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Advances in the therapeutic approaches to feline sporotrichosis: A review

Avanços na abordagem terapêutica da esporotricose felina: uma revisão

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Abstract: Feline sporotrichosis is an emerging zoonosis of growing concern, primarily transmitted through scratches, bites, or direct contact with secretions from infected cats. This mycosis significantly impacts public and animal health, particularly in urban areas with uncontrolled cat populations. Clinical signs typically include skin lesions, which may progress to systemic manifestations in severe cases. Standard antifungal treatment has proven effective in most cases, playing a crucial role in controlling disease progression and preventing zoonotic transmission. This literature review synthesizes available therapeutic strategies for the treatment of feline sporotrichosis to provide resources that assist professionals in improving the management of this mycosis. Despite significant advances in understanding and treating this condition, important knowledge gaps remain, particularly concerning the standardization of therapeutic protocols, the management of refractory cases, and the mitigation of treatment-associated adverse effects. Therefore, it is concluded that, despite advancements in available therapies, there is a continued need for additional clinical trials to establish more precise protocols for most of the therapeutic options discussed.

Keywords: Fungal infection, *Sporothrix spp.*, treatment.

Resumo: Esporotricose felina é uma zoonose emergente de crescente preocupação, transmitida principalmente por meio de arranhões, mordidas ou contato direto com secreções de gatos infectados. Essa micose impacta significativamente a saúde pública e animal, especialmente em áreas urbanas com populações de gatos descontroladas. Os sinais clínicos incluem, tipicamente, lesões cutâneas, que podem progredir para manifestações sistêmicas em casos graves. O tratamento padrão com antifúngicos tem se mostrado eficaz na maioria dos casos, desempenhando um papel fundamental no controle da progressão da doença e na prevenção da transmissão zoonótica. Esta revisão de literatura sintetiza estratégias terapêuticas disponíveis para o tratamento da esporotricose felina, a fim de oferecer subsídios que ajudem os profissionais a melhorar o manejo dessa micose. Apesar dos avanços significativos no entendimento e tratamento dessa condição, ainda existem lacunas importantes no conhecimento, especialmente no que diz respeito à padronização de protocolos terapêuticos, ao manejo de casos refratários e à mitigação dos efeitos adversos associados aos tratamentos. Desse modo, conclui-se que, apesar dos avanços nas terapias disponíveis, persiste a necessidade de ensaios clínicos adicionais que possam estabelecer protocolos mais precisos para a maioria das opções terapêuticas abordadas.

Palavras-chave: Infecção fúngica, *Sporothrix spp.*, tratamento.

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Introduction

Sporotrichosis is an emerging zoonosis of growing relevance caused by fungi of the *Sporothrix* genus (RIBEIRO et al., 2023). In Brazil, its dissemination has been linked to the predominance of *Sporothrix brasiliensis*, a species with higher virulence and transmission capacity compared to other species within the genus (GREMIÃO et al., 2021, AGUIAR et al., 2023). This subcutaneous mycosis can be transmitted through various routes, with cat-to-human and cat-to-cat transmission being the most common. The primary modes of transmission involve bites, scratches, or direct contact with secretions from infected cats (SANTI et al., 2022).

Cats play an important role in the epidemiological cycle of sporotrichosis, as their lesions carry a high fungal load of yeast-like cells, which facilitates fungal dissemination. Clinically, feline sporotrichosis presents as cutaneous lesions that can be either single or multiple, characterized by nodules and ulcers at various anatomical sites (Figure 1). The nasal mucosa is the most frequently affected site, although other mucous membranes, such as conjunctival, oral, and genital mucosa, may also be involved (GREMIÃO et al., 2021).

In addition to cutaneous lesions, extracutaneous signs, particularly respiratory symptoms such as sneezing, nasal discharge, and dyspnea, may also be observed (GREMIÃO et al., 2021). It is important to note that these respiratory signs can precede the appearance of skin

lesions or, in some cases, be present in cats without any apparent external lesions (GREMIÃO et al., 2024).

