An Approach to Rectovaginal Fistulae in Advanced Cancer: The Central Role of Palliative Care

Abordagem das Fístulas Rectovaginais na Neoplasia Avançada: O Papel Central dos Cuidados Paliativos

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10.48687/lsj.v2i4.76

Abstract

The development of rectovaginal fistulae in patients with advanced pelvic malignancies can lead to significant morbidity and suffering. It represents a heavy burden on patients, dealing with local symptoms, psychological distress, and self-image issues, contributing to poor quality of life. It also represents a challenge for clinicians due to the need for multiple professional interventions, need for continuity of care and regular clinical reevaluation. Palliative care professionals play a central role in these cases. Nevertheless, literature in this specific context is lacking. We present a narrative review on this topic, focusing on conservative treatment with both pharmacological measures to control fistula effluent and local care to prevent complications; psychological and spiritual support addressing self-image, self-esteem, and sexuality issues. A summary review of the aetiology, symptomatology, diagnosis and surgical approach is also carried out.

Keywords: Palliative Care; Pelvic Neoplasm/complications; Rectovaginal Fistula/diagnosis; Rectovaginal Fistula/etiology; Rectovaginal Fistula/therapy

Resumo

O desenvolvimento de fístulas rectovaginais em doentes com neoplasias pélvicas avançadas pode levar a morbilidade e sofrimento significativos. Representa um fardo para os doentes, que lidam com sintomas locais, sofrimento psíquico e problemas de autoimagem, contribuindo para a baixa qualidade de vida. Representa também um desafio para os clínicos devido à necessidade de intervenções multidisciplinares, necessidade de continuidade de cuidados e revisão clínica regular. Os profissionais de cuidados paliativos desempenham, por isso, um papel central nesses casos. No entanto, a literatura neste contexto específico é escassa. Apresentamos uma revisão narrativa sobre o tema, focando no tratamento conservador, com medidas farmacológicas para controlo do efluente da fístula e cuidados locais para prevenção de complicações; apoio psicológico e espiritual abordando questões de autoimagem, autoestima e sexualidade. É também realizada uma revisão sumária da etiologia, sintomatologia, diagnóstico e abordagem cirúrgica.

Palavras-chave: Cuidados Paliativos; Fístula Rectovaginal/diagnóstico; Fístula Rectovaginal/etiologia; Fístula Rectovaginal/tratamento; Neoplasias Pélvicas/complicações

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Received/Recebido: 01/11/2021 **- Accepted/Aceite:** 08/12/2021 **- Published/Publicado:** 31/12/2021

Introduction

The development of rectovaginal fistulae (RVF) in patients with advanced pelvic malignancies is not uncommon and represents a complex challenge for clinicians. Beyond the impact on the patient, which ranges from physic to psychologic, correct management places a significant strain on healthcare resources, evolving symptom control, self-image and psychological issues, multidisciplinary treatment, discussion of goals of care and advanced care planning. In this situation, palliative care (PC) teams can make a difference. However, evidence-based guidance is scarce, and most reports found in the literature focus on surgical approaches, with PC being mentioned as an umbrella term with few specifications of actual measures.

Early introduction of PC in all patients with cancer is currently recommended.[1-7] In gynaecological cancer populations, studies have demonstrated improvement in symptoms, and goals of care at the end of life.[8,9] Despite these recommendations, and the growing evidence in favour of the benefits of PC, gaps in its access remain. In some studies, nearly one-third of gynaecological oncologic patients died without ever receiving a referral to PC[4,10] and over three-quarters died without a Medical Power of Attorney or Living Will.[10]

The current article provides an up-to-date summary of the existing medical evidence on RVF and a comprehensive overview of the management of these patients. This includes a thorough evaluation of symptom burden and goals of care to define a treatment strategy, that may include local care, pharmacological approach, psychosocial support, and palliative surgery, most often in combination.

