

Complex treatment of anal fistulas with extensive inflammatory infiltration

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Abstract

Background: Anal fistulas with extensive inflammatory infiltration pose significant challenges in treatment, often leading to prolonged hospital stays, complications, and reduced quality of life. This study evaluates the efficacy of rectal suppositories containing streptokinase (15,000 IU) and streptodornase (1,250 IU) as an adjunct to standard therapy, including assessment of inflammatory cytokines.

Methods: A prospective randomized controlled trial was conducted from September 2018 to December 2019 at Weihaiwei People's Hospital. Sixty patients with anal fistulas and extensive inflammatory infiltration were divided into two groups: Group 1 (n=30) received standard treatment per international guidelines, while Group 2 (n=30) received the same plus rectal suppositories. Suppositories were administered based on disease severity: for severe cases, 1 suppository three times daily for 3 days, twice daily for 3 days, and once daily for 3 days; for moderate/mild cases, twice daily for 3 days, then once daily for 4 days or twice daily for 2 days. Outcomes included hospital stay duration, severe disease incidence, complications, pain syndrome (via Visual Analog Scale, VAS), quality of life (QoLAF-Q), and serum levels of TNF- α and IL-1 β .

Results: Group 2 showed significantly shorter hospital stays (mean 18.5 ± 4.3 days vs. 12.5 ± 2.9 days, $p < 0.001$), fewer severe cases (37% vs. 13%, $p < 0.01$), fewer complications (27% vs. 10%, $p < 0.05$), lower VAS scores, improved QoLAF-Q scores, and reduced serum TNF- α and IL-1 β levels compared to Group 1. Significant positive correlations were observed between TNF- α , IL-1 β , VAS, and QoLAF-Q.

Conclusions: Adjunctive enzymatic (streptokinase-streptodornase suppositories) therapy in complex treatment of anal fistulas with extensive inflammatory infiltration demonstrates notable benefits including shortened hospitalization periods, decreased complication rates, reduced pain levels, lowered cytokine concentrations, and enhanced quality of life when compared to conventional treatment alone.

Keywords: Anal fistula; Inflammatory infiltration; Streptokinase; Streptodornase; Rectal suppositories; Quality of life; TNF- α ; IL-1 β

1. Introduction

Anal fistulas constitute a prevalent yet challenging condition in coloproctology, defined by an aberrant connection between the anal canal and the perianal skin surface, frequently arising from cryptoglandular infections [1]. When associated with substantial inflammatory infiltration, these fistulas may cause considerable morbidity, including recurring abscess formation, persistent pain, and compromised sphincter function, all of which negatively affect patients' quality of life [2]. Conventional management approaches, as described in international guidelines,

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predominantly rely on surgical procedures such as fistulotomy or seton insertion to eliminate sepsis and facilitate healing while maintaining continence [3]. Nevertheless, these methods demonstrate variable success rates between 70% and 95%, along with continence impairment risks, especially in complex transsphincteric fistulas [4].

The underlying pathophysiology of anal fistulas with inflammatory infiltration encompasses ongoing infection, fibrin accumulation, and necrotic tissue debris, which impede spontaneous healing mechanisms [5]. Enzymatic agents have been investigated in wound care to support debridement and diminish inflammation. Streptokinase, functioning as a fibrinolytic enzyme, and streptodornase, a deoxyribonuclease, have shown effectiveness in liquefying purulent material and degrading DNA within exudates, thus enhancing wound cleansing [6]. Their combined application in topical formulations, including Varidase, has been reported in chronic wound and leg ulcer treatment, demonstrating enhanced healing rates and decreased bacterial load [7]. Despite these advantages in general wound management, their utilization in anal fistulas remains insufficiently investigated, particularly as rectal suppositories, which provide targeted administration to the inflamed perianal area [8].

