






The Efficacy of Porcine Dermal Collagen to Treat Complex Anal Fistulae. Results of a Multicenter Cohort

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Abstract

Introduction The management of complex anal fistulae remains a topical surgical problem. The choice and success of surgical management are based on the balance between healing and continence. Although porcine dermal collagen (Permacol Collagen Paste [PCP]- Covidien plc, Gosport, Hampshire, UK) represents a new generation of non-solid biomaterials, its results in anal fistulae are mixed.

Methods A multicenter observational retrospective analysis of consecutive patients with cryptoglandular anal fistula treated in four colorectal surgery units was performed between 2015 and 2020. Clinical cure of the fistula was the main outcome measure. Adverse events and alterations in anal continence were secondary outcomes.

Results The study included 119 patients (87 males, 71.1%), with a mean age of 53 years (IR 44–65). Most patients had complex (80.6%) and recurrent (91.6%) fistulae. With the first PCP treatment, the overall cure rate was 41.2% (49 patients) and 45.4% with the second treatment (5 out of 17 patients). The mean follow-up period was 17 months (IR 5–25). Healing was not affected by the location and type of fistula, the existence or not of a cavity, the number of tracts, or the administration of prophylactic antibiotics. After the PCP treatment, no patient in the series had worsening of continence. Morbidity affected 22.7% of the patients (27), with postoperative abscesses being the most frequent adverse event. There were no statistical differences between the four hospitals studied.

Conclusions Permacol collagen paste is a safe and easily reproducible therapy for complicated anal fistulae that has moderate efficacy. The overall success rate is slightly over 40%, with no detriment to fecal continence.

Keywords

- Permacol paste
- anal fistula
- complex anal fistula

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Introduction

The management of complex anal fistulae (CAF), those that cannot be resolved by simple fistulotomy, remains a major surgical problem. There are many available treatments, but they are limited by the balance between cure, persistence/recurrence, and continence. In recent decades, greater emphasis has been placed on continence preservation, which has made sphincter-preserving procedures the surgical approach of choice, though with a predictably lower cure rate. According to a recent meta-analysis of RCTs,¹ there is no difference in efficacy between the most commonly used therapies, which is supported by a 2010 Cochrane review.² In addition, due to the wide range of definitions, outcomes, and evaluation methodologies, comparing strategies is extremely challenging.³

With satisfactory healing rates, the loose or tight seton is still one of the most commonly used techniques in CAF, both as a way to tutor and prepare the fistulous tract for future treatment and to perform a slow stepwise cutting fistulotomy, but its influence on continence is significant.⁴ The advancement flap has long been considered the gold standard for the treatment of these fistulae; however, in many patients (male, with long and narrow anal canal, horseshoe tracts, posterior cavities, fibrous scars from previous surgeries, etc.), it is a demanding approach, highly technique-dependent, and with success rates ranging from 30 to 70%, but with alterations in continence of up to 20%.⁵ As a sphincter-preserving procedure, ligation of the intersphincteric fistula tract (LIFT) has gained popularity over time. However, although its overall results are 50 to 70% successful, in posteriorly located fistulas, which tend to be more complex, its results are markedly lower, down to 20%.⁶ Sphincter section with immediate reconstruction has good results, ranging from 50 to 80% of success, in some studies, but requires healthy muscle section and posterior adequate healing, which can affect continence, so it is not commonly used.⁷ The use of plugs, which appeared very promising in early research, has resulted in cure rates of less than 30%,⁸ and their use has declined. Other treatments aimed at treating the fistulous tract by ablation or collapse (fistula-tract laser closure [FILAC], photodynamic therapy, radio-frequency, etc.), provided similar mixed results in series of small patient groups. The low porosity of rigid biologics hinders rapid cellular infiltration and, consequently, implant integration, which may lead to simple expulsion.