Aetiology

A fistula is an abnormal opening that attaches two or more organs or spaces that do not normally connect.[11,12] The development of fistulae can result from congenital malformations or acquired causes, such as inflammatory bowel disease, obstetric trauma, radiotherapy, surgery, among others. In this article, we focus only on acquired RVF from malignant causes. They may occur as a direct complication of some cancers - most often rectum, endometrium, cervix or vagina, with meaningful local expression,[11,13-18] or as a consequence of its treatment: radiotherapy,[11,14-22] immunotherapy,[23-25] or surgery.[26]

It is difficult to assess the exact incidence and prevalence of RVFs due to their relative rarity, lack of structured reporting, and small number of patients included in the published series.[16]

Classification

According to their anatomical location, RVF can be classified as "high" if they originate proximally to the anorectal sphincter, or "low" if they originate distally to the anorectal sphincter (also called anovaginal fistulae or transphincteric fistulae).[11,16] They can also be classified as "simple" or "complex". The simple fistulae are characterized by a diameter < 2.5 cm and location in the lower and middle third of the vagina. The complex fistulae have a diameter > 2.5 cm and are located in the upper third of the vagina (the most frequently associated with malignancy).[13,16,27] Distinction is important because it has implications for the surgical strategy, if indicated.[11] Fistulae can also be classified regarding their aetiology and from a physiological point of view (high, moderate or low output).[28]

Symptoms

Small fistulae can be asymptomatic. When symptomatic, signs and symptoms will depend on the parts of the body that are affected:

- Vaginal symptoms: vaginal discharge, vaginitis, vulvitis, passing of air or stool through the vagina, dyspareunia, perineal pain and recurrent vaginal infections[11,13,16,18,20,29-31];
- Bowel symptoms: diarrhoea, abdominal pain, anorectal burning sensation.[13,20]

In addition to the physical dimension of suffering, there is also a psychosocial aspect that affects the well-being of the person.[11,30] Depression and anxiety are the most common psychological comorbidities in cancer patients and some data points towards lower quality of life, worse outcomes and longer hospitalizations in these patients.[29,32-34] Besides the psychological burden of suffering from cancer, gynaecological malignancies also interfere directly with women sexuality, motivating a change in sexual identity and expression.[29,32] Studies addressing the psychosocial consequences of vaginal fistulae come from the developing world, where obstetric traumatic fistulae are frequent.[35] Regardless of aetiology, age and cultural background, leakage of stool through the vagina and consequent discomfort and odour interfere with daily life activities and interpersonal relationships.[36] Feelings of shame, loss of self-esteem, sadness, suicidal thoughts, anxiety, decreased libido, and loneliness leading to social isolation are frequently reported.[35,36]

Diagnosis

When a RVF is suspected, a vaginal examination (with/without colposcope) should be done, and it can be sufficient for diagnosis. However, identifying fistulae can be difficult on vaginal examination. For the diagnosis of simple fistulae, the use of enemas with warm saline solution with a few drops of methylene blue is an alternative. The passage of the dye to the vaginal route confirms the diagnosis. In complex fistulae, performing an imaging exam is mandatory, as it is the understanding of

the anatomy and the aetiology that will guide the subsequent approach.[37]

There are several complementary imaging methods for the diagnosis of fistulae, namely, fistulography, ultrasonography (US), computed tomography (CT) and magnetic resonance imaging (MRI).

Fistulography was the first method described for evaluating RVF. It consists of the injection of radiographic contrast through a catheter in the external orifice of the fistula, and subsequent radiographs are taken from different angles.[37] This technique has, however, some disadvantages. First, contrast instillation can be painful and contribute to the spread of the fistula content, with an inherent risk of infection. Second, the location of the path is ambiguous in relation to the sphincter complex, as it is not possible to visualize the anorectal musculature.