Cat owners whose pets are diagnosed with sporotrichosis are at risk of becoming infected during the course of the animal's treatment, particularly during medication administration and restraint during veterinary consultations, as reported by ARAÚJO (2020). Therefore, it is essential to inform pet owners about the risk of contracting the disease and to provide guidance on strategies to minimize the chances of scratches and bites.

Considering the growing importance of this disease in Brazil (Gremião et al., 2021) and the recent detection of the *Sporothrix brasiliensis* fungus in the city of Fortaleza (Aguiar et al., 2023), this literature review aims to synthesize the available therapeutic approaches for the treatment of feline sporotrichosis. In doing so, it is expected to provide valuable information to assist veterinary professionals in the region in the effective management of this mycosis.

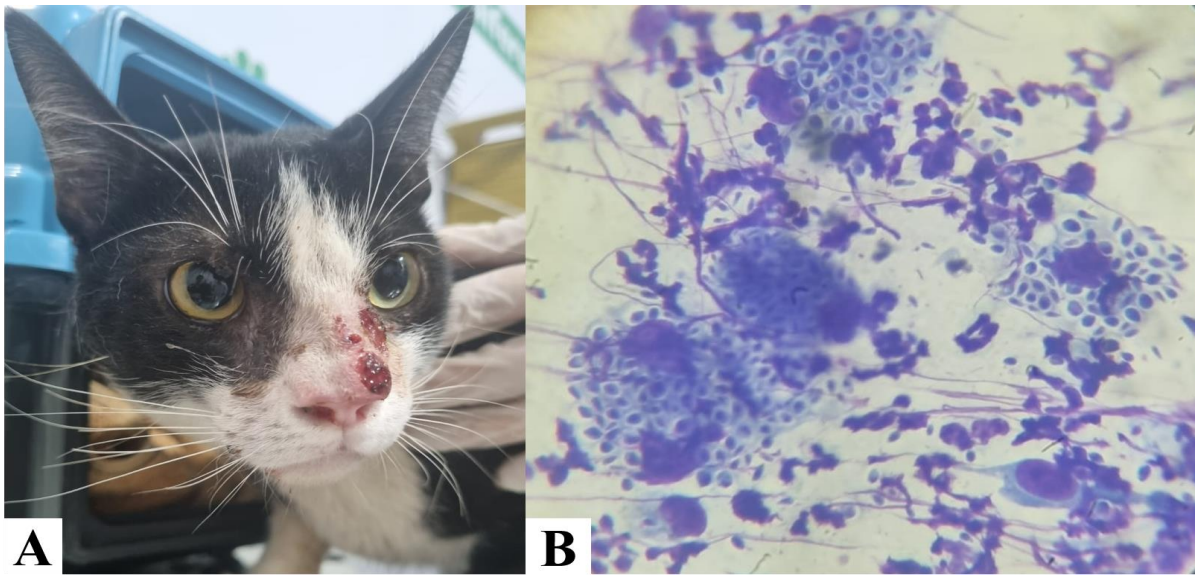

Figure 1. Clinical and cytological aspects of sporotrichosis in cats. (A) Feline patient presenting with eroded and ulcerative cutaneous lesions in the nasal region. (B) Cytology showing numerous yeast cells consistent with *Sporothrix* spp. within macrophages and in the extracellular environment.

Therapeutic Strategies

The therapeutic strategies for feline sporotrichosis identified in the reviewed studies include: itraconazole (ITZ) (Gremião et al., 2021), ITZ combined with potassium iodide (KI) (Reis et al., 2024), ITZ with clotrimazole (Santi et al., 2022), ITZ with acylhydrazone (Gremião et al., 2024), isavuconazole (ISA) (Barrs et al., 2024), posaconazole (PCZ) (Barrs et al.,

2024), amphotericin B (AMB) (Gremião et al., 2011; Souza et al., 2016; Gremião et al., 2021; Carneiro et al., 2024), buparvaquone (BPQ) (Santos et al., 2021), miltefosine (MFS) (Carneiro et al., 2024; Silva et al., 2018), cryosurgery (Souza et al., 2016), laser therapy (Ribeiro et al., 2023), and photodynamic therapy (RIBEIRO et al., 2023; RAMOS et al., 2024). The doses, frequency, and routes of administration for each treatment are summarized in Table 1.