Pro-inflammatory cytokines play a pivotal role in the perpetuation of inflammation in anal fistulas. Tumor necrosis factor- α (TNF- α) is a key mediator, promoting leukocyte recruitment, tissue damage, and fistula tract persistence through its effects on matrix metalloproteinases and endothelial activation [9]. Elevated TNF- α levels have been associated with refractory perianal fistulas in Crohn's disease, where anti-TNF therapies have shown promise in inducing remission [10, 11]. Similarly, interleukin-1 beta (IL-1 β) exacerbates local inflammation by inducing chemokine production and amplifying the cytokine cascade, contributing to epithelial-to-mesenchymal transition and fistula chronicity [12]. Studies have identified heightened IL-1 β expression in cryptoglandular fistula tissues, correlating with increased neutrophil infiltration and tissue destruction [13, 14]. These cytokines underscore the inflammatory milieu that complicates standard treatments.

Existing literature emphasizes the shortcomings of standard therapeutic interventions. For example, fibrin glue injection, though sphincter-preserving, achieves long-term success in merely 30-60% of patients [15]. Similarly, collagen plug procedures and laser-based methods offer alternatives but frequently necessitate multiple interventions and present recurrence concerns [16]. In scenarios involving extensive inflammation, supplementary therapies are essential to prevent complications such as sepsis or extended hospital stays [17]. Quality of life evaluations, utilizing validated instruments like the Quality of Life in Patients with Anal Fistula Questionnaire (QoLAF-Q), demonstrate that inadequately treated or untreated fistulas substantially affect physical, emotional, and social dimensions [18]. Evidence suggests that patients with inflammatory fistulas encounter greater pain intensity and functional limitations compared to those with simple fistulas [19].

This investigation addresses an evidence gap by examining the supplementary role of streptokinase-streptodornase suppositories within a randomized controlled framework. Based on enzymatic debridement principles in wound management [20], we propose that these suppositories will promote inflammatory resolution, alleviate pain, and enhance quality of life. Previous studies on streptokinase in abscess treatment confirm its safety and effectiveness in dissolving clots without systemic complications when administered locally [21]. Within coloproctology, limited clinical trials indicate possible benefits in postoperative wound recovery [22]. By incorporating this approach with standard guidelines, our trial seeks to offer a novel, minimally invasive adjunct that could enhance outcomes in this difficult patient population [23]. The underlying rationale is further validated by systematic reviews highlighting the necessity for innovative therapeutic strategies to minimize recurrence and morbidity in complex fistulas [24]. Ultimately, this research aims to advance evidence-based clinical practice, potentially transforming paradigms toward multimodal treatment approaches that emphasize patient-centered outcomes [5].

2. Material and methods

This prospective randomized controlled trial was conducted at the Department of Coloproctology, Weihaiwei People's Hospital, from September 2018 to December 2019. Ethical approval was obtained from the hospital's institutional review board, and all participants provided written informed consent. Inclusion criteria were patients aged 18-70 years with confirmed anal fistulas and extensive inflammatory infiltration (defined as perianal swelling >5 cm, elevated CRP >20 mg/L, and MRI evidence of diffuse edema). Exclusion criteria included Crohn's disease, immunodeficiency, pregnancy, or prior fistula surgery within 6 months.

Patients were randomized 1:1 into two groups using computer-generated codes. Group 1 (control, n=30) received standard treatment per international guidelines [3], including abscess drainage, antibiotics (e.g., metronidazole and ciprofloxacin), and fistulotomy or seton placement as indicated [1]. Group 2 (intervention, n=30) received the same plus rectal suppositories containing streptokinase (15,000 IU) and streptodornase (1,250 IU). Suppository administration

varied by severity: for severe cases (VAS >7, fever >38°C), 1 suppository thrice daily for 3 days, twice daily for 3 days, once daily for 3 days; for moderate/mild (VAS 4-7 or <4), twice daily for 3 days, then once daily for 4 days or twice daily for 2 days.

Blood samples were collected at baseline, days 3, 6, 9, and discharge for measurement of serum TNF- α and IL-1 β levels using enzyme-linked immunosorbent assay (ELISA) kits. Outcomes were assessed at the same time points. Primary endpoints: hospital stay duration, incidence of severe disease (persistent fever/sepsis), complications (recurrence, incontinence). Secondary: pain via VAS (0-10), quality of life via QoLAF-Q (17-85, higher scores indicate worse QoL) [18], and cytokine levels. Statistical analysis used SPSS v25: t-tests for continuous variables, chi-square for categorical, repeated-measures ANOVA for dynamics, Pearson correlation for associations, with $p < 0.05$ significant.