The availability of non-solid biomaterials offers a theoretical advantage over rigid biomaterials, maintaining the same objective of obliterating the fistulous tract. Fibrin glue has been used to repair anal fistulae for many years, and although its efficacy in CAF has historically been limited (15–28%),⁹ recent studies in Crohn disease fistulae have shown cure rates of up to 45% when combined with biological treatments.¹⁰ Porcine dermal collagen (Permacol Collagen Paste [PCP]- Covidien plc, Gosport, Hampshire, UK) is another new generation biomaterial with few published studies, yet a wide range of healing results, ranging from 20 to 77%.^{11,12} It is a cross-linked, acellular, and sterile porcine dermal

collagen matrix (with type I and III fibers) that acts as a scaffold for the healing of the fistulous tract by inducing angiogenic activity through the release of VEGF by local cells.¹³

The aim of this study was to provide a repeatable experience with PCP in a multicenter trial and assess its effectiveness.

Methods

Observational, multicenter, retrospective study conducted between 2015 and 2020 in 4 colorectal surgery units of academic centers. The study was authorized by the Ethics Committees of all participating centers, and all patients gave their consent. The research followed the Standards for Reporting Observational Studies in Epidemiology (STROBE) guidelines.¹⁴

All patients with anal fistula who were treated with Permacol Collagen Paste (Covidien plc, Gosport, Hampshire, UK) (PCP) were included in the study. The exclusion criteria were age < 18 years, diagnosis of inflammatory bowel disease, history of local radiation, concomitant hidradenitis suppurativa, existence of more than one internal fistulous orifice, presence of numerous fistulous tracts or active abscesses, and history of rectal carcinoma.

In addition to the clinical examination and anoscope, all complex patients underwent an imaging test (magnetic resonance imaging [MRI] or endoanal ultrasound, depending on clinical preference) and in some cases also an examination under anesthesia (EUA) and curettage of the cavities and conditioning of the tract prior to PCP placement if required. The type of anal fistula was determined using Parks' anatomical classification. Suprasphincteric, extrasphincteric anal and upper transphincteric fistulas involving more than 1/3 of the sphincteric apparatus were considered anatomically complex. In addition, anteriorly placed fistulae in women, multi-operated fistulae, or patients with anal continence already at risk were also classified as complex.

Patient demographics as well as known clinical risk factors affecting fistula healing, such as smoking, diabetes, steroid use, body mass index (BMI), anatomical characteristics of fistulae (types, presence of cavities, and number of tracts), and previous treatments were collected as variables. In addition, data were collected regarding patient preparation, including mechanical bowel cleansing, administration or not of antibiotics and their duration, as well as data regarding the surgical technique, or amount of Permacol utilized.

Endpoint Measurements and Outcomes

Fistula healing was defined as the complete closure of the external fistula orifice and the absence of symptoms (pain, discharge, swelling or bulging), as determined by history and examination. Imaging techniques were used on an ad hoc basis in cases of any abnormality detected during digital rectal examination.³ Failure of healing was defined if complete closure of the external opening did not occur at 3 months after surgery. Recurrence was defined as reappearance of the external opening after complete healing or recurrence of symptoms after complete resolution.

Adverse events, alteration of anal continence (considered as such any related symptom non-existent prior to the procedure), and related clinical and/or technical aspects were secondary outcomes.

Surgical Procedure

The position of the patient (lithotomy or jackknife) was decided by each surgeon according to his or her discretion and preference. After identification of the internal fistulous orifice (IFO), the fistulous tract, and possible related cavities, a complete curettage and saline lavage were performed. The PCP was introduced into the fistulous tract through a guiding-catheter for PCP (Neuromedex, Hamburg, Germany). When the paste is seen to appear through the IFO, its introduction is stopped; the IFO is then sealed by digital pressure, and the catheter is slowly withdrawn while filling the fistulous tract until the paste overflows out through the external fistulous orifice (EFO). The IFO is then closed with absorbable suture. Finally, the EFO is loosely closed to prevent further leakage or extrusion of PCP.

There were no contraindications to repeat a second PCP treatment if the first failed.

Each center followed its postoperative procedure concerning mechanical bowel preparation, antibiotic prophylaxis, or empirical antibiotic use.