Table 1. Pharmacological and non-pharmacological therapies for feline sporotrichosis: doses, frequencies, and supporting literature.

THERAPY	DOSE	FREQUENCY	REFERENCE
Itraconazole (ITZ)	≥ 3kg → 100 mg P.O. ≥ 1kg < 3kg → 50 mg P.O. < 1kg → 25 mg/kg P.O.	S.I.D. S.I.D. S.I.D.	Gremião *et al*., 2021
ITZ + Potassium Iodide (KI)	ITZ 100 mg/cat + KI 2.5 – 20 mg/kg P.O.	S.I.D.	Reis *et al.*, 2024
ITZ + Clotrimazole	ITZ 100 mg/cat P.O. + 1mL per nostril	S.I.D.	Santi *et al*.,2022
ITZ+ Acylhydrazone (D13)	ITZ 100 mg/cat P.O. + 20 mg/Kg P.O.	S.I.D.	Gremião *et al*.,2024
Amphotericin B (AMB)	0.5 mL a 1.5 mL intralesional (5mg/ml solution with a 1% lidocaine)	Weekly or biweekly	Souza *et al*., 2016 Gremião *et al.*, 2021
Miltefosine (MFS)	2 mg/kg P.O.	S.I.D.	Silva *et al., 2018*
Isavuconazole (ISA)	100 mg/cat P.O. or 5 mg/kg I.V. (40 mg/mL solution diluted in 0.9% NaCl to 0.8 mg/mL)	S.I.D. S.I.D.	Barrs *et al*., 2024
Posaconazole (PCZ)	15 mg/kg PO (loading dose); 7.5 mg/kg PO (maintenance)	S.I.D.	Barrs *et al*., 2024
Cryotherapy + ITZ	3 sessions + ITZ 10 mg/kg P.O.	- S.I.D.	Souza *et al.*, 2016
Laser Therapy + ITZ	4 to 8 sessions + ITZ 100 mg/cat P.O.	4 to 8 sessions S.I.D.	Ribeiro *et al.*, 2023
Photodynamic Therapy	4 to 6 sessions	Every 7 days	Ribeiro *et al.*, 2023 Ramos *et al.*, 2024

Azole derivatives

According to the study conducted by Gremião et al. (2021), itraconazole as a monotherapy is the treatment of choice frequently employed, with its efficacy previously reported in cats presenting with cutaneous lesions. The recommended dosage ranges from 25 to 100 mg/kg/day, administered orally, depending on the animal's weight. However, some studies indicate that the use of ITZ monotherapy in cats with multiple lesions and high fungal loads, especially those with persistent lesions, tends to result in higher rates of therapeutic failure and recurrence. Therefore, the combination of antifungal agents is essential to achieve a synergistic effect (GREMIÃO et al., 2021; REIS et al., 2024).

It is important to highlight that compounded itraconazole and generic itraconazole are not bioequivalent to the reference drug (GREMIÃO et al., 2021). In addition, while the generic version is recommended due to its affordability and its ability to achieve plasma concentrations similar to the reference drug, compounded itraconazole should be avoided, as it has been associated with treatment failure due to low average plasma concentrations (RENSCHLER et al., 2018).

According to Reis et al. (2024), treatment with potassium iodide capsules (2.5–20 mg/kg/day) can be an effective option when combined with itraconazole (100 mg/cat/day) in cats that have not previously undergone antifungal therapy, as well as in cases refractory to ITZ monotherapy. This combination therapy is particularly recommended for cats with multiple cutaneous lesions, nasal mucosa involvement, and/or respiratory issues. The combined approach has been described as the best therapeutic option due to its positive outcomes, including higher clinical cure rates, shorter treatment duration, and lower abandonment rates.

In cases of recurrence after clinical cure, there is a possibility of persistence or worsening of the initial cutaneous or mucosal lesions, as well as respiratory signs. In such cases, the dose of potassium iodide (KI) can be increased to 10–20 mg/kg/day. It is important to continue the treatment for at least one month after clinical cure to reduce the risk of relapse (GREMIÃO et al., 2021).