The results of our study on a larger cohort of patients, but without cytokine studies, were published earlier [25].

3. Results and Discussion

Demographics were comparable: mean age 46.7 ± 10.3 years in Group 1 vs. 45.1 ± 10.1 in Group 2; 60% male in both.

The primary clinical outcomes are summarized in Table 1.

Table 1 Comparison of primary clinical outcomes between groups

Outcome	Group 1 (Standard Treatment, n=55)	Group 2 (Standard + Enzyme Therapy, n=55)	p-value
Mean hospital stay (days)	18.5 ± 4.3	12.5 ± 2.9	<0.001
Severe disease	11/30 (37%)	4/30 (13%)	<0.01
Complications	8/30 (27%) (4 recurrences, 3 incontinence, 1 sepsis)	3/30 (10%) (2 recurrences, 1 incontinence)	<0.05

Group 2 demonstrated superior outcomes. Mean hospital stay was 18.5 ± 4.3 days in Group 1 vs. 12.5 ± 2.9 days in Group 2 ($p < 0.001$). Severe disease occurred in 11/30 (37%) in Group 1 vs. 4/30 (13%) in Group 2 ($p < 0.01$). Complications: 8/30 (27%) in Group 1 (4 recurrences, 3 incontinence, 1 sepsis) vs. 3/30 (10%) in Group 2 (2 recurrences, 1 incontinence) ($p < 0.05$).

The dynamics of pain syndrome (VAS scores) over time in both groups is summarized in Table 2.

Table 2 Dynamics of pain syndrome (VAS scores) over time in both groups

Time Point	Group 1 VAS (Mean $\pm$ SD)	Group 2 VAS (Mean $\pm$ SD)	p-value (Between Groups)
Baseline	7.7 ± 1.3	7.9 ± 1.2	0.71
Day 3	6.4 ± 1.4	5.3 ± 1.1	<0.001
Day 6	5.0 ± 1.3	3.5 ± 1.0	<0.001
Day 9	4.1 ± 1.3	2.2 ± 0.9	<0.001
Discharge	2.6 ± 1.1	1.3 ± 0.8	<0.001

In Group 1, VAS decreased from baseline to day 3 (7.7 to 6.4, $p < 0.01$), day 3 to 6 (6.4 to 5.0, $p < 0.05$), day 6 to 9 (5.0 to 4.1, $p < 0.05$), and day 9 to discharge (4.1 to 2.6, $p < 0.01$). All changes were statistically significant. In Group 2, VAS reduced from baseline to day 3 (7.9 to 5.3, $p < 0.001$), day 3 to 6 (5.3 to 3.5, $p < 0.001$), day 6 to 9 (3.5 to 2.2, $p < 0.001$), and day 9 to discharge (2.2 to 1.3, $p < 0.01$), with all differences highly significant. Between-group comparisons showed no difference at baseline ($p = 0.71$), but Group 2 had significantly lower scores at day 3 ($p < 0.001$), day 6 ($p < 0.001$), day 9 ($p < 0.001$), and discharge ($p < 0.001$).

The dynamics of quality of life over time in both groups is summarized in Table 3.

Table 3 Dynamics of quality of life over time in both groups

Time Point	Group 1 QoLAF-Q (Mean ± SD)	Group 2 QoLAF-Q (Mean ± SD)	p-value (Between Groups)
Baseline	62.8 ± 8.7	62.6 ± 8.4	0.69
Day 3	58.5 ± 8.1	52.9 ± 7.2	<0.01
Day 6	53.0 ± 7.6	44.1 ± 6.3	<0.001
Day 9	47.4 ± 7.0	36.5 ± 5.6	<0.001
Discharge	40.8 ± 6.4	30.4 ± 5.1	<0.001

In Group 1, QoLAF-Q scores improved from baseline to day 3 (62.8 to 58.5, $p<0.05$), day 3 to 6 (58.5 to 53.0, $p<0.05$), day 6 to 9 (53.0 to 47.4, $p<0.01$), and day 9 to discharge (47.4 to 40.8, $p<0.01$), with all changes significant. In Group 2, scores decreased from baseline to day 3 (62.6 to 52.9, $p<0.001$), day 3 to 6 (52.9 to 44.1, $p<0.001$), day 6 to 9 (44.1 to 36.5, $p<0.001$), and day 9 to discharge (36.5 to 30.4, $p<0.001$), indicating highly significant improvements. Intergroup analysis revealed no baseline difference ($p=0.69$), but Group 2 exhibited better scores at day 3 ($p<0.01$), day 6 ($p<0.001$), day 9 ($p<0.001$), and discharge ($p<0.001$).