Statistical Analysis

For the categorical variables, the most relevant statistics for the nature and measurement scale of each variable were used: absolute and relative frequencies in percentages. For quantitative variables, the mean and standard deviation (SD) or the median and interquartile range (IQR) were chosen. To evaluate the relationship between the categorical variables, the Chi2 or Fisher test was used. The normality of the quantitative variables was evaluated using the Kolmogorov-Smirnov fit test, and depending on the results, the Student t-test or the Mann-Whitney U-test was performed. A binary logistic regression analysis using the Wald method includes univariate studies with a significance of $p > 0.20$. The significance threshold was set at 0.05. For statistical analysis, IBM SPSS Statistics for Windows, v.26.0 software (IBM Corp., Armonk, NY, USA) was used.

Results

During the study period, 119 patients (87 men, 71.1%) with a median age of 53 years (IQR 44–65) were included. The mean follow-up time was 17 months (IQR 5–25). ► **Table 1** shows the demographic variables of the series and the anatomical and clinical characteristics of the fistulas. Most of the patients had previously undergone fistula surgery (91.6 percent). For the anatomical characterization of the fistulas, endoanal ultrasound was used as an imaging test in 25.2% of the patients, MRI in 63.1%, and an examination under anesthetic (EUA) was also performed in 21.8% of the cases. Most of the patients (80.6 percent) had a complex fistula of the transphincteric type (80.7 percent).

In total, 49 (41.2%) of the 119 patients in the study were cured after the first PCP treatment. Seventeen patients received a second PCP therapy, and 5 (29.4%) of them were cured. Among patients who achieved a cure, EFO closure was achieved in an average of 8 weeks (CI 4–41). It is noteworthy that after treatment with PCP, even repeated, no patient in the series presented any significant postoperative worsening of anal continence.

No differences were observed in the univariate analysis between cured and non-cured patients with respect to demographic and clinical data, except for the existence of cigarette consumption, which was not statistically significant (► **Table 2**). There were no differences between cured and non-cured patients regarding the anatomy of the fistula and its complexity. Neither the use of mechanical bowel preparation, the administration of prophylactic antibiotics or their maintenance during the postoperative period affected the success of PCP.

Finally, no statistical differences were found in the type of fistulas or in the results obtained with the use of PCP among the four institutions participating in the study.

Morbidity affected 22.7% of patients, with postoperative abscesses being the most common adverse event, although in only 6 (5%) of these patients did the abscess require surgical drainage, while the others presented spontaneous drainage through the EFO. On the other hand, patients who did not receive antibiotic prophylaxis had a higher rate of postoperative abscesses (4/11 vs. 11/108, $p = 0.032$); however, this did not alter the overall cure rate. It was found in 4.2% of cases that the PCP was detached or extruded during the early postoperative period, with healing in one patient.

The multivariate analysis using logistic regression did not show any independent factors influencing the overall success rate. The existence of associated cavities ($p = 0.082$, OR 3.338, 95% CI 0.858–12.988) and a high tract of the fistulas ($p = 0.055$, OR 5.371, 95% CI 0.964–29.919) showed relevance without statistical differences.

Finally, 69 (98.5%) of the 70 uncured patients had fistula persistence, with only one case of recurrence at two years.

Discussion

Permacol collagen paste is a safe, easily reproducible treatment with moderate efficacy in the management of complex anal fistulae. With a median follow-up of 17 months, the overall success rate was 41.2%. In case of initial failure, the treatment can be repeated just as safely and easily, increasing cure rates by up to 47%. Moreover, in case of failure, it does not alter anal continence and allows for any subsequent surgery. This is what would, according to our data, make this technique attractive as a first approach for highly complex anal fistulae or those with compromised anal continence, albeit at the expense of a loss in terms of time and money.