CT is an imaging test that assures the visualization of surrounding structures, which, in some cases, allows for the exclusion of differential diagnoses (perianal abscesses, perirectal abscesses, inflammation, cellulitis). Disadvantages of CT include the use of ionizing radiation and low yield in making the distinction between inflammatory soft tissue streaking and the fistula tract, except in cases where air or contrast material is documenting extending from the bowel. Notwithstanding, CT remains a practical means of evaluating possible RVF in those who are not candidates for MRI.[37]

The disadvantages of both fistulography and CT have meant that MRI has come to play an increasingly important role in the characterization of RVF,[37,38] and today it is the method of choice.[37] It allows not only for the identification of the fistula, but also a recognition of regional anatomy, integrity of the sphincter, relationship between the fistula and adjacent structures, and the presence of associated conditions such as abscesses or disease progression.[37,39]

Endoluminal US is a technique that allows for an excellent sphincter evaluation[16,39] but very limited assessment of surrounding structures.[37]

Treatment

1. Conservative treatment

Conservative treatment is recommended for patients suffering from RVF who are waiting or are not eligible for surgical intervention. In these cases, focus is placed on addressing symptoms and improving quality of life. Nevertheless, to date, most evidence on PC come from studies on non-malignant aetiologies, and isolated case reports.

Conservative measures aim to regulate bowel function and control fistula output, manage accompanying inflammation and infection, provide proper nutrition and hydration, maintain skin integrity, promote hygiene and comfort and offer psychosocial support.[14,34]

1.1. Nonpharmacological measures

Nutritional support

The type of gastrointestinal fluid lost depends on the fistula's location and may lead to dehydration, electrolyte imbalances, vitamin deficits and malnutrition.[28] Enteric losses, lower protein intake and cancer-related continuous inflammation cause hypoalbuminemia preventing further spontaneous closure.[28] Higher caloric and protein needs due to hypercatabolism require parenteral or enteral nutrition that may not be attainable, tolerated or desired in the final weeks/months of life.[28,40] Focus should be on providing adequate hydration and avoiding diarrhoea and constipation, possibly with a low residue, high fibre and high protein diet suited to the patient's goals of care.[41]

Skin care/local wound measures

Passage of stool through the vagina, either continuously or intermittently, can lead to perineal irritation, odour and discomfort. Adequate dressings, impermeable bed sheets, absorbent pads, diapers and skin care with barrier creams such as zinc oxide are of paramount importance.[28,34,42] The topical use of metronidazole solutions has been recommended to control malodorous discharge.[34,43] Frequent hygiene and sitz baths are helpful and pads should be changed as often as needed to keep the patient comfortable.[34,41] Cloths soaked in intravenous metronidazole solution or a dilution of crushed pills packet into the vagina have been suggested.[34] This could be an option for patients with low output fistulae and cloths should be kept in place for no more than a couple of hours since stasis of fistula effluent can be prejudicial.[34] Fanning, air fresheners and aromas may provide additional comfort to the patient and caregivers in disguising odour.[44] Particularly in end-of-life context, consideration can be given to "bolder" strategies such as the use of a faecal management system applied in the vagina.[45]

1.2. Pharmacological treatment

Pharmacological treatment aims to control fistula effluent and preserve vaginal mucosal integrity. Attention should be paid to the route of administration as patients with advanced cancer frequently present swallowing difficulties and, in some, enteral feeding is in place. Some drugs may be compatible with administration by enteral tube and involvement of pharmacy services is desired in optimizing drugs administration and interaction. During hospitalisation, and as disease progresses, subcutaneous (sc) route becomes the preferred one and careful revision of potential interactions is essential. Even though the therapeutic arsenal may be narrower, bioavailability is usually acceptable and more potent agents are used. Of note, when introducing a new drug, the maximal effect is generally not immediate and so it is reasonable to wait 48 to 72 hours

before increasing doses or changing drugs.[46] All the follow proposed pharmacological treatments are summarized on Table 1.

Gastric acid neutralizers

Acid suppression decreases the acidity and volume of gastric secretions and helps to control the fistula effluent. Sucralfate 1 g bid per os (p.o.), histamine-2 receptor antagonists as ranitidine 50 mg sc bid-qid, and proton pump inhibitors (as lansoprazole 30 mg p.o. qd) are useful.[28,40] Histamine-2 receptor antagonists are more effective than proton pump inhibitors in reducing the volume of secretions and offer the advantage of sc administration when oral route is no longer possible.[47] Additionally, *Clostridioides* infection is a well know adverse event related to proton pump inhibitors and warrants suspicion if new-onset diarrhoea or fistula output increases.[48]

Table 1. Pharmacological treatments used on conservative approach of RVF Agents.

