wound therapy[10]; enterocutaneous fistula following stab wound[11]; and a persistent gastrocutaneous fistula treated with a porcine anal fistula plug[12].

ANAL FISTULA

Conventional treatments for anal fistulas include fistulotomy/fistulectomy, endorectal/anal sliding flaps, seton drains, and fibrin glue. Evidence from randomized controlled trials (RCTs) are necessary to establish how fistula plugs compare with conventional treatment on outcomes including safety, healing, fistula recurrence, and sphincter function. Evidence from RCTs as well as nonrandomized studies on outcomes of anal fistula plug (AFP) procedures are limited overall in quantity and quality.

Systematic Reviews

In 2016, Narang published a systematic review of the Gore Bio-A plug for anal fistulas, which included six studies (total N=221 patients) in a qualitative synthesis.[13] Fistula healing rates ranged from 15.8% to 72.7%. Reviewers assessed the overall quality of the underlying studies as poor.

In 2016, Nasseri reported on a systematic review of AFP for patients with Crohn disease and anal fistulas.[5] Twelve studies were included: eight nonrandomized prospective studies and four retrospective studies (total N=84 patients; range, 1-20 per study). Due to study heterogeneity, reviewers did not perform a weighted analysis with summary efficacy estimates. The total success rate of AFPs was 49 (58.3%) of 84 placed (95% confidence interval [CI], 47% to 69%).

Also in 2016, Xu reported on a meta-analysis of comparative studies of AFPs and mucosal advancement flaps for complex anal fistulas, which included 10 studies (total N=778 patients).[6] Three studies were randomized trials; the remaining were observational studies or did not describe designs. In pooled analysis, there were no significant differences in healing rates at the end of follow-up between the AFP and mucosal advancement flap groups (odds ratio [OR], 0.79; 95% CI, 0.36 to 1.73; p=0.55, I2=74%). None the seven studies reporting on recurrence rates found significant differences in recurrence rates (OR=2.29; 95% CI, 0.59 to 8.88; p=0.23, I2=83%). However, conclusions were limited by shortcomings in the underlying evidence base.

Narang reviewed six articles in a systematic review of GORE® BIO-A® for the treatment of fistula-in-ano.[13] Fistula healing rate ranged from 15.8 to 72.7 percent at 2 to 19 months follow-up. Of the 187 patients included in the review, 16 (8.5%) experienced early or delayed plug extrusion, and 11 (5.8%) experienced deterioration in continence. Meaningful conclusions cannot be drawn from the small number of included studies, limited follow-up duration, and noncomparative nature of the studies presented.

In 2013, Cirocchi published results of a systematic review with meta-analysis of studies that compared biologically derived products for fistula repair, including fibrin glue, AFPs, and acellular dermal matrix, with surgical therapy for fistula repair.[14] Seven studies were considered eligible for their evidence review, four of which included comparisons of AFPs with surgery, and two of which were RCTs (Ortiz 2009 and van Koperen 2011, described next). In a combined analysis, AFP placement was not significantly different than surgical treatment in terms of rates of healing (pooled risk ratio [RR]=1.19, 95% confidence interval [CI], 0.51 to 2.76). Recurrence of anal fistulas was not significantly different between patients treated with AFP compared with those treated with surgery, although the confidence interval for the pooled analysis was very wide (pooled odds ratio [OR]=3.12, 95% CI, 0.52 to 18.83).

In 2012, three systematic reviews were published comparing AFP to conventional surgical treatments for anal fistulas.[15-17] The reviews reported either no difference between groups or a higher rate of recurrence in the AFP group. In addition, authors pooled data from RCTs and retrospective studies which may have compromised conclusions reached in all three reviews.

A 2010 systematic review reported a wide range of success rates.[18] In the 12 included studies, all case series reported success rates for the AFP procedure from 24% to 92%. Success rates in treating complex fistula-in-ano in the eight prospective studies reviewed were 35%–87%. The complications of abscess formation and/or sepsis ranged from 4 to 29%. The plug extrusion ranged from 4 to 41%.

In a Cochrane review of surgical intervention for anorectal fistula, Jacob found few randomized trials comparing procedures for surgical repair.[19] Anal fistula plug was one procedure noted as needing further study with randomized trials.

Randomized Controlled Trials

In 2016, Senejoux on an RCT comparing AFP to seton removal alone in 106 patients who had Crohn disease with non- or mildly active disease but at least one anoperitoneal fistula drained for at least 1 month.[20]The trial was powered for superiority of AFP, and analysis was intention-to-treat. At 12 weeks of follow-up, in the AFP group (n=54), clinical remission rates were 31.5% compared with 23.1% in the control group (RR=1.31; 95% CI, 0.59 to 4.02; p=0.19). Fistula tract healing rates on magnetic resonance imaging did not differ significantly between groups at 12 weeks.