The lack of adequate and safe treatment for complex anal fistula is highlighted by the existence of various surgical approaches and interventions. Despite the lack of unquestionable doctrinal support, the cryptoglandular theory

Table 1 Demographics and clinical characteristics of the patients

	Total (119)	Healed (49)	Unhealed (70)	P
Center: n (%)				
HUMV	44 (37)	17 (38.6)	27 (61.4)	
HUD	40 (33.6)	19 (47.5)	21 (52.5)	
HUB	23 (19.3)	8 (34.8)	15 (65.2)	
CUN	12 (10.1)	5 (41.6)	7 (58.4)	0.761 ^Σ
Age: mean (IR)	53 (44–65)	54 (40–63)	53 (46–66)	0.118 ^E
GENDER: n (%)				
Male	87 (71.1)	35 (71.4)	52 (74.3)	
Woman: (%)	32 (28.9)	14 (28.6)	18 (25.7)	0.729 ^Σ
BMI, median (IR)	27.7 (24.4–32.2)	27.7 (25–30.5)	27.7 (24.2–32.2)	0.224 ^E
TOBACCO: n (%)				
Yes	27 (22.7)	7 (14.3)	20 (28.6)	
Not	92 (77.3)	42 (85.7)	50 (71.4)	0.067 ^Σ
STEROIDS: n (%)				
Yes	3 (2.5)	1 (2)	2 (2.8)	
Not	116 (97.5)	48 (98)	68 (97.2)	0.780 ^Σ
DIABETES: n (%)				
Yes	6 (5)	3 (6.1)	3 (4.3)	
Not	113 (95)	46 (93.9)	67 (95.7)	0.689 ^Σ
PREVIOUS SURGERY: n (%)				
Yes	109 (91.6)	44 (79.8)	65 (92.9)	
Not	10 (8.4)	5 (10.2)	5 (7.1)	0.554 ^Σ
TECH. PREVIOUS SURGERY: n (%)				
None	10 (8.4)	5 (10.2)	5 (7.1)	
Drainage	14 (11.8)	3 (6.1)	11 (15.7)	
Seton	59 (49.6)	21 (4.3)	38 (54.3)	
LIFT	23 (19.4)	12 (2.4)	11 (15.7)	
Fistulotomy	7 (5.8)	3 (6.1)	4 (5.7)	
Flap	4 (3.3)	4 (8.1)	0 (0)	
Sphincteroplasty	2 (1.7)	1 (2)	1 (1.4)	0.114
FISTULA CLASS: n (%)				
Intersphincteric	11 (9.2)	4 (8.1)	7 (10)	
Transsphincteric	96 (80.7)	37 (75.5)	59 (84.3)	
Suprasphincteric	10 (8.4)	7 (14.3)	3 (4.3)	
Extrasphincteric	2 (1.7)	1 (2.1)	1 (1.4)	0.275 ^Σ
COMPLEX FISTULA (1)				
Yes	96 (80.6)	38 (77.5)	58 (82.8)	
Not	23 (19.4)	11 (22.5)	12 (17.2)	0.471 ^Σ
PREVIOUS SETON: n (%)				
Yes	59 (49.6)	21 (43)	38 (54.3)	
Not	60 (50.4)	28 (57)	32 (45.7)	0.220 ^Σ
LOCATION: n (%)				
Anterior	30 (25.2)	11 (22.4)	19 (27.1)	

(Continued)

Table 1 (Continued)

	Total (119)	Healed (49)	Unhealed (70)	P
Posterior	65 (54.6)	29 (59.2)	36 (51.4)	
Lateral	23 (19.2)	9 (18.4)	14 (20.5)	0.740 ^Σ
PRESENT CAVITY: n (%)				
Yes	24 (20.1)	8 (16.3)	16 (22.9)	
Not	95 (79.9)	41 (83.7)	54 (77.1)	0.382 ^Σ
DIAGNOSTIC TEST				
Clinic	26	13	13	
EBA	27	9	18	
Ultrasound	30	13	17	
MRI	43	18	25	0.775 ^Σ

Abbreviations: BMI, body mass index; CUN, Clínica Universidad Navarra; EBA; HUB, Hospital Universitario Basurto; HUD, Hospital Universitario Donostia; HUMV, Hospital Universitario Marqués de Valdecilla; LIFT, Ligation Intersphincteric Fistula Tract; M, men; MRI, magnetic resonance imaging; W, women.