Adverse reactions are equally common in both treatments, with temporary discontinuation and/or hepatoprotective therapy being recommended. This is due to the frequent occurrence of clinical and laboratory abnormalities, such as anorexias, lethargy, nausea, vomiting, diarrhea, and hepatotoxicity, including elevated serum alanine aminotransferase (ALT) levels.

Therefore, regular monitoring of these clinical and biochemical parameters is highly recommended (GREMIÃO et al., 2021).

In feline patients, the treatment of nasal sporotrichosis is particularly challenging, with many cases proving refractory to standard therapies (GREMIÃO et al., 2021).

As a result, other drugs are being explored to enhance the mechanism of action of itraconazole (ITZ), such as clotrimazole, which has been shown to be highly effective against *Sporothrix brasiliensis* in in vitro isolates (Santi et al., 2022). According to Santi et al. (2022), tests were conducted using the azole antifungal Clotrimazole as a 1% intranasal spray solution in combination with ITZ to treat the nasal form of feline sporotrichosis. The treatment involves administering one spray (approximately 1 mL) in each nostril as an adjunct to oral itraconazole (100 mg/cat/SID).

Additionally, Santi et al. (2022) stated that 1% clotrimazole proved effective in long-term refractory cases, which account for a significant proportion of feline patients diagnosed with nasal sporotrichosis. Moreover, this is considered a low-cost and non-invasive therapy that can be added in cases where standard therapy shows limited efficacy. The effectiveness of the treatment is evidenced by the clinical remission of lesions and symptoms such as nasal bridge swelling, ulceration, edema, airway obstruction, and sneezing. Furthermore, clinical signs of liver damage were absent in patients who received this treatment, and their biochemical parameters remained unchanged.

Another promising therapy currently being tested by Gremião et al. (2024) involves the combination of itraconazole with an acyl-hydrazone derivative (D13). Acyl-hydrazones (AHs) represent a novel class of antifungal molecules whose mechanism of action disrupts the vesicular transport within the fungal cell cycle, indirectly affecting glucosylceramide synthesis. This mechanism gives acyl-hydrazone compounds a high fungicidal potential, with the ability to eliminate fungal cells within a few hours (BONILLA et al., 2021).

Initially, the animals were treated with the standard itraconazole protocol (GREMIÃO et al., 2024). However, in cases of therapeutic failure, the acyl-hydrazone derivative (D13) was introduced into the treatment regimen at a dose of 20 mg/kg/SID.

During the use of this drug, certain parameters were monitored, such as ALT levels, which were increased in some

patients. Based on preliminary results, the combination of itraconazole with D13 proved to be effective in cats with sporotrichosis refractory to itraconazole monotherapy. Furthermore, D13 was shown to be safe and well-tolerated, with minimal or no laboratory abnormalities, suggesting a favorable safety profile (GREMIÃO et al., 2024).

In vitro tests indicate the emergence of antifungal resistance. Nakasu (2020) demonstrated the presence of *Sporothrix brasiliensis* strains with tolerance to high minimum inhibitory concentrations (MICs) of itraconazole (ITZ) in feline patients from southeastern Brazil. ITZ, a triazole antifungal, is considered the most important drug for the treatment of feline sporotrichosis. In light of these findings, other triazole-class antifungals, such as isavuconazole (ISA) and posaconazole (PCZ), have been suggested as possible alternatives for cases refractory to combination therapies with ITZ (BARRS et al., 2024).

According to Barrs (2024), the recommended dose of isavuconazole (ISA) is 100 mg/cat for oral administration and 5 mg/kg for intravenous administration (40 mg/mL solution diluted in 0.9% NaCl to a final concentration of 0.8 mg/mL of ISA). The only reported side effect in cats was emesis occurring between 6 to 8 hours after drug administration.

