SCIENTIA INTERNATIONAL PRESS SCIENTIA INTERNATIONAL OPEN BOOKS

AREA 6 · BIOLOGICAL, ENVIRONMENTAL, AGRICULTURAL AND EARTH SCIENCES SCIENTIFIC CHAPTER

CONTINUOUS PUBLICATION

Antimicrobial Therapy against *Conidiobolus lamprauges* (*Neoconidiobolus lamprauges*)

Terapia antimicrobiana contra Conidiobolus lamprauges *(*Neoconidiobolus lamprauges*)*

Eugênio Miranda Soares[1], Lara Baccarin Ianiski[2], Andressa Alves do Amaral[3], Bruna Gross[4], Isabelle Carneiro Rizzatti[5], Caroline Quintana Braga[6], Daniela Isabel Brayer Pereira[7], Sônia de Avila Botton[8]

[1] Federal University of Santa Maria, Santa Maria, RS, Brazil · ROR: https://ror.org/01b78mz79 · ORCID: https://orcid.org/0009-0004-0987-0122
[2] Federal University of Santa Maria, Santa Maria, RS, Brazil · ROR: https://ror.org/01b78mz79 · ORCID: https://orcid.org/0000-0002-4992-3610
[3] Federal University of Santa Maria, Santa Maria, RS, Brazil · ROR: https://ror.org/01b78mz79 · ORCID: https://orcid.org/0009-0006-3988-1871
[4] Federal University of Santa Maria, Santa Maria, RS, Brazil · ROR: https://ror.org/01b78mz79 · ORCID: https://orcid.org/0009-0006-2292-0790
[5] Federal University of Santa Maria, Santa Maria, RS, Brazil · ROR: https://ror.org/01b78mz79 · ORCID: https://orcid.org/0009-0009-4374-5815
[6] Federal University of Pelotas, Pelotas, RS, Brazil · ROR: https://ror.org/05msy9z54 · ORCID: https://orcid.org/0000-0003-1481-9829
[7] Federal University of Pelotas, Pelotas, RS, Brazil · ROR: https://ror.org/05msy9z54 · ORCID: https://orcid.org/0000-0003-4374-677X
[8] Federal University of Santa Maria, Santa Maria, RS, Brazil · ROR: https://ror.org/01b78mz79 · ORCID: https://orcid.org/0000-0002-8855-9217 · corresponding author: sabott20@gmail.com

THIS CHAPTER		PROGRAMME AND CYCLE	
DOI	https://doi.org/10.56365/nh9xg184	Editorial area	6 · Biological, Environmental, Agricultural and Earth Sciences
Received	09/09/2026	Editorial cycle	2026.2
Accepted	03/11/2026	Length	21 pages
Published online	13/11/2026	Consolidation	January-February 2027
Version	v1	Consolidated e-book	Biological, Environmental, Agricultural and Earth Sciences, v. 1 · https://doi.org/10.56365/32gm7427
Languages	Português - English	ISBN of the work	-
Licence	CC BY 4.0	Review	Peer review · 03/11/2026

Block completed by the editorial team. Do not write in this area. The area may be reassigned when there is greater fit with another volume.

HOW TO CITE

NOW	Soares, E. M., Ianiski, L. B., Amaral, A. A. do, Gross, B., Rizzatti, I. C., Braga, C. Q., Pereira, D. I. B., & Botton, S. de A. (2026). Antimicrobial therapy against *Conidiobolus lamprauges* (*Neoconidiobolus lamprauges*). In Scientia International Open Books: Biological, Environmental, Agricultural and Earth Sciences, editorial cycle 2026.2. Scientia International Press. https://doi.org/10.56365/nh9xg184
LATER	*At the end of the cycle, the chapter is included in a consolidated e-book and the reference will carry the definitive title of the work, the editors, the ISBN and the page range. The chapter DOI and the date of this publication do not change.*

Abstract

Conidiobolomycosis is an emerging fungal infection affecting both humans and animals, characterized by high mortality rates and significant therapeutic challenges resulting from the lack of standardized treatment protocols and the variable response to currently available antimicrobial agents. Among the species of the genus *Conidiobolus*, *Conidiobolus lamprauges* (*N. lamprauges*) is recognized as the primary etiological agent affecting sheep, horses, and dogs, representing an important concern in veterinary medicine. This chapter summarizes and discusses the available evidence on the *in vitro* susceptibility of *C. lamprauges* (*N. lamprauges*) to antifungal, antibacterial, and antiparasitic agents, as well as the interactions among these compounds, aiming to synthesize the current state of knowledge and identify promising therapeutic strategies. To achieve this, a descriptive and qualitative literature review was conducted. The available evidence indicates that terbinafine exhibits the highest *in vitro* antifungal activity, showing the lowest inhibitory concentrations among the drugs evaluated. In addition, the combinations of miltefosine plus azithromycin and sulfamethoxazole plus trimethoprim demonstrated promising synergistic effects, suggesting potential therapeutic benefits. Despite these advances, the limited number of available studies and clinical isolates highlight the need for further investigations and *in vivo* validation to support the development of safer and more effective therapeutic protocols for the management of conidiobolomycosis.

Keywords: conidiobolomycosis, *Conidiobolus lamprauges*, susceptibility testing, treatment.

Resumo

A conidiobolomicose é uma infecção fúngica emergente que acomete seres humanos e diversas espécies animais, caracterizada por elevada letalidade e importantes desafios terapêuticos decorrentes da ausência de protocolos padronizados e da variabilidade na resposta aos agentes antimicrobianos. Entre as espécies do gênero *Conidiobolus*, *Conidiobolus lamprauges* (*Neoconidiobolus lamprauges*) destaca-se como o principal agente etiológico em ovinos, equinos e caninos, assumindo relevância na medicina veterinária. Este capítulo reúne e discute as evidências disponíveis sobre a suscetibilidade *in vitro* de *C. lamprauges* (*N. lamprauges*) aos fármacos com atividade antifúngica, antibacteriana e antiparasitária, bem como as interações entre esses compostos, com o objetivo de sintetizar o conhecimento atual e identificar perspectivas terapêuticas promissoras. Para esse propósito, foi realizada uma revisão descritiva e qualitativa da literatura científica. As evidências analisadas indicam que a terbinafina apresenta a maior atividade antifúngica *in vitro*, com as menores concentrações inibitórias entre os fármacos avaliados. Além disso, as associações entre miltefosina e azitromicina e entre sulfametoxazol e trimetoprima demonstram efeito sinérgico promissor, sugerindo potencial para otimização das estratégias terapêuticas. Apesar desses avanços, a escassez de estudos e de isolados clínicos disponíveis evidencia a necessidade de investigações adicionais e da validação *in vivo* dessas abordagens, a fim de subsidiar o desenvolvimento de protocolos terapêuticos mais seguros e eficazes para o controle da conidiobolomicose.

Palavras-chave: conidiobolomicose, *Conidiobolus lamprauges*, testes de suscetibilidade, tratamento.

Origin of the text

This chapter was developed from the undergraduate monograph entitled Terapia antimicrobiana contra *Conidiobolus lamprauges*: uma revisão da literatura, submitted to the Pharmacy Program of the Federal University of Santa Maria (UFSM) in partial fulfilment of the requirements for the Bachelor's degree in Pharmacy. The text was revised, updated and adapted to the book chapter format, with a reorganized structure and an updated review of the scientific literature, while preserving the central theme of the original work, which had not been previously published.

Introduction

Conidiobolomycosis is a fungal infection caused by pathogens of the genus *Conidiobolus*, which is widely distributed in the environment in tropical regions. The species potentially pathogenic to mammals include *Conidiobolus coronatus*, *Conidiobolus incongruus* and *Conidiobolus lamprauges* (*N. lamprauges*). Immunocompromised hosts are the most susceptible to infection, and the main routes of entry of the etiological agent into the host are the airborne route, through inhalation of fungal spores, and lesions of the skin or oropharyngeal mucosa; infection by vectors may also occur (HUMBER *et al.*, 1989; NIE *et al.*, 2021; AQUINO *et al.*, 2023).