	Mechanism of action	Dose range	Route	Main adverse events	Notes
Gastric acid neutralizers					
Sucralfate	Antacid	1 g bid-qid	p.o.	Constipation	Administration by enteral feeding tube not recommended due to viscosity
Ranitidine	Histamine-2 receptors antagonist, weak antimuscarinic effect	- 150 mg id-bid p.o. - 50 mg bid-qid sc - 150-200 mg/ /24 h as sc continual infusion	p.o. or sc		More effective as anti-secretory than proton pump inhibitors and lower risk of *Clostridioides* infection Dose reduction in kidney impairment If once daily prefer bedtime administration
Lansoprazole	Proton pump inhibitor	30 mg id-bid	p.o.	Increased risk of pneumonia and *Clostridioides* infection, hypomagnesemia	Orodispersible formulations available; compatible with enteral feeding tube More effective as acid suppressors than Histamine -2 receptors antagonist Higher bioavailability and faster onset of action than other drugs of the same class
Antimotility and antisecretory agents					
Psyllium	Bulk-forming laxative	1 sachet daily	p.o	Flatulence, abdominal distension, bowel obstruction	Ensure proper hydration
Codeine	Weak opioid, weak antimuscarinic effect	30-60 mg qid or prn	p.o	Opioid intoxication	Adjust to renal and hepatic function
Loperamide	μ-opioid receptor agonist	First dose of 4 mg, followed by 2 mg p.o. after each discharge, up to 24 mg daily	p.o	Nausea, constipation, headache, dizziness	Orodispersible and oral solution formulations available More potent than codeine as antidiarrheal Consider adding octreotide if high doses are needed Downtitrate to maintenance dose as possible
Hyoscine/scopolamine butylbromide or atropine	Anticholinergic and antimuscarinic	- 20 mg sc tid or prn - 20-300 mg/ /24 h as sc continual infusion	sc	Delirium, blurred vision, xerostomia, constipation, urinary retention	May precipitate psychomotor agitation mostly in end of life, concurrent prescription of haloperidol or midazolam as needed
Octreotide	Somatostatin analogue	- 50-100 μg tid - 250-500 μg/ /24 h as sc continual infusion up to 750 μg/24 h	sc	Dysglicemia, xerostomia, flatulence, gallstones, arrythmias, local injection reaction	May have additional antiemetic and analgesic effect More potent than hyoscine/scopolamine butylbromide in reducing output
Antimicrobials					
Metronidazol	Anaerobic antibacterial and antiprotozoal	200 mg qd to 400 mg tid as sc continual infusion	p.o. or topical	Nausea, vomiting, abdominal pain, diarrhoea (p.o.) Skin irritation, photosensitivity (topical)	Dose adjustment in liver impairment Maintenance dose of 200 mg/daily may be needed long-term Topical administration id-bid after cleansing
Topical oestrogens					
Estradiol	Oestrogen	0.01 0mg daily	Vaginal	Local irritation	Ovule for intravaginal administration
Estriol	Oestrogen	50μ-1 mg/g	Vaginal	Local irritation	Less potent, less systemic effects Cream for external use

Antimotility and antisecretory agents

Slowing gastrointestinal transit and bulking the effluent can be achieved with antimotility or antisecretory agents such as psyllium (one sachet daily at breakfast), loperamide (2 mg p.o. after each discharge, up to 24 mg daily), codeine (60 mg qid), antimuscarinics and octreotide.[28,49,50]

Hyoscine butylbromide and atropine-diphenoxylate (20 mg sc tid or prn) are muscarinic antagonists that decrease intestinal motility and secretion, thereby contributing to reduce fistula output and alleviate colic pain.[47]