Table 2 Intraoperative and postoperative characteristics

	Total (119)	Healed (49)	Unhealed (70)	P
PERMACOL VOLUME (cc)				
Median (RI)	3 (2.5–3)	3 (3–3)	3 (2–3)	0.341 [£]
MATERIAL CLOSED IFO				
Vicryl	52 (43.7)	23 (47)	29 (41.4)	
Monosin	12 (10)	5 (10.2)	7 (10)	
Others	55 (46.3)	21 (42.8)	34 (48.6)	0.740
IFO closure				
Before Permacol	79 (66.4)	30 (61.2)	49 (70)	
After Permacol	40 (33.6)	19 (38.8)	21 (30)	0.319
AB PROPHYLAXIS: n (%)				
Yes	108 (90.7)	45 (91.8)	63 (90)	
Not	11 (9.3)	4 (8.2)	7 (10)	0.734 ^Σ
POSTOPERATIVE AB: n (%)				
Yes	81 (68)	35 (71.4)	46 (57)	
Not	38 (32)	14 (28.6)	24 (43)	0.580
INTESTINAL PREPARATION				
None	50 (42)	20 (40.8)	30 (42.8)	
Enema	65 (52.6)	28 (57.1)	37 (52.8)	
CitraFleet	4 (5.4)	1 (2.1)	3 (4.4)	0.757 ^Σ
COMPLICATIONS: n (%)				
Yes	27 (22.7)	8 (16.3)	19 (27.1)	
Not	92 (77.3)	41 (83.7)	51 (72.9)	0.166
COMPLICATION TYPE				
Abscess	15 (12.6)	5 (10.2)	10 (14.3)	
Lost Permacol	5 (4.2)	1 (2)	4 (5.7)	
Bleeding	3 (2.5)	1 (2)	2 (2.8)	
Others	4 (3.3)	1 (2)	3 (4.2)	.690

*T Student; £ U Mann-Whitney; Σ Chi²

remains the most recognized etiopathogenic theory for perianal abscesses and fistulae and is the basis for different therapies.¹⁵ The St. Mark's group published the first paper on the use of a non-solid collagen matrix for anal fistula in 2007,¹³ in an experimental series that demonstrated two important steps in fistula treatment: the removal of granulation tissue from the tract and its filling with the porous matrix.¹⁶ Their good results were validated in a second experiment with 100% healing using collagen matrix alone or in combination with another maneuver (flap or fibroblast infiltration).¹⁷

The few studies published so far indicate cure rates ranging from 20% to 77.4%,^{11,12,18–23} with significant differences depending on the number of complex patients and the length of the follow-up period. The two publications, both single-center, with the most disparate results had differences in relation to the technique of closure of the internal orifice and the proportion of complex fistulae, which, in the case of the series of Vollebregt et al.,¹¹ included 20% of cases with double fistulous tracts and a failure rate of 80% compared to 77.4% success in the series of Bayrak et al.¹² of non-complex fistulae.

No previous research has studied demographic risk factors associated with success or failure using PCP. Smoking was a detrimental factor in our study; however, there was no statistically significant variation in cure rates between smokers and non-smokers (25.9% vs. 45.6%, $p = 0.067$). Due to the sample size, a type II error cannot be ruled out. Both mechanical bowel preparation (enemas, antegrade lavage, etc.) and antibiotic prophylaxis had no effect on our findings, and published research has reached similar conclusions.^{11,12,18–23} Antibiotics are used in anal fistula surgery for both preventive and therapeutic purposes, and their use varies widely. A recent meta-analysis found that the use of an empirical antibiotic treatment regimen reduced fistula formation after drainage of a perianal abscess from 24 to 16%; however, the evidence is limited and does not define the duration or type of antibiotic indicated.²⁴ The data are conclusive regarding the use of preceding seton, both in our series and in the two most relevant series in terms of sample size^{11,21}: its use prior to definitive surgical treatment has no effect on the fistula outcome. Short fistulous tracts have been shown to have superior results in some studies, presumably because they are less complex fistulae. However, our findings, which were based on the amount of paste used, contradict these findings.^{12,21} Another important component of our study and not previously reported is that cavity-connected fistulae discovered during surgery or by previous imaging tests did not influence the results. Unlike Vollebregt's study,¹¹ which included a percentage of complexity similar to that of our series, the complexity of the fistula was not a determining factor in the failure rate of our case series. Given the convenience and reproducibility of PCP use, this is, in our opinion, the most crucial attribute for its use.