C. lamprauges (*N. lamprauges*) predominantly affects horses and ruminants, especially sheep and goats. In humans, infections by this species are rare, but cases of disseminated fungal infection have been reported (KIMURA *et al.*, 2011; MUSTAFA *et al.*, 2015; NIE *et al.*, 2021; AQUINO *et al.*, 2023).

In animals, the disease manifests clinically as granulomatous rhinitis, with increased nasal volume, craniofacial deformities, respiratory distress and chronic nasal discharge. In animals infected by the fungal agent, other changes include anorexia, dyspnea, nasal obstruction, noisy breathing and craniofacial asymmetry. Pathologically, the lesions appear macroscopically yellowish, friable and irregular, while histological analysis shows multifocal chronic granulomatous inflammation, with hyphae surrounded by material compatible with the Splendore-Hoeppli phenomenon (FURLAN *et al.*, 2010; PEDROSO *et al.*, 2018). This phenomenon is a histopathological feature defined by amorphous, eosinophilic material deposited around the fungal hyphae. Regarded as an antigen-antibody reaction resulting from eosinophil degranulation, it is a common finding in conidiobolomycosis in immunocompetent hosts, although it is not exclusive to this disease and may also be seen in pythiosis and basidiobolomycosis (UBIALI *et al.*, 2013). Its absence has been associated with immunosuppression (AGUIAR *et al.*, 2014).

Although the severity of the clinical signs is recognized, there is still no consensus on the exact mechanism of infection. However, the pathogen's predilection for the facial region, especially the nasal cavities, indicates that inoculation occurs mainly through the inhalation

of conidia present in soil or in decaying organic matter. Alternatively, infection may be facilitated by trauma to the nasal mucosa or by arthropod vectors, with the infectious process starting in the mucosa and extending to adjacent tissues, such as the paranasal sinuses and the orbit (HUMBER *et al.*, 1989; FURLAN *et al.*, 2010; BARBOSA *et al.*, 2025).

Cases of *Conidiobolus* spp. infection in animals have been recorded in all regions of Brazil, with higher occurrence in the Central-West and Northeast regions. Sheep are the animal species most frequently affected, which is related to their habit of grazing close to the ground, facilitating the inhalation of spores and the subsequent formation of nasopharyngeal and rhinofacial lesions. These epidemiological and clinical findings underscore the importance of considering environmental and behavioral factors in the approach to and management of the disease (SILVA *et al.*, 2007b; BOABAID *et al.*, 2008; RIET-CORREA *et al.*, 2008; DE PAULA *et al.*, 2010; AGUIAR *et al.*, 2014; PEIXOTO *et al.*, 2014; WEIBLEN *et al.*, 2016; DE CARMO *et al.*, 2020).

The absence of an effective therapy for *C. lamprauges* (*N. lamprauges*) results in high mortality in animals, particularly in sheep, in which outbreaks show lethality of up to 100% (BOABAID *et al.*, 2008; RIET-CORREA *et al.*, 2008; FURLAN *et al.*, 2010). Conventional treatments with azoles and iodides have proven ineffective in most cases (SILVA *et al.*, 2007; PORTELA *et al.*, 2010).

In vitro susceptibility tests have explored new antimicrobial approaches, including possible therapeutic combinations involving antifungal, antibacterial and antiparasitic agents. Some of these combinations have shown synergistic potential in *in vitro* studies, suggesting promising alternatives to be investigated for treatment. However, research remains limited, which highlights the need for further studies to define an effective therapeutic protocol and reduce the mortality associated with the infection (STEFANELLO *et al.*, 2018; TONDOLO *et al.*, 2018).

In view of the above, this chapter aims to analyze the available evidence on the *in vitro* efficacy of antimicrobials as potential therapeutic options for conidiobolomycosis caused by *C. lamprauges* (*N. lamprauges*). To this end, a descriptive and qualitative review of the scientific literature was carried out through searches in the following databases: Google Scholar, PubMed, Scientific Electronic Library Online (SciELO) and ScienceDirect. The searches used combinations of Health Sciences Descriptors (DeCS) and Medical Subject Headings (MeSH): “Entomophthorales”, “Conidiobolomycosis”, “Conidiobolomicose”, “*Conidiobolus lamprauges*”, “*Conidiobolus* spp.”, “therapy”, “treatment” and “tratamento”. The inclusion criteria were articles available in the aforementioned databases in Portuguese, English and/or Spanish that described *in vitro* antimicrobial therapy against *C. lamprauges*. Articles that did not provide information related to the research topic or that contained duplicate information were excluded from the analysis.

Conidiobolomycosis

Fungi of the genus *Conidiobolus* (order Entomophthorales, family Ancylistaceae) are saprophytic filamentous organisms with worldwide distribution in tropical and subtropical regions, frequently isolated from soil samples, insects and decaying organic matter (GRIGANSKY *et al.*, 1999; BOABAID *et al.*, 2008; VILELA *et al.*, 2010; SILVA *et al.*, 2022). Among the pathogenic species described, *Conidiobolus coronatus*, *Conidiobolus incongruus* and *Conidiobolus lamprauges* (*Neoconidiobolus lamprauges*) are associated with conidiobolomycosis, a fungal infection that manifests as granulomatous inflammation of the nasal structures and subcutaneous tissues of the face (VILELA *et al.*, 2010; NIE *et al.*, 2021). This infection may affect humans as well as several animal species, such as sheep, goats, horses and dogs, with reports in all Brazilian regions, although with higher incidence in the states of the Central-West and Northeast regions (WEIBLEN *et al.*, 2016; DE CARMO *et al.*, 2020).

Exposure to contaminated organic material is the main risk factor for conidiobolomycosis (AQUINO *et al.*, 2023). Although the exact mechanism of infection has not yet been fully elucidated, the most common route of entry is believed to be the inhalation of environmental spores or penetration through facial trauma, in addition to the possible involvement of arthropod vectors (HUMBER *et al.*, 1989; FURLAN *et al.*, 2010).

Conidiobolomycosis, also known as entomophthoromycosis or rhinoentomophthoromycosis, presents varied clinical manifestations depending on the host species and the fungal agent involved. Infection by *C. lamprauges* (*N. lamprauges*) is characterized by a marked tropism for the nasal and nasopharyngeal regions (DE CARMO *et al.*, 2020). In sheep, the most commonly observed clinical forms are the rhinopharyngeal form, which affects the ethmoidal region, and the rhinofacial form, which affects the nasal vestibule and the surrounding dermal structures (WEIBLEN *et al.*, 2016; AQUINO *et al.*, 2023). Clinical signs include serous or mucopurulent nasal discharge, fever, weight loss, respiratory distress and unilateral exophthalmos associated with facial asymmetry. Severe cases may progress to neurological involvement, including behavioral changes, lethargy, circling and head pressing, due to the extension of the infection to the frontal lobe of the brain (RIET-CORREA *et al.*, 2008; WEIBLEN *et al.*, 2016; DE CARMO *et al.*, 2020).

Infection by *C. lamprauges* (*N. lamprauges*) has also been reported in goats, with a clinical presentation involving nasal discharge, dermatitis of the extremities and weight loss, but without the typical craniofacial deformities observed in sheep (DE CARMO *et al.*, 2020).

Humber *et al.* (1989) described the first case of equine infection caused by *C. lamprauges* (*N. lamprauges*) in a mare that presented persistent nasal bleeding and

progressive weight loss. Necropsy revealed granulomatous masses containing nodules, "kunkers", similar to those observed in equine pythiosis caused by *Pythium insidiosum*; however, laboratory culture confirmed the presence of *C. lamprauges* (*N. lamprauges*).