Villalobos (2023) reports the first use of the combined therapy of isavuconazole (ISA) and potassium iodide (KI) in veterinary medicine. In this case report, a dose of 50 mg/cat of ISA and 5 mg/kg of KI every 24 hours was administered to a feline patient with sporotrichosis refractory to the combination therapy of itraconazole (ITZ) and KI. The patient showed no side effects, and complete resolution of cutaneous lesions and respiratory signs was achieved within three months of therapy, with no recurrence of lesions during a one-year follow-up. In humans, side effects are rare and generally limited to nausea, vomiting, and diarrhea. Hepatotoxicity and drug interactions are less common with ISA compared to other triazole antifungals (BARRS et al., 2024).

Regarding the use of posaconazole (PCZ) for treatment, the recommended loading dose for feline patients is 15 mg/kg, followed by a maintenance dose of 7.5 mg/kg every 24 hours. Reported adverse effects primarily include hepatotoxicity and drug interactions due to cytochrome P450 inhibition. However, these interactions are less common compared to itraconazole (ITZ). Similar to isavuconazole (ISA), PCZ should be reserved for fungal infections that

are not susceptible to ITZ or in cases where ITZ is not tolerated due to hepatotoxicity (Barrs et al., 2024).

Amphotericin b

Regarding amphotericin B (AMB), it is a first-line antifungal therapy primarily used in cases of disseminated feline sporotrichosis, often in combination with itraconazole (ITZ) (GREMIÃO et al., 2021; CARNEIRO et al., 2024). Intralesional or subcutaneous administration of AMB, combined with oral ITZ, has been reported as an effective option for the treatment of localized residual lesions (SOUZA et al., 2016; GREMIÃO et al., 2021).

A treatment protocol has been documented for cats refractory to oral therapy with itraconazole (ITZ), particularly those presenting with lesions in the nasal region. The treatment consisted of intralesional administration of amphotericin B (5 mg/mL solution combined with 1% lidocaine), with doses ranging from 0.5 to 1.5 mL to ensure complete infiltration of the affected tissue. Applications were performed weekly or every two weeks, with a total of 1 to 5 applications until complete lesion resolution. Among the 26 cats treated, 22 showed remission, and 16 achieved clinical cure, demonstrating the effectiveness of the evaluated therapeutic protocol (GREMIÃO et al., 2011).

However, a study conducted by Ramos et al. (2024) evaluated a protocol involving the intralesional administration of four doses of amphotericin B (AMB) under similar concentration standards to the previous study, but with 21-day intervals between applications. The feline patient presented with a lesion on the auricular pinna and was unresponsive to treatment with itraconazole and potassium iodide. Despite the new protocol, the results indicated that the treatment was ineffective, and the animal's clinical condition continued to deteriorate.

It is important to note that during intralesional administration of amphotericin B (AMB), feline patients may experience discomfort during tissue infiltration and, in the post-anesthetic period, lethargy and hyporexia. Additionally, adverse effects such as abscess formation and edema at the application site may occur. Intravenous administration also presents significant limitations due to the risk of severe adverse effects, including thrombosis of the cephalic and jugular veins.

On the other hand, lipid formulations of AMB, which have lower nephrotoxicity, are financially inaccessible in most cases due to their high cost (GREMIÃO et al., 2011; GREMIÃO et al., 2021).

Buparvaquone

Given this context, there is growing interest in the repositioning of already approved drugs for new indications in veterinary medicine. Buparvaquone (BPQ), an antiprotozoal agent used in the treatment of bovine theileriosis, was evaluated *in vitro* against *Sporothrix brasiliensis* isolates (SANTOS et al., 2021). According to Santos et al. (2021), in the *in vitro* model, BPQ, at concentrations four times lower than itraconazole, was able to inhibit fungal growth. Additionally, it demonstrated 408 times greater selectivity for *S. brasiliensis* compared to mammalian cells, highlighting its potential safety profile.

In *in vivo* experiments using the greater wax moth (*Galleria mellonella*) model, a single dose of buparvaquone (5 mg/kg), injected into the last left leg, was found to be more effective than itraconazole (ITZ), positioning itself as a potential alternative drug for the treatment of feline sporotrichosis (SANTOS et al., 2021).

However, despite these promising results, further *in vivo* studies using vertebrate models are essential to confirm its efficacy and safety before considering its clinical use in cats.