Finally, two essential factors to take into account are its safety, with a complication rate of less than 22% in our series and perianal abscesses being the most frequent complication, and no, or limited, impact on anal continence. These

findings are similar to those reported in other more limited case series.^{12,19} On the other hand, the absence of alterations in pre and postoperative anal manometry after PCP administration was reported by Hammond et al.²²

The retrospective and not controlled character of this study limits its conclusions. However, because of its multi-center design and large sample size with homogeneous results inter-center, it is possible to make relevant suggestions based on these results.

Despite its moderate success, PCP is a safe, repeatable, and simple procedure to perform for complex fistulae. It preserves anal continence and does not distort the anatomy, so that if subsequent salvage surgery is required, it can be performed in a field free of scar deformation. In cases of complex anal fistulae, persistent posterior fistulae in men, several previous surgeries, or patients with borderline anal continence, PCP would, in our opinion, be a good first choice, assuming a success rate of just over 40%.

Conflict of Interests

The authors have no conflict of interests to declare.

References

- Cheung XC, Fahey T, Rogers AC, Pemberton JH, Kavanagh DO. Surgical management of idiopathic perianal fistulas: A systematic review and meta-analysis. *Dig Surg* 2021;38(02):104–119. Doi: 10.1159/000512652
- Jacob TJ, Perakath B, Keighley MR. Surgical intervention for anorectal fistula. *Cochrane Database Syst Rev* 2010;(05): CD006319. Doi: 10.1002/14651858.CD006319.pub2
- Machielsen AJHM, Iqbal N, Kimman ML, et al. Heterogeneity in outcome selection, definition and measurement in studies assessing the treatment of cryptoglandular anal fistula: findings from a systematic review. *Tech Coloproctol* 2021;25(07):761–830. Doi: 10.1007/s10151-021-02452-5
- Ratto C, Grossi U, Litta F, et al. Contemporary surgical practice in the management of anal fistula: results from an international survey. *Tech Coloproctol* 2019;23(08):729–741. Doi: 10.1007/s10151-019-02051-5
- Balciscueta Z, Uribe N, Balciscueta I, Andreu-Ballester JC, García-Granero E. Rectal advancement flap for the treatment of complex cryptoglandular anal fistulas: a systematic review and meta-analysis. *Int J Colorectal Dis* 2017;32(05):599–609. Doi: 10.1007/s00384-017-2779-7
- Placer-Galán C, Enriquez-Navascués JM, Pastor-Bonel T, Aguirre-Allende I, Saralegui-Ansorena Y. The Use of Seton as a Bridge to Definitive Ligation of the Intersphincteric Fistula Tract Procedure for Fistula-in-ano: A Systematic Review and Meta-analysis. *J Coloproctol (Rio J)* 2021;41:308–315. Doi: 10.1055/s-0041-1730039
- Ratto C, Litta F, Donisi L, Parello A. Fistulotomy or fistulectomy and primary sphincteroplasty for anal fistula (FIPS): a systematic review. *Tech Coloproctol* 2015;19(07):391–400. Doi: 10.1007/s10151-015-1323-4
- Garg P, Song J, Bhatia A, Kalia H, Menon GR. The efficacy of anal fistula plug in fistula-in-ano: a systematic review. *Colorectal Dis* 2010;12(10):965–970. Doi: 10.1111/j.1463-1318.2009.01933.x
- Yeung JM, Simpson JA, Tang SW, Armitage NC, Maxwell-Armstrong C. Fibrin glue for the treatment of fistulae in ano—a method worth sticking to? *Colorectal Dis* 2010;12(04):363–366. Doi: 10.1111/j.1463-1318.2009.01801.x
- Vidon M, Munoz-Bongrand N, Lambert J, et al. Long-term efficacy of fibrin glue injection for perianal fistulas in patients with