At least one randomized controlled trial (RCT) has been conducted in patients with non- or mildly-active Crohn’s disease.[21] In a multicenter, open-label, RCT, Senéjoux randomized 106 participants with at least one ano-perineal fistula (drained at least one month) to AFP (N=54) versus seton removal (control, N=52). Fistulas were stratified according to American Gastroenterological Association classification for simple or complex randomization. A non-statistically significant higher fistula closure was found in the AFP group at twelve weeks follow-up (adjusted relative risk, 1.31; 95% confidence interval [CI], 0.59-4.02.), and 17 participants developed at least one adverse event in the AFP group, as compared to 8 in the

seton group (p = 0.07).

Ortiz compared use of porcine submucosal (Surgisis) anal fistula plug (AFP) with an endorectal anal flap (ERAF) procedure in an RCT with 43 patients who had high anal fistula.[22] The primary endpoint was fistula healing. Recurrence was defined as the presence of an abscess in the same area or obvious evidence of fistulization. Five patients in the AFP group and six in the ERAF group did not receive the allocated intervention, leaving 32 patients. One patient in the AFP group was lost to follow-up. A large number of recurrences in the fistula plug group led to premature closure of the trial. After one year, fistula recurrence was seen in 12 of 15 patients treated with an anal fistula plug versus 2 of 16 patients who underwent the flap procedure (relative risk 6.40 [95% confidence interval 1.70-23.97]); p<0.001). Fistulas recurred in 9 of 16 patients who had previously undergone fistula surgery; 8 of the 9 patients had an AFP. A trend for more sphincter involvement and more females in the ERAF group was noted. Complications were not reported in this paper.

Van Koperen reported on a double-blinded multicenter randomized trial comparing anal fistula plug with mucosal advancement flap in 60 patients with high perianal fistulas.[23] The authors reported results at 11 months in both treatment groups with fistula recurrence in 22 patients (71%) in the anal plug group and 15 patients (52%) in the advancement flap group; these rates were not significantly different (p = 0.126). Postoperative pain scores, quality of life after surgery and functional outcomes were not significantly different between groups. Despite disappointing results, the authors indicated the plug might be considered as an initial treatment option because the plug procedure is simple and minimally invasive.

Nonrandomized Studies

Nonrandomized studies in patients with anal fistulas (including transsphincteric fistulas, and with and without inflammatory bowel disease) comparing AFP with fistulotomy, ligation of the intersphincteric fistula tract (LIFT) technique, endorectal advancement flap, fibrin glue, draining seton, and cutting seton have been reported in single-center and multi-center settings.[24-29] Follow-up has ranged from twelve weeks to median of 819 days. Though non-differing complication rates have been reported between AFP and conventional procedure groups, healing rates have been reported with wide, and non-statistically significant confidence intervals (suggesting underpowered studies), and in heterogeneous patient groups. The remainder of the published evidence for anal fistula plug consists of case series, most with small numbers of subjects, and studies which did not compare fistula plug to conventional treatment options.[30-36] Authors have repeatedly called for longer term and larger RCTs to fully evaluate the utility of AFP for the treatment of anal fistula.

PRACTICE GUIDELINE SUMMARY

AMERICAN SOCIETY OF COLON AND RECTAL SURGEONS

The 2016 practice guidelines on the treatment of anorectal abscess, fistula-in-ano, and rectovaginal fistula from the American Society of Colon and Rectal Surgeons provided a weak recommendation with moderate-quality evidence.[1] With recent evidence of success rates of less than 50% in most studies for the treatment of complex anal fistulas with an anal fistula plug, the guidelines concluded that the fistula plug is relatively ineffective in the treatment of fistula-in-ano.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

The National Institute for Health and Care Excellence (NICE) updated its guidance on the suturable bioprosthetic plug in November 2011.[21] NICE determined that while there are no major safety concerns, evidence on the efficacy of the procedure is not adequate for it to be used without special arrangements for consent, audit, or research.

SUMMARY

There is not enough research to show that the use of anal fistula plug and non-anal enteric fistulae treatments improves health outcomes. The current research reports a wide range of results and does not demonstrate that anal fistula plugs improve healing rates or reduce recurrence. No practice guidelines recommend the use of these plugs for any indication. Therefore, biosynthetic fistula plugs, including plugs made of porcine small intestine submucosa or of synthetic material, are considered investigational for the repair of enteric and anal fistulas.

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CODES

Codes	Number	Description
CPT	46707	Repair of anorectal fistula with plug (e.g., porcine small intestine mucosa [SIS])
	44799	Unlisted procedure, small intestine
	45499	Unlisted laparoscopy procedure, rectum
	58999	Unlisted procedure, female genital system (nonobstetrical)
HCPCS	None	

Date of Origin: *August 2010*