Miltefosine

In the context of alternative drugs, miltefosine (MFS) has also demonstrated strong fungicidal activity against various strains of *Sporothrix brasiliensis* and *Sporothrix schenckii*. Additionally, it significantly reduced the parasitic load of *S. brasiliensis* in human and mouse cells and exhibited an immunomodulatory effect (Carneiro et al., 2024). Furthermore, according to Carneiro et al. (2024), the combination of MFS with drugs such as itraconazole and amphotericin B enhanced antifungal activity against all tested *Sporothrix* strains, demonstrating effective synergy between these drugs.

Despite the previously described studies, one investigation evaluated the efficacy of MFS in cats with refractory sporotrichosis that had been previously treated with ITZ and KI. It was observed that most cats treated with miltefosine (2 mg/kg PO/SID) for periods ranging from 3 to 45 days showed disease progression (Silva et al., 2018), highlighting a discrepancy between *in vitro* and *in vivo* studies. Moreover, although most pet owners did not report difficulties in administering the medication, adverse effects such as hyporexia, sialorrhea, vomiting, diarrhea, and weight loss secondary to gastrointestinal alterations were observed, directly influencing the clinical progression of the animals.

Adjuvant therapies

With the aim of reducing the duration and costs of conventional

treatment, new therapeutic alternatives or adjuncts to antifungal agents have been utilized to combat sporotrichosis, including cryosurgery, laser therapy, and photodynamic therapy. These methods are recommended in cases of therapeutic failure with oral antifungal agents, recurrence of lesions, and/or signs of hepatotoxicity (SOUZA et al., 2016; RIBEIRO et al., 2023; RAMOS et al., 2024). However, their use should be evaluated and tailored to each case, based on the clinical presentation and the animal's response to treatment (GREMIÃO et al., 2021).

In a study conducted by Souza et al. (2016), the combination of cryosurgery (three cycles of freezing and thawing per lesion) with itraconazole (10 mg/kg/SID/PO) proved effective in treating 11 out of 13 cats with feline sporotrichosis, all of whom were considered clinically cured (Figure 2).

The treatment duration ranged from 14 to 64 weeks, and none of the cured animals experienced a recurrence during the evaluation period. However, the combined therapy was ineffective in two cases, resulting in therapeutic failure for these animals. Although the location of lesions in the nasal region poses challenges for surgical procedures, potentially hindering infection resolution (Gremião et al., 2021), the exact cause of therapeutic failure in the two animals was not identified.

Figure 2. Progression of an ulcerative lesion in the nasal region of a feline patient following cryosurgery: (A) Before the procedure. (B) After one cycle of freezing and thawing during cryosurgery. (C) Five days post-cryosurgery. (D) Healing process, 19 weeks post-cryosurgery. Source: Adapted from Souza *et al.*, 2016.

Regarding laser therapy, it has become popular in veterinary medicine for reducing inflammation and promoting wound healing, as well as for eliminating resistant microorganisms (Ribeiro et al., 2023). According to Ribeiro et al. (2023), the application of laser therapy with light intensity ranging from 1 to 6 joules and between 4 to 8 sessions until clinical cure demonstrated good efficacy in inducing tissue healing and fungal eradication in eight cases (Figure 3). The treatment duration ranged from 30 to 70 days, with follow-up periods of one to five years after treatment. Additionally, it is important to emphasize the necessity of combining laser therapy with itraconazole (100 mg/cat/SID/PO) to prevent disease recurrence.