Octreotide is a synthetic somatostatin analogue that mimics its physiological effect with longer half-life. Octeotride inhibits pancreatic endocrine and exocrine secretion, intestinal motility, gastric emptying, gallbladder drainage and decreases splanchnic blood flow, which leads to decreased intestinal secretions and stretching of the bowel wall.[28,32,40,51] In PC, octreotide indications include malignant bowel obstruction and chemotherapy-induced diarrhoea. Starting doses of 50-100 µg sc tid can be titrated to continuous infusion as needed. Its use in fistulae management has been studied in enterocutaneous fistulae of non-malignant aetiologies, where it showed decreased fistula output and shorter time to spontaneous closure.[28,40,49,51]

Prokinetics such as metoclopramide should be avoided as they can increase fistula output. Therefore, we recommend an anti-secretory strategy in patients with concomitant fistulae and malignant bowel obstruction.[49]

Corticosteroids

The indication for corticosteroids such as dexamethasone is well established for malignant intestinal obstruction in the setting of peritoneal carcinomatosis, as it can help reduce bowel wall oedema and associated nausea.[32,50] It has been shown to help achieve symptom control, although without advantages in survival.[32] The use of systemic and topical steroids has been only described in fistulae associated with inflammatory bowel disease and radiation proctitis.[42,52] Evidence of systemic and topical steroids is lacking in RVF and, therefore it should be used to control tumour burden or address other symptoms, as indicated.

Antibiotics

The sole presence of a fistula is not an indication for antibiotic therapy. Antibiotics can be used to treat concomitant abdominal collections, urinary or soft tissue infection if they are in line with established goals of care.[28] It should be noted that secondary bacterial overgrowth and fungal vaginitis are possible complications and should be treated with antibiotics and antifungals, respectively.[34]

Malodorous vaginal discharge is due to bacterial proliferation in the vagina, either by direct stool contamination or the presence of cancer tissue, promoting anaerobic necrosis.[34,43] Studies in cervical cancer with and without fistulizing disease suggested the use of oral metronidazole for odour control. Doses range from 200 mg qd to 400 mg tid depending on severity and can be titrated as needed.[43,53] A proposed approach is to start with 400 mg tid for a week and then keep 200 mg daily as a maintenance dose. If breakthrough malodour appears, a new cycle of 400 mg tid can be tried.[53] The study also suggests low-dose metronidazole reduces the risk of rectovaginal and vesicovaginal fistula development in cervical cancer, similarly to what has been shown in other conditions as perianal abscess and Crohn's disease.[53]

Topical oestrogens

Vaginal lubricants and moisturizers can be used as needed. Topical oestrogens improve the mucosa vascularity, muscle extensibility and lubrification of the vagina in postmenopausal women.[54,55] Evidence suggests their role as an adjuvant in rectovaginal and vesicovaginal fistulae since they can improve symptoms, and promote the healing of surrounding tissues and fistulous tract in patients both awaiting surgery or who are not good surgical candidates.[52,54-57] Localized hormone therapy includes preparations containing estradiol, as well as estriol. They can be used daily for two weeks and then possibly reduced two to three times a week according to clinical response[58] although no specific recommendations in palliative setting were found.

1.3. Psychological and social support

Psychosocial support for patients and their families is essential to improve the quality of life and alleviate emotional/existential suffering, along with assistance in decision making and goals of care.[32] It should be carried out by a multidisciplinary team including doctors, nurses, psychologist, chaplains, social workers, and others. Intervention should aim to explore topics such as mortality, faith, loss and hope, promoting coping skills and improving patients' resources and support network.[18] Gynaecological malignancies interfere with female sexuality, either as a result of local disease effects or their psychological implications,[29,32] and conversations exploring her concerns about sex should be encouraged.[34]

In patients suffering from depression and/or anxiety, pharmacological therapy with anxiolytics and antidepressants is recommended along with psychological support.[18,32] However, one should bear in mind that mood-elevating agents may take up to six weeks to influence symptoms and patients with briefer prognosis may not benefit from it.[32] As disease progresses readjustment of goals and strategies may be required and stimulants such as methylphenidate may be used off-label to address fatigue and listlessness associated with depression at the end-of-life.[32,42]