- Crohn's disease. *Colorectal Dis* 2021;23(04):894–900. Doi: 10.1111/codi.15477
- 11 Vollebregt PF, Vander Mijnsbrugge GJ, Molenaar CBH, Felt-Bersma RJF. Efficacy of Permacol injection for perianal fistulas in a tertiary referral population: poor outcome in patients with complex fistulas. *Colorectal Dis* 2021;23(08):2119–2126. Doi: 10.1111/codi.15696
 - 12 Bayrak M, Altıntaş Y. Permacol™ Collagen Paste Injection in Anal Fistula Treatment: A Retrospective Study with One-Year Follow-Up. *Adv Ther* 2018;35(08):1232–1238. Doi: 10.6084/m9.figshare.6552704
 - 13 Keshaw H, Thapar N, Burns AJ, et al. Microporous collagen spheres produced via thermally induced phase separation for tissue regeneration. *Acta Biomater* 2010;6(03):1158–1166. Doi: 10.1016/j.actbio.2009.08.044
 - 14 von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *J Clin Epidemiol* 2008;61(04):344–349. Doi: 10.1016/j.jclinepi.2007.11.008
 - 15 Gosselink MP, van Onkelen RS, Schouten WR. The cryptoglandular theory revisited. *Colorectal Dis* 2015;17(12):1041–1043. Doi: 10.1111/codi.13161
 - 16 Himpson RC, Cohen CR, Sibbons P, Phillips RKS. Histological evidence for enhanced anal fistula repair using autologous fibroblasts in a dermal collagen matrix. *Comp Clin Pathol* 2007; 16:9–14. Doi: 10.1007/s00580-006-0659-6
 - 17 Himpson RC, Cohen CR, Sibbons P, Phillips RK. An experimentally successful new sphincter-conserving treatment for anal fistula. *Dis Colon Rectum* 2009;52(04):602–608. Doi: 10.1007/DCR.0b013e31819ece3e
 - 18 Brunner M, Schneider I, Günther K, Grützmann R, Matzel KE. Permacol™ collagen paste for cryptoglandular and Crohn's anal fistula. *Tech Coloproctol* 2019;23(02):135–141. Doi: 10.1007/s10151-019-01932-z
 - 19 Schiano di Visconte M, Braini A, Moras L, Bruscianno L, Docimo L, Bellio G. Permacol Collagen Paste Injection for Treatment of Complex Cryptoglandular Anal Fistulas: An Observational Cohort Study With a 2-Year Follow-up. *Surg Innov* 2019;26(02):168–179
 - 20 Fabiani B, Menconi C, Martellucci J, Giani I, Toniolo G, Naldini G. Permacol™ collagen paste injection for the treatment of complex anal fistula: 1-year follow-up. *Tech Coloproctol* 2017;21(03): 211–215. Doi: 10.1007/s10151-017-1590-3
 - 21 Giordano P, Sileri P, Buntzen S, et al. Final results of a European, multicentre, prospective, observational study of Permacol™ collagen paste injection for the treatment of anal fistula. *Colorectal Dis* 2018;20(03):243–251. Doi: 10.1111/codi.13715
 - 22 Hammond TM, Porrett TR, Scott SM, Williams NS, Lunniss PJ. Management of idiopathic anal fistula using cross-linked collagen: a prospective phase 1 study. *Colorectal Dis* 2011;13(01): 94–104. Doi: 10.1111/j.1463-1318.2009.02087.x
 - 23 D'Urso AP, Chisari A, Cassaro V. Anal fistula: an observational study. *Tech Coloproctol* 2014;18:967–978. Doi: 10.1007/s10151-014-1217-x
 - 24 Mocanu V, Dang JT, Ladak F, et al. Antibiotic use in prevention of anal fistulas following incision and drainage of anorectal abscesses: A systematic review and meta-analysis. *Am J Surg* 2019;217 (05):910–917. Doi: 10.1016/j.amjsurg.2019.01.015