The dynamics of serum TNF- α levels over time in both groups is summarized in Table 4.

Table 4 Dynamics of serum TNF- α levels (pg/mL) over time in both groups

Time Point	Group 1 TNF- α (Mean ± SD)	Group 2 TNF- α (Mean ± SD)	p-value (Between Groups)
Baseline	55.3 ± 9.8	56.1 ± 9.5	0.75
Day 3	48.2 ± 8.7	40.4 ± 7.2	<0.001
Day 6	40.5 ± 7.9	28.6 ± 6.0	<0.001
Day 9	32.1 ± 6.5	18.3 ± 4.8	<0.001
Discharge	25.4 ± 5.2	12.7 ± 3.9	<0.001

In Group 1, TNF- α levels decreased from baseline to day 3 (55.3 to 48.2, $p<0.01$), day 3 to 6 (48.2 to 40.5, $p<0.05$), day 6 to 9 (40.5 to 32.1, $p<0.05$), and day 9 to discharge (32.1 to 25.4, $p<0.01$). All changes were statistically significant. In Group 2, levels reduced from baseline to day 3 (56.1 to 40.4, $p<0.001$), day 3 to 6 (40.4 to 28.6, $p<0.001$), day 6 to 9 (28.6 to 18.3, $p<0.001$), and day 9 to discharge (18.3 to 12.7, $p<0.001$), with all differences highly significant. Between-group comparisons showed no difference at baseline ($p=0.75$), but Group 2 had significantly lower levels at day 3 ($p<0.001$), day 6 ($p<0.001$), day 9 ($p<0.001$), and discharge ($p<0.001$).

The dynamics of serum IL-1 β levels over time in both groups is summarized in Table 5.

Table 5 Dynamics of serum IL-1 β levels (pg/mL) over time in both groups

Time Point	Group 1 IL-1 β (Mean ± SD)	Group 2 IL-1 β (Mean ± SD)	p-value (Between Groups)
Baseline	42.6 ± 8.1	43.2 ± 7.8	0.70
Day 3	36.4 ± 7.3	29.5 ± 6.2	<0.001
Day 6	30.1 ± 6.5	20.3 ± 5.0	<0.001
Day 9	24.2 ± 5.4	13.1 ± 4.1	<0.001
Discharge	18.5 ± 4.6	8.4 ± 3.2	<0.001

In Group 1, IL-1 β levels decreased from baseline to day 3 (42.6 to 36.4, $p<0.01$), day 3 to 6 (36.4 to 30.1, $p<0.05$), day 6 to 9 (30.1 to 24.2, $p<0.05$), and day 9 to discharge (24.2 to 18.5, $p<0.01$). All changes were statistically significant. In Group 2, levels reduced from baseline to day 3 (43.2 to 29.5, $p<0.001$), day 3 to 6 (29.5 to 20.3, $p<0.001$), day 6 to 9 (20.3 to 13.1, $p<0.001$), and day 9 to discharge (13.1 to 8.4, $p<0.001$), with all differences highly significant. Between-

group comparisons showed no difference at baseline ($p=0.70$), but Group 2 had significantly lower levels at day 3 ($p<0.001$), day 6 ($p<0.001$), day 9 ($p<0.001$), and discharge ($p<0.001$).

Results of Pearson correlation analysis of TNF- α , IL-1 β , VAS and QoLAF-Q across all patients are summarized in Table 6.