In humans, the disease manifests as chronic rhinophycomycosis, with progressive erythema, edema and thickening of the skin in the nasal region, often leading to visible deformities (KIMURA *et al.*, 2011). Although effective treatments have been reported in humans and horses, cases in sheep in Brazil have a guarded to poor prognosis, with high mortality and therapeutic failures associated with late diagnosis and rapid disease progression (TADANO *et al.*, 2005; MUSTAFA *et al.*, 2015; WEIBLEN *et al.*, 2016; SILVA *et al.*, 2022).

Diagnosis

The diagnosis of conidiobolomycosis involves an integrated approach combining clinical, histopathological and microbiological examinations and, when available, molecular methods. In cases observed in sheep, necropsies revealed characteristic macroscopic lesions, with yellowish to whitish areas of flaccid consistency and nodular appearance, resembling friable tumor masses. These lesions have an irregular surface, indicating a chronic and severe inflammatory process (TAN *et al.*, 2010; AGUIAR *et al.*, 2014; AQUINO *et al.*, 2023). Microscopically, the inflammation is characterized by the proliferation of connective tissue infiltrated by lymphocytes, macrophages, neutrophils, giant cells and eosinophils, the latter arranged around necrotic areas. Fungal hyphae are seen at the center of these lesions, associated with the Splendore-Hoeppli phenomenon, which indicates a specific immune response to the presence of the pathogen (FURLAN *et al.*, 2010; AGUIAR *et al.*, 2014).

Histological examination also shows that conidiobolomycosis follows an insidious clinical course, with slow development of the lesions, which hinders early recognition of the infection. This frequently leads to late diagnosis, increasing the extent of the affected tissue and hampering therapeutic efficacy, which contributes to the high lethality rates observed (RIET-CORREA *et al.*, 2008; SILVA *et al.*, 2022). Direct observation of the morphological characteristics of the fungus is an important step: colonies of this microbial agent show hyaline, coenocytic hyphae with sparse branching and a diameter of 5 to 30 µm, and rare septa may occasionally be observed, predominantly in distal regions. In some cases, bulbous dilations are noted at the tips of the hyphae or conidia (VILELA *et al.*, 2010; AQUINO *et al.*, 2023). The use of special stains, such as Grocott's methenamine silver and periodic acid-Schiff (PAS), is essential to reveal the presence of hyphae in tissues, increasing the sensitivity of histological diagnosis (ISA-ISA *et al.*, 2012; PEIXOTO *et al.*, 2014; PEDROSO *et al.*, 2018).

Microbiological isolation is performed mainly on culture media such as Sabouraud dextrose agar and potato agar, on which growth is abundant. Initially, the colonies are creamy and smooth, becoming wrinkled over time. The species grows well at high temperatures, such as 37°C, a feature that may explain its higher prevalence in warm regions of Brazil, such as the Central-West and Northeast (HUMBER *et al.*, 1989; SILVA *et al.*, 2022). In addition, molecular methods, such as the Polymerase Chain Reaction (PCR) and gene sequencing, as well as immunohistochemical techniques, are indispensable for the definitive identification of the fungal species involved in the infection (DE PAULA *et al.*, 2010; TAN *et al.*, 2010; NIE *et al.*, 2020; BARBOSA *et al.*, 2025).

Treatment

The ideal treatment for conidiobolomycosis has not yet been established, and the reports available in the literature indicate high mortality rates among diagnosed cases (AQUINO *et al.*, 2023). This scenario is particularly evident in sheep, in which, even with the administration of antifungal therapies, the clinical course is generally unfavorable. In a case reported in India, treatment with sulfamethoxazole-trimethoprim (44 mg/kg) was not effective for three sheep infected by *C. incongruus*, as reported by Morris *et al.* (2001).

Ximenes *et al.* (2007) described a case of *Conidiobolus* spp. in which the use of intravenous sodium iodide (100 mg/kg, four weekly applications) resulted in regression of the clinical signs without recurrence in two animals affected by early-stage rhinofacial conidiobolomycosis.

In another outbreak of conidiobolomycosis described by Boabaid *et al.* (2008), 12 sheep were infected and all died within approximately 20 days. Three of these animals were treated with potassium iodide (1 g/day for up to 15 days), but without therapeutic success.

Furthermore, in a case reported by Riet-Correa *et al.* (2008), oral administration of potassium iodide (7 mg/kg) resulted in a reduction of the lesion after five days, but the animal died. In another case from the same study, combined treatment with potassium iodide for two months and local application of 2% ketoconazole for a further three months was also ineffective, leading to clinical deterioration and euthanasia of the animal after six months.

In Paraíba, Portela *et al.* (2010) diagnosed seven outbreaks of the disease in sheep and treated six of the eight affected animals with fluconazole (10 mg/kg); however, all cases progressed to death. Sheep with clinical manifestations usually die or require euthanasia between 7 and 15 days after the onset of clinical signs. The rapid progression of conidiobolomycosis after the appearance of the first clinical signs may explain the low efficacy of the therapies used, especially potassium iodide, which is frequently associated with therapeutic failure (RIET-CORREA *et al.*, 2008; AGUIAR *et al.*, 2014).

However, in horses infected by *Conidiobolus* spp., treatment proved effective. Taintor *et al.* (2004) reported the treatment of two pregnant mares with fluconazole (dose not specified in the study). A significant improvement in clinical signs was observed within a few days, allowing treatment to be discontinued after approximately 6 to 8 weeks (about 42 to 56 days). In addition, Steiger & Williams (2000) described successful treatment of a horse infected by *Conidiobolus coronatus*. The protocol involved the use of sodium iodide (20%) for seven days, combined with organic iodide (ethylenediamine dihydroiodide 4.57%) administered for more than one year.

In dogs, itraconazole has proven to be a drug with therapeutic potential. Bauer *et al.* (1997) reported complete resolution of oral and nasal conidiobolomycosis lesions in a dog treated with itraconazole at 10 mg/kg. In addition, Hawkins *et al.* (2006) described successful itraconazole therapy at the same dosage in a dog with nasal and pulmonary infection, even while the animal was receiving immunosuppressive therapy and chemotherapy.

The treatment of conidiobolomycosis in humans still represents a clinical challenge, mainly due to the rarity of cases and the lack of consensus on the most effective therapy, since the ideal treatment, its dosage and its appropriate duration are not yet well established (PORTELA *et al.*, 2010; KIMURA *et al.*, 2011; ISA-ISA *et al.*, 2012). Some promising studies of drugs as possible therapeutic options in hosts require long-term therapy, which is also problematic. Nevertheless, saturated solutions of drugs such as potassium iodide, ketoconazole, itraconazole, fluconazole, amphotericin B and terbinafine have been used with highly variable results (GUARRO *et al.*, 1999; TADANO *et al.*, 2005; FISCHER *et al.*, 2008; VILELA *et al.*, 2010; TONDOLO *et al.*, 2018).

Fischer *et al.* (2008) reported therapeutic success in a case of *C. coronatus* infection with the combination of itraconazole (200 mg/day) and terbinafine (250 mg/day) for one year, even though the isolate showed resistance to both drugs in monotherapy. Similarly, Tadano *et al.* (2005) described a significant response of human conidiobolomycosis to the combined use of ketoconazole and saturated potassium iodide solution for 180 days, resulting in progressive regression of the lesions, although the report does not describe complete cure of the patient.

Other combinations have also shown good results against *Conidiobolus* spp., such as potassium iodide with itraconazole (ARORA *et al.*, 2016; SHARATH *et al.*, 2024) and itraconazole combined with amphotericin B (CHOWDHARY *et al.*, 2010). It is important to note that, when treatment is started early, the prognosis in humans tends to be favorable, with rare mortality (ISA-ISA *et al.*, 2012).

Overall, however, treatment remains challenging, since the most promising therapies require long periods of administration, which may compromise liver and kidney function due to the toxicity associated with prolonged use of antifungal drugs (TADANO *et al.*, 2005;

KIMURA *et al.*, 2011), as well as treatment adherence and efficacy. In addition, facial deformities resulting from the infection may require corrective surgical interventions (VILELA *et al.*, 2010).