2. Surgical repair

Palliative surgery is that which is performed during the stages of incurable disease with the goal of reducing the patient's symptoms.[59] It may be required in the setting of cancers of the abdominal or pelvic cavity, such as the occurrence of fistulae formation, intestinal obstruction, and genital and lower gastrointestinal haemorrhage.[42,59,60] The choice of the surgical method must be based on the patient's prognosis, the cause, and the location of the fistula.[15] Surgical treatment is extremely difficult, and no standard surgical procedure is accepted worldwide.[61]

Low RVF are potentially treatable with local repair (trans-anal, trans-vaginal or trans-perineal approach).[16,17] The high RVF, must be treated with faecal diversion (loop transverse colostomy), abdominal perineal resection or low anterior resection of the rectum (with diversion or primary anastomosis).[15,17,21,31,62] Although a loop transverse colostomy is a frequent cause of complications (prolapse and paracolostomy hernias), a few authors advocate this technique because it does not require a laparotomy and may be performed with a local incision.[59] It is a safe option for some patients with unresectable recurrent or primary malignancy and in patients with multiple comorbidities.[11]

Low anterior resection of the rectum is often the procedure of choice in patients with cancers of the gastrointestinal tract. In some cases, due to advanced stages of disease or diffuse organ infiltration, a multivisceral resection of neighbouring organs is needed.[15] Regarding the approach, laparoscopic management seems to be safer and feasible compared with open surgery, although more studies are needed.[62,63] In the repair of complex fistulae, interposition grafts are also used, in order to provide a new blood supply by inserting healthy tissue around the fistula.[18,64]

Although pelvic exenteration is described in a palliative setting[60] it should only be considered as a last resort and in rare indications (large necrotizing tumours with a high bleeding risk or impending development of a cloaca) because it is associated with a high perioperative morbidity and mortality, besides need of urostomy and enterostomy and their related complications.[15]

The endoscopic approach can be considered in patients who are not candidates for surgery. The trans-anal endoscopic microsurgery involving repair of the fistula with an advanced flap and temporary colostomy,[29] endoscopic endoluminal stenting,[17] endoscopic use of clipping devices in combination with endoloops,[65] anal fistula plug and fibrin glue[66] are reported techniques. There are also some reports of the use of occlude devices in intervention radiology.[17] The existing literature is scarce in terms of advanced cancer disease and outcomes but seems to point to some improvement in morbidity.[13,29]

Conclusion

Palliative management of RVF remains an overlooked topic. The literature is scarce and addresses mainly curative contexts. In malignant aetiology, surgical management is possible only in very select cases and probably not in those with advanced cancer. Malignant fistulae rarely close spontaneously and treatment is often prolonged until the death of the patient. As fistula closure is unlikely in the setting of active cancer and lack of source control, focus should be placed on addressing symptoms and improving quality of life. This narrative review emphasizes conservative measures. We hope to shed some light on this topic and underline the importance of early involvement of PC specialized teams. As key points of this review, we would like to highlight:

- Conservative treatment, with early referral to PC team, promoting global and shared management and continuity of care (hospital/community/different professionals or specialities);
- Strict symptom control, based on the right drug treatment (pain and fistulae losses control) and regular review;
- The exploration of dignity and self-image issues focusing on more than the physical losses and the illness.

Responsabilidades Éticas

Conflitos de Interesse: Os autores declaram não possuir conflitos de interesse.

Suporte Financeiro: O presente trabalho não foi suportado por nenhum subsídio ou bolsa.

Proveniência e Revisão por Pares: Não comissionado; revisão externa por pares.

Ethical Disclosures

Conflicts of Interest: The authors have no conflicts of interest to declare.

Financial Support: This work has not received any contribution grant or scholarship.

Provenance and Peer Review: Not commissioned; externally peer reviewed.

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