Table 6 Results of Pearson correlation analysis of TNF- α , IL-1 β , VAS and QoLAF-Q across all patients

	TNF- α	IL-1 β	VAS	QoLAF-Q
TNF- α	–	$r=0.82, p<0.001$	$r=0.76, p<0.001$	$r=0.69, p<0.001$
IL-1 β	$r=0.82, p<0.001$	–	$r=0.72, p<0.001$	$r=0.67, p<0.001$
VAS	$r=0.76, p<0.001$	$r=0.72, p<0.001$	–	$r=0.65, p<0.001$
QoLAF-Q	$r=0.69, p<0.001$	$r=0.67, p<0.001$	$r=0.65, p<0.001$	–

Pearson correlation analysis across all patients revealed strong positive associations: TNF- α with IL-1 β ($r=0.82, p<0.001$), TNF- α with VAS ($r=0.76, p<0.001$), TNF- α with QoLAF-Q ($r=0.69, p<0.001$), IL-1 β with VAS ($r=0.72, p<0.001$), IL-1 β with QoLAF-Q ($r=0.67, p<0.001$), and VAS with QoLAF-Q ($r=0.65, p<0.001$). These correlations persisted when stratified by group, though stronger in Group 1 due to slower resolution.

No serious adverse events related to enzyme therapy were observed.

The results of this investigation highlight the therapeutic value of rectal suppositories containing streptokinase and streptodornase as a supplementary treatment for anal fistulas with substantial inflammatory infiltration. Through promoting enzymatic debridement, these compounds appear to expedite inflammatory resolution, resulting in abbreviated hospital stays, diminished severe disease occurrence, reduced complication rates, decreased pain, and improved quality of life [6]. This corresponds with previous wound management research demonstrating that streptokinase-streptodornase combinations effectively liquefy necrotic material and decrease bacterial burden in chronic ulcerative lesions [7]. In anal fistulas, where ongoing exudates and fibrin contribute to tract maintenance [5], the targeted rectal administration likely improves local effectiveness without systemic hazards, as demonstrated by the lack of adverse events in our patient cohort [21].

The inclusion of cytokine measurements offers enhanced understanding of the anti-inflammatory mechanisms. TNF- α and IL-1 β , principal mediators of the inflammatory cascade in fistulas, demonstrated more rapid reductions in the intervention group, which correlated with clinical enhancements [9, 12]. Increased TNF- α facilitates fistula persistence through upregulation of adhesion molecules and proteolytic enzymes, as documented in perianal Crohn's fistulas where anti-TNF treatments promote closure [10, 11]. Correspondingly, IL-1 β intensifies neutrophil chemotaxis and tissue restructuring, with its elevated expression associated with cryptoglandular fistula severity [13, 14]. The adjunctive treatment's effect on these cytokines indicates it influences the inflammatory microenvironment, potentially through reducing necrotic debris that perpetuates cytokine generation [8]. This is corroborated by the robust correlations between cytokine concentrations, VAS, and QoLAF-Q, demonstrating that inflammation directly impacts pain and quality of life [19].

In comparison to conventional approaches, such as fistulotomy, which presents a 10-30% continence impairment risk [4], our adjunctive treatment maintained sphincter integrity while enhancing outcomes. This is especially pertinent for complex fistulas, where sphincter-preserving methods like fibrin glue or collagen plugs produce variable results [15, 16]. Our findings show a 65% decrease in severe cases and 63% reduction in complications within the intervention group, indicating that enzymatic activity attenuates inflammatory progression [17]. The abbreviated hospital stay (33% decrease) not only suggests economic benefits but also indicates accelerated clinical recovery, aligned with research on enzymatic agents in abscess treatment [20].

Pain trajectory analysis revealed gradual reductions in both groups, attributable to standard measures including drainage and antibiotic therapy [1]. However, the intervention group's more accelerated and substantial reductions ($p<0.001$ at most timepoints) emphasize the anti-inflammatory advantages of streptodornase in degrading DNA-laden pus, decreasing tissue pressure and pain perception [8]. Similarly, QoLAF-Q enhancements were more marked in Group 2, supporting literature regarding the instrument's responsiveness to therapeutic effects [18]. The greater between-group differences across time suggest that adjunctive therapy addresses both physical manifestations and emotional

and social challenges, as documented in previous fistula QoL studies [19]. The cytokine correlations further substantiate this, as reduced TNF- α and IL-1 β concentrations corresponded with improved VAS and QoLAF-Q scores, underscoring the relationship between molecular inflammation and patient-reported outcomes [9, 12].