In vitro antimicrobial susceptibility testing against *Conidiobolus lamprauges* (*Neoconidiobolus lamprauges*)

The search for effective therapeutic alternatives for the treatment of infections caused by *C. lamprauges* (*N. lamprauges*) has motivated drug repurposing studies, involving evaluations of different drug classes in *in vitro* susceptibility assays. Among the compounds investigated are antifungal, antibacterial and antiprotozoal agents, whose activity has been determined by the broth microdilution method, following the recommendations of the Clinical and Laboratory Standards Institute (CLSI) protocol M38-A2. This approach allows the determination of the minimum inhibitory concentration (MIC), a parameter widely used to compare the activity of different substances against the pathogen. Overall, the studies show important differences in the susceptibility of *C. lamprauges* (*N. lamprauges*) to the compounds evaluated, with terbinafine standing out for showing the lowest MIC values and, consequently, the highest antifungal activity among the drugs tested. These findings reinforce the potential of terbinafine as a promising alternative for the treatment of conidiobolomycosis, although additional studies, especially *in vivo*, are needed to confirm its efficacy and safety in the different affected species. Table 1 brings together the main results of the susceptibility assays described in the literature.

The *in vitro* susceptibility of *C. lamprauges* (*N. lamprauges*) to different antimicrobial drugs has been investigated, revealing varied susceptibility and resistance profiles and important interactions between antimicrobials. In a study by Guarro *et al.* (1999), the susceptibility of one *C. lamprauges* (*N. lamprauges*) isolate to several antifungal agents was investigated. The results indicated resistance or variable susceptibility for most of the compounds tested, with minimum inhibitory concentrations (MIC) of 8 µg/ml for amphotericin B (AMB), ketoconazole (CTZ) and miconazole (MCZ) (MIC 100%). For fluconazole (FLZ) and itraconazole (ITZ), the MICs were 32 µg/ml, while flucytosine (FCT) showed an MIC of 256 µg/ml.

Subsequently, Kimura *et al.* (2011) determined the susceptibility of one *C. lamprauges* (*N. lamprauges*) isolate of human origin. This study found MICs of 0.5 and 1 µg/ml for itraconazole (ITZ) (MIC 100% after 24 and 48 hours, respectively) and 0.25 and 1 µg/ml for miconazole (MCZ) (MIC 50%). Terbinafine (TRB) showed MIC 50% values of 0.03 and 0.125 µg/ml. However, resistance was observed for AMB, with MICs of 4 and 8 µg/ml (MIC 100%), posaconazole (POS), with 4 µg/mL, and voriconazole (VOR), with MICs above

16 µg/ml (MIC 100%). Synergy tests of ITZ+TRB and POS+TRB were interpreted as indifferent.

Tondolo *et al.* (2013) evaluated six *C. lamprauges* (*N. lamprauges*) isolates from sheep for susceptibility to different antifungal agents. The MIC 100% values after 48 hours were: AMB (1 µg/ml), ITR (1-32 µg/ml), POS (2-32 µg/ml) and VOR (>16 µg/ml). Ketoconazole showed MIC 50% values between 8 and 32 µg/ml, while fluconazole and flucytosine showed MIC 50% values above 64 µg/ml, indicating low antifungal activity. Terbinafine performed best, with MIC 80% values ranging from 0.06 to 0.5 µg/ml.

Stefanello *et al.* (2018) and Tondolo *et al.* (2018) were the first to investigate the *in vitro* activity of azithromycin (AZI), dapsone (DAP) and miltefosine (MTF) against seven *C. lamprauges* (*N. lamprauges*) isolates. In addition to these compounds, previously known antifungal and antibacterial drugs were also analyzed. Individually, the MICs found were: amphotericin B (0.25-1.0 µg/ml), MCZ (2.0-8.0 µg/ml), TRB (0.25-2.0 µg/ml), VOR (512 µg/ml), sulfamethoxazole+trimethoprim (32/6.4-256/51.2 µg/ml), AZI (>64 µg/ml), DAP (>32 µg/ml) and MTF (2-16 µg/ml). Overall, the isolates were considered resistant or poorly susceptible to most drugs, except for terbinafine, which effectively inhibited the isolates tested.

Table 1
In vitro *susceptibility of* Conidiobolus lamprauges *(*Neoconidiobolus lamprauges*) to antimicrobials*

Drug class	Mechanism of action (reference)	Drugs	No. of isolates evaluated	MIC (µg/mL)	Reference
Polyenes	Binds to ergosterol, forming membrane pores (a)	Amphotericin B	1	8	Guarro *et al.*, 1999.
			6	1	Tondolo *et al.*, 2013.
			1	4 (24h), 8 (48h)	Kimura *et al.*, 2011.
			7	0.25 - 1	Stefanello *et al.*, 2018.
Triazoles	Inhibits ergosterol synthesis (b)	Itraconazole	1	32	Guarro *et al.*, 1999.
			6	1 - 32	Tondolo *et al.*, 2013.
			1	0.5 (24h), 1 (48h)	Kimura *et al.*, 2011.
		Voriconazole	6	> 16	Tondolo *et al.*, 2013.
			1	> 16	Kimura *et al.*, 2011.
			7	512	Stefanello *et al.*, 2018.
		Posaconazole	6	2 - > 32	Tondolo *et al.*, 2013.
			1	4 (24h), 4 (48h)	Kimura *et al.*, 2011.
Imidazoles	Inhibits ergosterol synthesis (b)	Ketoconazole	1	8	Guarro *et al.*, 1999.
			6	8 - 32	Tondolo *et al.*, 2013.

		Miconazole	1	8	Guarro *et al.*, 1999.
			1	0.25 (24h), 1 (48h)	Kimura *et al.*, 2011.
			7	2 - 8	Stefanello *et al.*, 2018.
Allylamines	Inhibits squalene epoxidase (c)	Terbinafine	1	0.03 (24h), 0.125 (48h)	Kimura *et al.*, 2011.
			6	0.06 - 0.5	Tondolo *et al.*, 2013.
			7	0.25 - 2	Stefanello *et al.*, 2018.
		Anidulafungin	1	> 8	Kimura *et al.*, 2011.
			6	> 8	Tondolo *et al.*, 2013.
Echinocandins	Inhibit cell wall β-(1,3)-D-glucan synthesis (d)	Caspofungin	1	> 8	Kimura *et al.*, 2011.
			6	> 8	Tondolo *et al.*, 2013.
		Micafungin	1	> 8	Kimura *et al.*, 2011.
			6	> 8	Tondolo *et al.*, 2013.
Sulfonamides	Sequential inhibition of nucleic acid and protein synthesis (e)	Sulfamethoxazole + Trimethoprim	7	32/6,4-256/51.2	Stefanello *et al.*, 2018.
Macrolides	Blocks bacterial protein synthesis by binding to the 50S ribosomal subunit (f)	Azithromycin	7	> 64	Stefanello *et al.*, 2018.
Sulfones	Inhibits folate synthesis, similarly to sulfonamides (e)	Dapsone	7	> 32	Stefanello *et al.*, 2018.
Antiprotozoals	Disrupts plasma membrane integrity and has antifungal properties (g)	Miltefosine	7	2 - 16	Stefanello *et al.*, 2018.

MIC: minimum inhibitory concentration; (a): Hamill *et al.*, 2013; (b): Xu *et al.*, 2010; (c): Ryder *et al.*, 1992; (d): Kartsonis *et al.*, 2003; (e): Hitchings *et al.*, 1973; (f): Heidary *et al.*, 2022; (g): Pinto-Martinez *et al.*, 2018.