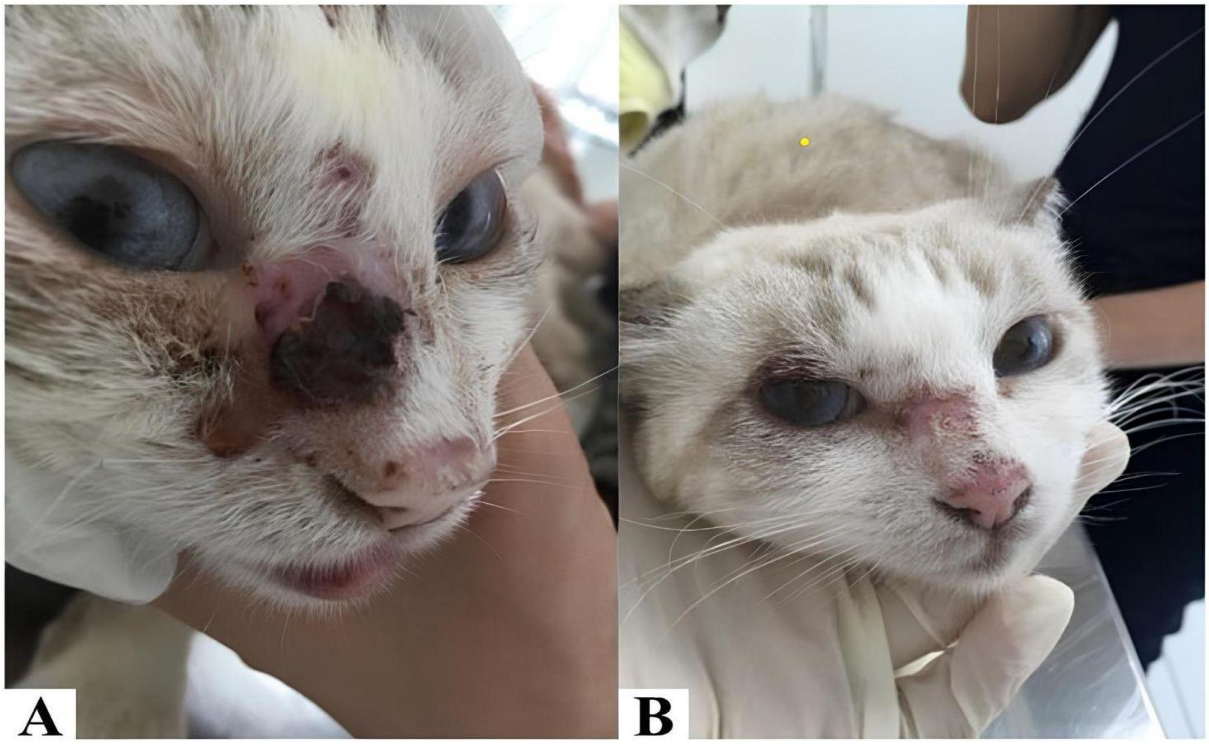

Figure 3. Progression of ulcerative and necrotic lesion on the nasal planum of a feline patient after laser therapy: (A) Before laser therapy. (B) Healing after four sessions of laser therapy. Source: Adapted from Ribeiro et al., 2023.

In two studies, the applicability of combining photodynamic therapy (PDT) with a 0.01% methylene blue photosensitizer (four to six sessions of 5 to 10 minutes with 7-day intervals) and laser therapy with red light was observed in a feline patient with refractory sporotrichosis associated with bacterial infection (RIBEIRO et al., 2023; RAMOS et al., 2024). This technique was documented to enhance the effects of laser therapy, proving effective in healing by reducing the

parasitic load of the lesions (Figure 4) (RIBEIRO et al., 2023). Ramos et al. (2024) advocate for the early use of this therapy in cases of therapeutic challenges. In their study, the feline patient, while showing clinical improvement in the lesion on the auricular pinna, developed additional systemic lesions and did not respond to systemic therapy. Therefore, late implementation of this approach may not be as effective for complete cure due to the systemic spread of the disease.