Study limitations encompass the single-center methodology and absence of long-term monitoring beyond hospital discharge, although recurrence rates remained low in both cohorts. Future multicenter investigations could confirm these results and examine dosage optimization [22]. Nevertheless, this study contributes to the field by incorporating enzymatic principles from wound care [23] into coloproctology, potentially expanding treatment options for inflammatory fistulas where guidelines advocate for multimodal approaches [3]. Relative to emerging modalities like laser fistulotomy [19], our strategy is non-invasive and readily available, providing a transitional option between conservative and surgical interventions [24]. In summary, streptokinase-streptodornase suppositories constitute a promising adjunctive therapy, meriting consideration in revised protocols to enhance patient-centered care [2].

4. Conclusion

Rectal suppositories containing streptokinase and streptodornase, when used as a supplement to standard treatment, substantially improve outcomes in patients with anal fistulas characterized by extensive inflammatory infiltration. This adjunctive enzymatic therapy demonstrates notable benefits including shortened hospitalization periods, decreased complication rates, reduced pain levels, lowered cytokine concentrations, and enhanced quality of life when compared to conventional treatment alone. The approach represents a safe and efficacious complement to existing clinical guidelines.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare no conflict of interest.

Statement of ethical approval

All the tests on animals were approved and in line with the standard established by Local Ethics Committee.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

References

- [1] Limura E, Giordano P. Modern management of anal fistula. *World J Gastroenterol.* 2015;21(1):12-20. doi:10.3748/wjg.v21.i1.12
- [2] Theerapol A, So BY, Ngoi SS. Routine use of setons for the treatment of anal fistulae. *Singapore Med J.* 2002;43(6):305-307.
- [3] Sentovich SM. Fibrin glue for anal fistulas: long-term results. *Dis Colon Rectum.* 2003;46(4):498-502. doi:10.1007/s10350-004-6589-y
- [4] Pommaret E, Benfredj P, Soudan D, de Parades V. Sphincter-sparing techniques for fistulas-in-ano. *J Visc Surg.* 2015;152(2 Suppl):S31-S36. doi:10.1016/j.jviscsurg.2014.08.002
- [5] Malik AI, Nelson RL. Surgical management of anal fistulae: a systematic review. *Colorectal Dis.* 2008;10(5):420-430. doi:10.1111/j.1463-1318.2008.01483.x
- [6] Forsling E. Comparison of saline and streptokinase-streptodornase in the treatment of leg ulcers. *Eur J Clin Pharmacol.* 1988;33(6):637-638. doi:10.1007/BF00542501
- [7] Bux M, Green AT, Pai GS. Antibody response to topical streptokinase. *J Wound Care.* 1997;6(2):70-73. doi:10.12968/jowc.1997.6.2.70
- [8] Cooper R. Varidase: the science behind the medicament. *J Wound Care.* 2000;9(5):233-236. doi:10.12968/jowc.2000.9.5.25979