Given the limited antifungal activity of single agents against *C. lamprauges* (*N. lamprauges*), studies have shown that certain antimicrobial combinations may produce promising synergistic effects (STEFANELLO *et al.*, 2018; TONDOLO *et al.*, 2018). The theoretical basis for the use of drug combinations rests on the premise that pharmacological synergy occurs when the combination of two or more compounds results in an inhibitory activity greater than the sum of the effects observed individually (ODDS, 2003).

Stefanello *et al.* (2018) and Tondolo *et al.* (2018) highlighted the therapeutic potential of drug combinations, together with drug repurposing. This strategy aims to identify new uses for substances already available on the market, accelerating the development of effective therapies for rare and emerging fungal infections.

Among the combinations tested *in vitro*, synergy rates of 100% were observed for miltefosine combined with azithromycin or dapsone, and for the classic combination of sulfamethoxazole with trimethoprim. Terbinafine, when combined with azole antifungals such as miconazole, posaconazole and voriconazole, showed synergy in 71% of cases. The combination of azithromycin and dapsone also stood out, with 85.7% synergy. These findings reinforce the potential of these combinations for the development of new therapeutic approaches against *C. lamprauges* (*N. lamprauges*) infections (STEFANELLO *et al.*, 2018; TONDOLO *et al.*, 2018).

On the other hand, the tests also revealed indifferent interactions and relevant antagonism. The combination of dapsone and terbinafine showed antagonism in 42.9% of the assays, as did the combination of dapsone with amphotericin B. In addition, the combination of sulfamethoxazole + trimethoprim with antifungal agents showed no additional synergistic effect and was classified as indifferent in all cases evaluated (STEFANELLO *et al.*, 2018; TONDOLO *et al.*, 2018).

The drug combinations evaluated, including antifungal, antibacterial and antiparasitic agents, showed varied responses against the *C. lamprauges* (*N. lamprauges*) isolates, as presented in Table 2. The results ranged from promising synergistic effects to indifferent or even antagonistic interactions, which underscores the complexity of the pharmacological interactions involved. Although some combinations proved promising, the variability of responses reinforces the need for broader and more systematic studies.

Table 2
In vitro *drug combinations against* Conidiobolus lamprauges *(*Neoconidiobolus lamprauges*)*

Combined drugs (A/B)	No. of isolates	MIC alone (A/B) (µg/mL)	MIC in combination (µg/mL)	Synergy (%)	Indifference (%)	Antagonism (%)	Reference
AZI+AMB	7	AZI: > 64/ AMB: 0.25-1	AZI: 0.5-64/ AMB: 0.5-1	0	85.70	14.30	Stefanello *et al*., 2018.
AZI+CTX	7	AZI: > 64/ CTX: 32/6,4-256/51,2	AZI: 0.03-128/ CTX: 16/3,2-512/102.4	14.30	57.10	28.60	Stefanello *et al*., 2018.
AZI+DAP	7	AZI: > 64/ DAP: > 32	AZI: 0.5-0.5/ DAP:8-32	85.70	14.30	0	Stefanello *et al*., 2018.
AZI+MCZ	7	AZI: > 64/ MCZ: 2-8	AZI: 0.5-128/ MCZ: 0.25-64	57.10	28.60	14.30	Stefanello *et al*., 2018.
AZI+MTF	7	AZI: > 64/ MTF: 2-16	AZI: 4-16/ MTF: 0.25	100	0	0	Stefanello *et al*., 2018.
AZI+TRB	7	AZI: > 64/	AZI: 0.5-64/	0	100	0	Stefanello *et*

		TRB: 0.25-2	TRB: 0.125-1				*al*., 2018.
AZI+VOR	7	AZI: > 64/ VOR: 512	AZI: 0.5-64/ VOR: 4-512	0	100	0	Stefanello *et al*., 2018.
CTX + AMB	7	CTX: 32/6,4-256/51.2/AMB: 0.25-1	CTX: 4/0,8-128/25.6/AMB: 0.03-0.5	14.30	85.70	0	Stefanello *et al*., 2018.
CTX + DAP	7	CTX: 32/6,4-256/51.2/ DAP: > 32	CTX: 64/12,8-256/51.2/DAP: 0.125-0.125	0	85.70	14.30	Stefanello *et al*., 2018.
CTX + MCZ	7	CTX: 32/6,4-256/51.2/MCZ: 2-8	CTX: 4/0,8-64/12.8/MCZ: 0.3-2	42.90	57.10	0	Stefanello *et al*., 2018.
CTX + MTF	7	CTX: 32/6,4-256/51.2/MTF: 2-16	CTX: 4/0,8-64/12.8/MTF: 0.25-8.0	14.30	87.70	0	Stefanello *et al*., 2018.
CTX + TER	7	CTX: 32/6,4-256/51.2/TER: 0.25-2	CTX: 4/0,8-256/51.2/TER: 0.03-0.25	14.30	71.40	14.30	Stefanello *et al*., 2018.
CTX + VOR	7	CTX: 32/6,4-256/51.2/VOR: 512	CTX: 4/0,8-4/0.8/VOR 256-512	14.30	85.70	0	Stefanello *et al*., 2018.
DAP + AMB	7	DAP: > 32/ AMB: 0.25-1	DAP: 0.125-8 /AMB: 0.03-2	14.30	42.85	42.85	Stefanello *et al*., 2018.
DAP + MCZ	7	DAP: > 32/ MCZ: 2-8	DAP: 0.125-32/ MCZ: 2-4	42.90	57.10	0	Stefanello *et al*., 2018.
DAP + MTF	7	DAP: > 32/MTF: 2-16	DAP: 2-8/MTF: 0.25-0.25	100	0	0	Stefanello *et al*., 2018.
DAP + TRB	7	DAP: > 32/ TRB: 0.25-2	DAP: 0.25-32/ TRB: 0.50-4	0	57.10	42.90	Stefanello *et al*., 2018.
DAP + VOR	7	DAP: > 32/ VOR: 512	DAP: 0.25-32/ VOR: 256-512	0	100	0	Stefanello *et al*., 2018.
ITZ + TRB	1	ITZ: 0.5-1/TRB: 0.03-0.125	ITZ: 1/TRB: 0.06	0	100	0	Kimura *et al*., 2011.
MTF + AMB	7	MTF: 2-16/ AMB: 0.25-1	MTF: 8-32/ AMB: 0.03-0.06	0	71.40	28.60	Stefanello *et al*., 2018.
MTF + MCZ	7	MTF: 2-16/ MCZ: 2-8	MTF: 0.25-16/ MCZ: 0.25-8	0	85.70	14.30	Stefanello *et al*., 2018.
MTF + TRB	7	MTF: 2-16/ TRB: 0.25-2	MTF: 8-16/ TRB: 0.03-0.03	0	85.70	14.30	Stefanello *et al*., 2018.
MTF + VOR	7	MTF: 2-16/ VOR: 512	MTF: 0.25-8/ VOR: 64-512	0	100	0	Stefanello *et al*., 2018.
POS + TRB	1	POS: 4/TRB: 0.03-0.125	POS: < 0.03/TRB: 0.125	0	100	0	Kimura *et al*., 2011.
SMX + TMP	6	SMX: 128-1024/ TMP: 256-512	SMX: 4-8/ TMP: 8-32	100	0	0	Tondolo *et al*., 2018.
SMX/TMP* + AMB	6	SMX/TMP*: 128-1024/256-512/ AMB: 1-2	SMX/TMP: 0.25/1-8/32/ AMB: 1-2	0	100	0	Tondolo *et al*., 2018.
SMX/TMP* +	6	SMX/TMP*:	SMX/TMP:	0	100	0	Tondolo *et*