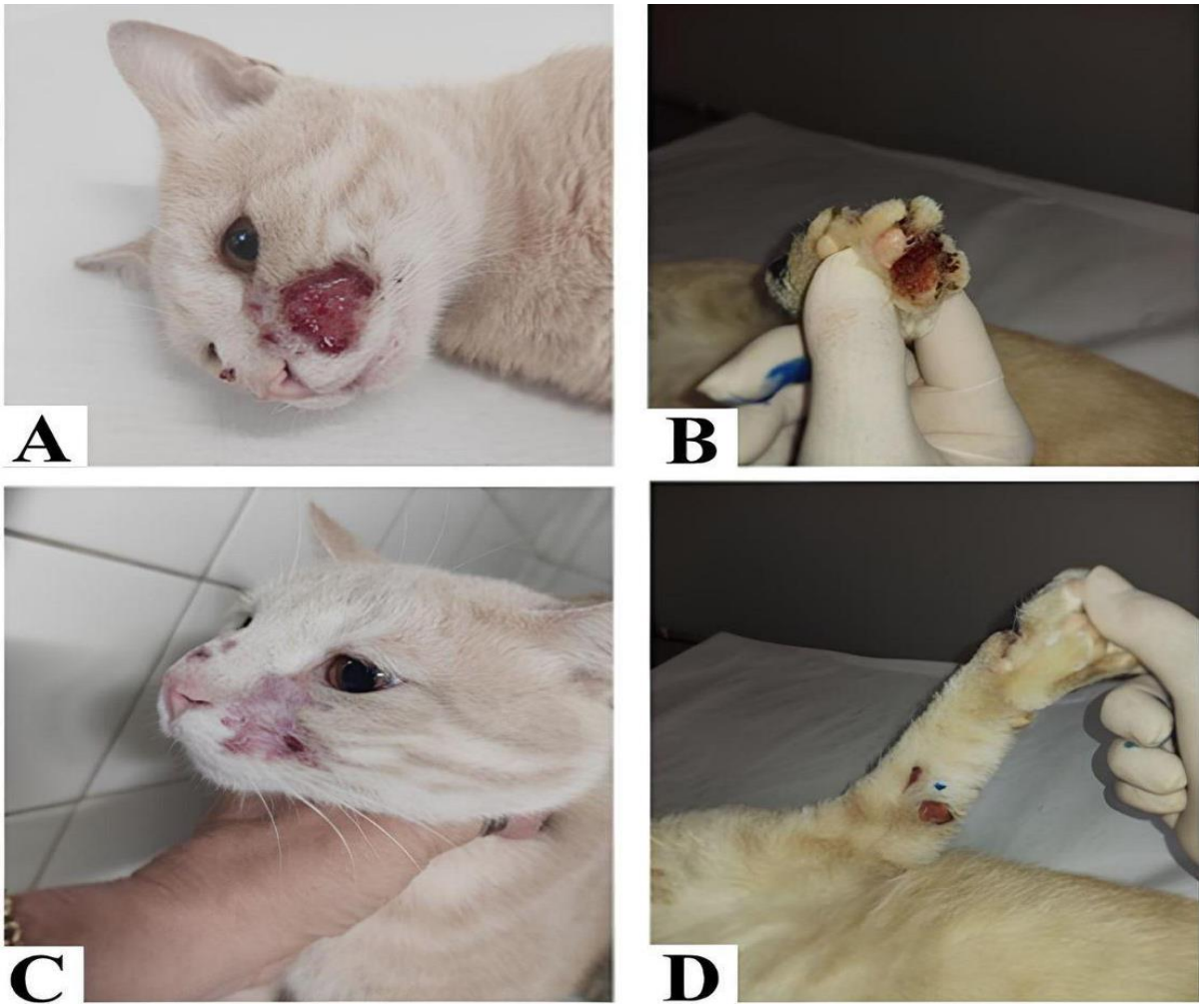

Figure 4. Progression of disseminated cutaneous sporotrichosis in a feline patient following photodynamic therapy combined with laser therapy: (A) Ulcerative lesions on the rostral planum. (B) Ulcerative lesion on the limb (both A/B before the procedure). (C) and (D) Healing process 10 days after the first session. Source: Adapted from Ribeiro et al., 2023.

Final considerations

Despite the strong evidence supporting the use of antifungal agents, there remains a significant lack of randomized and controlled clinical trials to establish comprehensive and optimized therapeutic protocols for feline sporotrichosis. The variability in clinical response among patients and the potential for resistance to existing treatments emphasize the need for research into complementary and alternative approaches,

including adjuvant and immunomodulatory therapies. Furthermore, continuous monitoring and periodic re-evaluation of the adopted therapeutic strategies are essential to ensure sustained remission of clinical signs, reduce the risk of relapses, minimize adverse effects, and promote animal well-being.

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