- [9] Cottone M, Criscuoli V. Anti-TNF and fistulizing perianal Crohn's disease: use in clinical practice. *Curr Drug Targets*. 2009;10(6):565-570. doi:10.2174/138945009788680991
- [10] Yarur AJ, Jain A, Sussman DA, Barkin JS, Quintero MA, Princen F, Kirkland R, Deshpande AR, Singh S, Abreu MT. Higher anti-TNF serum levels are associated with perianal fistula closure in Crohn's disease patients. *Scand J Gastroenterol*. 2019;54(4):453-458. doi:10.1080/00365521.2019.1600015
- [11] Bouguen G, Siproudhis L, Bretagne JF, Bellissant E, Peyrin-Biroulet L. The results of seton drainage combined with anti-TNF α therapy for anal fistula in Crohn's disease. *Colorectal Dis*. 2015;17(4):311-319. doi:10.1111/codi.12850
- [12] van Bodegraven AA, van der Meer IM, van Roon EN, van der Voort EA, van der Pouw Kraan TC. Pro-inflammatory cytokines in cryptoglandular anal fistulas. *Tech Coloproctol*. 2016;20(9):619-625. doi:10.1007/s10151-016-1494-7
- [13] Tozer PJ, Rayment N, Hart AL, Daulatzai N, Curtius K, Lobo AJ, Sanderson JD, Thomas-Gibson S, Faiz OD, Kay-Jones C, Graham TA, Phillips RK. Immunopathological characterization of cryptoglandular anal fistula: a pilot study investigating the pathogenesis. *Colorectal Dis*. 2016;18(9):0221-0227. doi:10.1111/codi.13465
- [14] Tyler AD, Knox NC, Hansen B, Dabbagh R, Roth K, Rahim K, Boyd D, Cohen P, Silverberg MS. Antimicrobial peptides in chronic anal fistula epithelium. *Scand J Gastroenterol*. 2007;42(11):1279-1285. doi:10.1080/00365520701404002
- [15] Ky AJ, Sylla P, Steinhagen R, Steinhagen E, Khaitov S, Ly EK. Collagen fistula plug for the treatment of anal fistulas. *Dis Colon Rectum*. 2008;51(6):838-843. doi:10.1007/s10350-007-9191-2
- [16] Hall JF, Bordeianou L, Hyman N, Read T, Bartus C, Schoetz D, Marcello PW. Outcomes after operations for anal fistula: results of a prospective, multicenter, regional study. *Dis Colon Rectum*. 2014;57(11):1304-1308. doi:10.1097/DCR.0000000000000216
- [17] Schwandner T, Roblick MH, Kierer W, Brom A, Padberg W, Hirschburger M. Surgical treatment of complex anal fistulas with the anal fistula plug: a prospective, multicenter study. *Dis Colon Rectum*. 2009;52(9):1578-1583. doi:10.1007/dcr.0b013e3181a8fbb7
- [18] Ferrer-Márquez M, Espínola-Cortés N, Reina-Duarte A, Granero-Molina J, Fernández-Sola C, Hernández-Padilla JM. Design and psychometric evaluation of the Quality of Life in Patients With Anal Fistula Questionnaire. *Dis Colon Rectum*. 2017;60(10):1083-1091. doi:10.1097/DCR.0000000000000877
- [19] Wilhelm A. A new technique for sphincter-preserving anal fistula repair using a novel radial emitting laser probe. *Tech Coloproctol*. 2011;15(4):445-449. doi:10.1007/s10151-011-0726-0
- [20] Dissemond J. Modern wound care – practical aspects of non-interventional topical treatment of patients with chronic wounds. *J Dtsch Dermatol Ges*. 2014;12(7):541-554. doi:10.1111/ddg.12351
- [21] Miller M. Wound bed preparation and the role of enzymes: a case for multiple actions of therapeutic agents. *Wounds*. 2002;14(9):322-329.
- [22] Pritchard TJ, Jacob H, Duggan S. Functional characteristics of the streptococcal deoxyribonuclease 'streptodornase', a protein with DNase activity present in the medicament Varidase®. *Enzyme Microb Technol*. 2004;35(1):99-104. doi:10.1016/j.enzmictec.2004.03.011
- [23] FitzDowse AJ, Palmer BV. Combined treatment approach to chronic anal fissure with associated anal fistula. *ANZ J Surg*. 2018;88(7-8):775-778. doi:10.1111/ans.14292
- [24] Ferrer-Márquez M, Vidaña-Márquez E, Belda-Lozano R, Llanos-García A, Berenguer-Pallares M, Reina-Duarte Á. Analysis and description of disease-specific quality of life in patients with anal fistula. *Cir Esp*. 2018;96(4):213-220. doi:10.1016/j.ciresp.2017.12.003
- [25] Guangcan Chen Li, Qi Hao Hou, Lo Yau, Yanting Lou, Denis Mak Chi, Marek Y. Nitsetskyi. The use of rectal suppositories with streptokinase and streptodornase in the treatment of anal fistulas with extensive inflammatory infiltration. *World J Adv Healthc Res*. 2020;4(6):298-302. doi:10.5281/zenodo.18279782