ANI		128-1024/256-512/ ANI: > 512	8/32-16/64/ ANI: 0.06-4				*al.*, 2018.
SMX/TMP* + CAS	6	SMX/TMP*: 128-1024/256-512/ CAS: 256-> 512	SMX/TMP: 4/16-16/64 CAS: 0.125-16	0	100	0	Tondolo *et al.*, 2018.
SMX/TMP* + MFG	6	SMX/TMP*: 128-1024/256-512/ MFG: 64-256	SMX/TMP: 0.25/1-16/64/ MFG: 0.06-64	0	100	0	Tondolo *et al.*, 2018.
SMX/TMP* + MCZ	6	SMX/TMP*: 128-1024/256-512/ MCZ: 4-16	SMX/TMP: 0.25/1-0.5/2/ MCZ: 4-16	0	100	0	Tondolo *et al.*, 2018.
SMX/TMP* + POS	6	SMX/TMP*: 128-1024/256-512/ POS: > 32	SMX/TMP: 4/16-8/32/POS: 0.003-0.03	0	100	0	Tondolo *et al.*, 2018.
SMX/TMP* + TRB	6	SMX/TMP*: 128-1024/256-512/TRB: 1-4	SMX/TMP: 0.25/1-4/16/TRB: 0.25-4	0	100	0	Tondolo *et al.*, 2018.
SMX/TMP* + VOR	6	SMX/TMP*: 128-1024/256-512/ VOR: > 512	SMX/TMP: 4/16-8/32/VOR: 0.015-4	0	100	0	Tondolo *et al.*, 2018.
TRB + AMB	6	TRB: 1-4/ AMB: 1-2	TRB: 0,06-4/ AMB: 0.003-2	0	100	0	Tondolo *et al.*, 2018.
TRB + ANI	6	TRB: 1-4/ ANI: > 512	TRB: 0,5-4/ ANI: 0.06-1	0	100	0	Tondolo *et al.*, 2018.
TRB + CAS	6	TRB: 1-4/ CAS: 256->512	TRB: 1-2/CAS: 0.125-4	0	100	0	Tondolo *et al.*, 2018.
TRB + MFG	6	TRB: 1-4/ MFG: 64-256	TRB: 0,06-2/ MFG: 8-64	29	71	0	Tondolo *et al.*, 2018.
TRB + MCZ	6	TRB: 1-4/ MCZ: 4-16	TRB: 0,06-1/ MCZ: 0.06-8	71	29	0	Tondolo *et al.*, 2018.
TRB + POS	6	TRB: 1-4/ POS: > 32	TRB: 0,06-4/ POS: 0.003-4	71	29	0	Tondolo *et al.*, 2018.
TRB + VOR	6	TRB: 1-4/ VOR: > 512	TRB: 0.25-2/ VOR: 0.015-0.5	71	29	0	Tondolo *et al.*, 2018.

MIC: minimum inhibitory concentration; AMB: amphotericin B; ANI: anidulafungin; AZI: azithromycin; CAS: caspofungin; CTX: cotrimoxazole (sulfamethoxazole/trimethoprim at a 5:1 ratio); DAP: dapsone; MCZ: miconazole; MFG: micafungin; MTF: miltefosine; POS: posaconazole; SMX: sulfamethoxazole; TMP: trimethoprim; TRB: terbinafine; VOR: voriconazole; *: sulfamethoxazole/trimethoprim at a 1:4 ratio.

Final considerations

Conidiobolomycosis represents an important challenge in both human and veterinary medicine, mainly due to the high lethality in small ruminant herds, therapeutic failure and considerable economic losses in livestock production. The difficulties in treatment are aggravated by the reduced susceptibility to available antifungal agents, as well as by the lack

of standardized therapeutic protocols and of timely diagnosis of the infection (VILELA *et al.*, 2010; AGUIAR *et al.*, 2014; WEIBLEN *et al.*, 2016).

In this scenario, research on new therapeutic approaches is crucial. The literature analyzed shows that terbinafine stood out as the most promising antifungal agent in monotherapy, with the best *in vitro* inhibitory activity against *C. lamprauges* (*N. lamprauges*) isolates. In this context, this literature review brought together and analyzed the scientific evidence on the *in vitro* activity of different antimicrobial drugs, alone or in combination, including antifungal, antibacterial and antiparasitic agents, against *C. lamprauges* (*N. lamprauges*).

High synergy rates were reported for several combinations, such as miltefosine + azithromycin (100%), miltefosine + dapsone (100%) and azithromycin + dapsone (85.7%). Synergy was also observed between sulfamethoxazole and trimethoprim (100%) and between terbinafine and azole antifungals (miconazole, posaconazole and voriconazole, with 71% synergistic interactions) (STEFANELLO *et al.*, 2018; TONDOLO *et al.*, 2018). These combinations proved promising and deserve attention as candidates for the development of more effective treatment protocols for conidiobolomycosis.

Therefore, to advance in the fight against this important disease, future research should prioritize *in vitro* and *in vivo* studies of new drug classes and the establishment of standardized therapeutic protocols. An in-depth understanding of the biology and pathogenesis of the fungus offers innovative paths. The ability of *C. lamprauges* (*N. lamprauges*) to adapt and proliferate at high temperatures, such as mammalian body temperature (37°C-39°C), is an important virulence factor (GODOY *et al.*, 2014; WEIBLEN *et al.*, 2016). The overexpression of proteins such as enolase at 37°C, a glycolytic enzyme associated with pathogenicity and host-pathogen interaction in other microorganisms, highlights the need to elucidate its function and specific cellular location in *C. lamprauges* (*N. lamprauges*) (DA SILVA *et al.*, 2012). In addition, the identification of immunoreactive proteins, such as those of 53 kDa and 198 kDa, which proved immunodominant in naturally infected sheep, opens perspectives for the development of early serological diagnostic methods and even vaccines (SILVA *et al.*, 2015).

Early diagnosis, enhanced by molecular and immunological advances (AQUINO *et al.*, 2023), is fundamental to enable the implementation of treatment strategies in the early stages of the disease, increasing the chances of therapeutic success. Therefore, investment in research that unravels the molecular and immunological aspects of *C. lamprauges* (*N. lamprauges*) is necessary to improve the control and treatment of the infection caused by this etiological agent.

Although terbinafine stands out as the most promising antifungal agent *in vitro*, the varied response of the isolates to the different drugs highlights the complexity of treatment

and the urgent need for alternative therapeutic strategies. Combinations such as miltefosine + azithromycin and sulfamethoxazole + trimethoprim showed synergy in 100% of the isolates evaluated, emerging as viable therapeutic options in view of the resistance observed in single-agent assessments. On the other hand, antagonistic interactions, such as dapsone combined with terbinafine, point to the importance of a careful selection of drug combinations.

Non-antifungal drugs, such as azithromycin and miltefosine, show repurposing potential for addressing the mycosis caused by *C. lamprauges* (*N. lamprauges*). However, translating laboratory findings into clinical practice still depends on *in vivo* studies that assess not only efficacy but also pharmacokinetics, adverse effects and the clinical stage of the infection. Added to this is the need to standardize early diagnostic methods that allow interventions before progression to irreversible stages.

The gaps in the current management of conidiobolomycosis are critical, and they can be overcome through an integrated approach involving basic research, clinical validation and pharmaceutical development, thereby reducing the lethality of outbreaks, promoting animal welfare and mitigating economic impacts on livestock production.

Declarations

Funding. There was no external funding.

Conflicts of interest. There are no conflicts of interest.

Research ethics. Not applicable.

Use of artificial intelligence. ChatGPT (OpenAI), version GPT-5.5, was used exclusively to assist with grammatical correction and refinement of the wording of the text. All information was reviewed by the authors.

Data availability. The data presented in this chapter derive from a literature review based on scientific articles available in the Google Scholar, PubMed, ScienceDirect and Scientific Electronic Library Online (SciELO) databases.

Author contributions. The authors contributed equally to the development of the chapter.

References

Aguiar, G. M. N. de, Simões, S. V. D., Santos, S. A., Marques, A. L. A., Silva, T. R. da, Dantas, A. F. M., & Riet-Correa, F. (2014). Epidemiological aspects of conidiobolomycosis in sheep in the semi-arid region of Northeast Brazil. *Ciência Rural*, 44(12), 2210-2216, 2014. https://doi.org/10.1590/0103-8478CR20131472

Aquino, C. A. Q. (2023). Surto de conidiobolomicose causado por *Conidiobolus lamprauges* em ovinos da região Alto-Oeste do Rio Grande do Norte, Brasil: relato de caso. 2023. 43 f.

Trabalho de Conclusão de Curso (Graduação em Medicina Veterinária) – Universidade Federal Rural do Semi-Árido, Mossoró.

Arora, N., Bhargava, E. K., & Rai, V. (2016). Nasal Conidiobolomycosis-The Unknown Threat. Journal of Clinical and Diagnostic Research, 10(12), 1-2. https://doi.org/10.7860/JCDR/2016/21480.8946

Barbosa, C. C., Ferreira Filho, C. E. S., Silveira, N. S. S., Oliveira, C. M. C., Ferreira, T. T. A., Silveira, J. A. S., Duarte, M. D., Costa, P. S. C. da, Pereira, G. O., Brito, M. de F., & Barbosa, J. D. (2025). Conidiobolomycosis with neurological commitment in sheep in Pará, Brazil. *Ciência Rural*, 55(2), e20240016. https://doi.org/10.1590/0103-8478cr20240016

Bauer, R., Lemarié, S., & Roy, A. (1997). Oral conidiobolomycosis in a dog. *Veterinary Dermatology*, 8(2), 115-120. https://doi.org/10.1046/j.1365-3164.1997.d01-9.x

Bento, D. P., Tavares, R., Martins, M. L., Faria, N., Maduro, A. P. Araújo, C. Ventura, F., & Mansinho, K. (2010). Atypical presentation of entomophthoromycosis caused by *Conidiobolus coronatus*. *Medical Mycology*, 48(8), 1099-1104. https://doi.org/10.3109/13693786.2010.497973

Boabaid, F. M., Ferreira, E. V., Peixoto, L., Gasparetto, N. D., Souza, R. L., Silva, M. C., Dutra, V., Nakazato, L., & Colodel, E. M. (2008). Conidiobolomicose em ovinos no estado de Mato Grosso. *Pesquisa Veterinária Brasileira*, 28(1), 77–81. https://doi.org/10.1590/S0100-736X2008000100012

Carmo, P. M. S., Uzal, F. A., Pedroso, P. M. O., & Riet-Correa, F. (2020). Conidiobolomycosis, cryptococcosis, and aspergillosis in sheep and goats: a review. *Journal of Veterinary Diagnostic Investigation*, 32(6), 826-834. https://doi.org/10.1177/1040638720958338

Chowdhary, A., Randhawa, H. S., Khan, Z. U., Ahmad, S., Khanna, G., Gupta, R., Chakravarti, A., & Roy, P. (2010). Rhinoentomophthoromycosis due to *Conidiobolus coronatus*: a case report and an overview of the disease in India. *Medical Mycology*, 48(6), 870-879. https://doi.org/10.3109/13693786.2010.486010

Clinical and Laboratory Standards Institute. (2017). *Reference method for broth dilution antifungal susceptibility testing of filamentous fungi* (2nd ed.; CLSI standard M38-A2). Clinical and Laboratory Standards Institute.

da Silva, J. A. G., Paula, D. A. J., Silveira, M. M., Silva, M. C., Brandão, L. N. S., Pitchenin, L. C., Nakazato, L., & Dutra, V. (2012). Thermoregulated genes differentially expressed in *Conidiobolus lamprauges. Ciência Rural*, 42(9), 1610–1613. https://doi.org/10.1590/0103-8478cr20150935

de Paula, D. A. J., Oliveira Filho, J. X., Silva, M. C., Colodel, E. M., Broetto, L., Pinto, P. M., Schrank, A., Nakazato, L., Dutra, V. (2010). Molecular characterization of ovine zygomycosis in Central Western Brazil. *Journal of Veterinary Diagnostic Investigation*, 22(2), 274–277. https://doi.org/10.1177/104063871002200220

Fischer, N., Ruef, C., C. Ebnöther, & Bächli, E. B. (2008). Rhinofacial *Conidiobolus coronatus* infection presenting with nasal enlargement. *Infection*, 36(6), 594–596. https://doi.org/10.1007/s15010-008-8056-5

Furlan, F. H., Lucioli, J., Veronezi, L. O., Fonteque, J. H., Traverso, S. D., Nakazato, L., & Gava, A. (2010). Conidiobolomycosis caused by *Conidiobolus lamprauges* in sheep in the state of Santa Catarina. *Pesquisa Veterinária Brasileira*, 30(7), 529–532. https://doi.org/10.1590/S0100-736X2010000700003

Godoy, I., De Paula, D. A. J., Silveira, M. M., Brandão, L. N. S., Dutra, V., & Nakazato, L. (2014). Differential expression of proteins from the fungus *Conidiobolus lamprauges* grown at different temperatures. *Ciência Rural*, 44(3), 473-478. https://doi.org/10.1590/S0103-84782014000300014

Guarro, J., Aguilar, C., & Pujol, I. (1999). *In-vitro* antifungal susceptibilities of *Basidiobolus* and *Conidiobolus* spp. strains. *Journal of Antimicrobial Chemotherapy*, 44(4), 557–560. https://doi.org/10.1093/jac/44.4.557

Hawkins, E. C., Grooters, A. M., Cowgill, E. S., Proulx, D. R., Davainis, G. M., Ruslander, D. M. & Grindem, C.B. (2006). Treatment of *Conidiobolus* sp. pneumonia with itraconazole in a dog receiving immunosuppressive *Therapy. Journal of Veterinary Internal Medicine*, 20, 1479-1482. https://doi.org/10.1111/j.1939-1676.2006.tb00769.x

Hamill, R. J. (2013). Amphotericin B Formulations: A comparative review of efficacy and toxicity. *Drugs*, 73, 919-934. https://doi.org/10.1007/s40265-013-0069-4

Heidary, M., Ebrahimi Samangani, A., Kargari, A., Kiani Nejad, A., Yashmi, I., Motahar, M., Taki, E., & Khoshnood, S. (2022). Mechanism of action, resistance, synergism, and clinical implications of azithromycin. *Journal of Clinical Laboratory Analysis*, 36(6), e24427. https://doi.org/10.1002/jcla.24427

Hitchings, G. H. (1973). Mechanism of action of trimethoprim-sulfamethoxazole--I. *Journal of Infectious Diseases*, 128(Supplement 3), S433–S436. https://doi.org/10.1093/infdis/128.supplement_3.s433

Humber, R. A., Brown, C. C., & Kornegay, R. W. (1989). Equine zygomycosis caused by *Conidiobolus lamprauges*. *Journal of Clinical Microbiology*, 27(3), 573–576. https://doi.org/10.1128/JCM.27.3.573-576.1989

Isa-Isa, R., Arenas, R., Fernández, R. F., & Isa, M. (2012). Rhinofacial conidiobolomycosis (entomophthoramycosis). *Clinics in Dermatology*, 30(4), 409–412. https://doi.org/10.1016/j.clindermatol.2011.09.012

Ishikawa, F., Oishi, K., & Aida, K. (1983). Purification and immunological properties of chitin-binding hemagglutinin and β-n-acetylglucosaminidase produced by *Conidiobolus lamprauges*. *Agricultural and Biological Chemistry*, 47(1), 149–151. https://doi.org/10.1080/00021369.1983.10865601

Kartsonis, N. A., Nielsen, J., & Douglas, C. M. (2003). Caspofungin: the first in a new class of antifungal agents. *Drug Resistance Updates*, v. 6, n. 4, p. 197-218, 2003. https://doi.org/10.1016/S1368-7646(03)00064-5

Kimura, M., Yaguchi, T., Sutton, D. A., Fothergill, A. W., Thompson, E. H., Wickes, B. L. (2011). Disseminated human conidiobolomycosis due to *Conidiobolus lamprauges*. *Journal of Clinical Microbiology*, 49(2), 752-756. https://doi.org/10.1128/JCM.01484-10

Morris, M., Ngeleka, M., Adogwa, A. O., Lalla, G., St-Germain, G., Higgins. R. (2001). Rhinocerebral zygomycosis in a sheep. *Canadian Veterinary Journal*, 42(3), 227-228. https://pmc.ncbi.nlm.nih.gov/articles/PMC1476464/?page=2

Mustafa, V. S., Guedes, K. M. R., Lima, E. M. M., Borges, J. R. J., & Castro, M. B. (2015). Diseases of the nasal cavity in small ruminants in the Federal District and the State of Goiás. *Pesquisa Veterinária Brasileira*, 35(7), 627–636. https://doi.org/10.1590/S0100-736X2015000700005

Nie, Y., Wang, Z.-M., Liu, X.-Y., & Huang, B. (2021). A morphological and molecular survey of *Neoconidiobolus* reveals a new species and two new combinations. *Mycological Progress*, 20, 1233-1241. https://doi.org/10.1007/s11557-021-01720-w

Odds, F. C. (2003). Synergy, antagonism, and what the chequerboard puts between them. *Journal of Antimicrobial Chemotherapy*, 52(1), 1-1. https://doi.org/10.1093/jac/dkg301

Pinto-Martinez, A. K., Rodriguez-Durán, J., Serrano-Martin, X., Hernandez-Rodriguez, V., & Benaim, G. (2018). Mechanism of action of miltefosine on *Leishmania donovani* involves the impairment of acidocalcisome function and the activation of the sphingosine-dependent plasma membrane Ca^{2+} channel. *Antimicrobial Agents and Chemotherapy*, 62(1), e01614-17. https://doi.org/10.1128/AAC.01614-17

Pedroso, P. M. O., Raymundo, D. L., Bezerra Júnior, P. S., Oliveira, E. C. de, Sonne, L., Dalto, A. G. C., & Driemeier, D. (2018). Rhinopharyngeal mycotic rhinitis in a Texel sheep in Rio Grande do Sul. *Acta Scientiae Veterinariae*, 37(2), 181–185. https://doi.org/10.22456/1679-9216.16248

Peixoto, T. C., Farias, S. S., Madureira, K. M., Macêdo, A. G. C., Filho, C. H. C. V., Lima, E. B., Nakazato, L., & Pescador, C. A. (2014). Conidiobolomicose nasofaríngea e rinocerebral em ovinos no Estado da Bahia. In *VII Encontro Nacional de Diagnóstico Veterinário (ENDIVET) e II Encontro Internacional de Sanidade de Animais de Produção* (pp. 1–2).

Portela, R. A., Riet-Correa, F., Garino Júnior, F., Dantas, A. F. M., Simões, S. V. D., & Silva, S. M. S. (2010). Diseases of the nasal cavity in ruminants in Brazil. *Pesquisa Veterinária Brasileira*, 30(10), 844-854. https://doi.org/10.1590/S0100-736X2010001000007

Presley, S. J., Mello, J. H. F. & Willig, M. R. (2019). Checkerboard metacommunity structure: an incoherent concept. *Oecologia*, 190(2), 323-331. https://doi.org/10.1007/s00442-019-04420-1

Ribes, J. A., Vanover-Sams, C. L., Baker, D. J. (2000) .Zygomycetes in human disease. *Clinical Microbiology Reviews*, 13(2), 236-301. https://doi.org/10.1128/CMR.13.2.236-301.2000

Ryder, N. S. (1992). Terbinafine: Mode of action and properties of the squalene epoxidase inhibition. British *Journal of Dermatology*, 126(Supplement 39), 2-7. https://doi.org/10.1111/j.1365-2133.1992.tb00001.x

Riet-Correa, F., Dantas, A. F. M., Azevedo, E. O., Simões, S. D. V., Silva, S. M. S., Vilela, R., & Mendoza, L. (2008). Outbreaks of rhinofacial and rhinopharyngeal zygomycosis in sheep in Paraíba, northeastern Brazil. *Pesquisa Veterinária Brasileira*, 28(1), 29-35. https://doi.org/10.1590/S0100-736X2008000100006

Sharath, S., Bansal, A., Sinha, S. & Ahuja, A. (2024). Successful management of rhinofacial *Conidiobolus coronatus* infection with itraconazole monotherapy.*The American Journal of Tropical Medicine and Hygiene*, 112(1), 158-160. https://doi.org/10.4269/ajtmh.24-0196

Silva, S. M. M. S., Castro, R. S., Costa, F. A. L., Vasconcelos, A. C., Batista, M. C. S., Riet-Correa, F., & Carvalho, E. M. S. (2007a). Conidiobolomycosis in sheep in Brazil. *Veterinary Pathology*, 44(3), 314-319. https://doi.org/10.1354/vp.44-3-314

Silva, S. M. M. S Castro, R. S., Costa, F. A. L., Vasconcelos, A. C., Batista, M. C. S., Riet-Correa, F., Carvalho, E. M. S., & Lopes, J. B. (2007b). Epidemiology and clinical signs of conidiobolomycosis in sheep in the State of Piauí. *Pesquisa Veterinária Brasileira*, 27(4), 184-190. https://doi.org/10.1590/S0100-736X2007000400010

Silva, M. C., Godoy, I., Ubiali, D. G., Silveira, M. M., Pitchenin, L. C., Brandão, L. N. S. Dutra, V., & Nakazato, L. (2015). Immunoreactive proteins of *Conidiobolus lamprauges* isolated from naturally infected sheep. *Pesquisa Veterinária Brasileira*, 35(4), 344-348. https://doi.org/10.1590/S0100-736X2015000400006

Silva, R. B., Maggi, L. E., Santos, F. G. A., Araújo, A. V., Diniz, J. V. A., & Carvalho, C. M. (2022). Conidiobolomycosis in sheep in the state of Acre, Brazil. *Ars Veterinaria*, 38(1), 05-12. https://doi.org/10.15361/2175-0106.2022v38n1p05-12

Stefanello, J. R., Piasentin, F. B., Tondolo, J. S. M., Loreto, E. S., Dutra, V., Alves, S. H., & Santurio, J. M. (2018). *In vitro* assessment of antifungal, antibacterial, and antiprotozoal drugs against clinical isolates of *Conidiobolus lamprauges*. *Medical Mycology*, 57(5), 649-652. https://doi.org/10.1093/mmy/myy092

Steiger, R. R., & Williams, M. A. (2000). Granulomatous tracheitis caused by *Conidiobolus coronatus* in a horse. *Journal of Veterinary Internal Medicine*, 14(3), 311-314. https://doi.org/10.1892/0891-6640(2000)014

Tadano, T., Paim, N. P., Hueb, M., & Fontes, C. J. (2005). Entomophthoramycosis (zygomycosis) caused by *Conidiobolus coronatus* in Mato Grosso (Brazil): case report. *Revista da Sociedade Brasileira de Medicina Tropical*, 38(2), 188-190. https://doi.org/10.1590/s0037-86822005000200013

Taintor, J., Crowe, C., Hancock, S., Schumacher, J., & Livesey, L. (2004). Treatment of Conidiobolomycosis with fluconazole in two pregnant mares. *Journal of Veterinary Internal Medicine*, 18, 363-364. https://doi.org/10.1111/j.1939-1676.2004.tb02560.x

Tan, R. M. T. S. L., DeFrancisco, A. L., & Singh, K. (2010). Pathology in practice. *Journal of the American Veterinary Medical Association*, 236(8), 831-833. https://doi.org/10.2460/javma.236.8.831

Tondolo, J. S. M., Loreto, E. S., Dutra, V., Nakazato, L., Paula, D. A. J., Zanette, R. A., Alves, S. H., & Santurio, J. M. (2013). *In vitro* susceptibility of *Conidiobolus lamprauges* recovered from sheep to antifungal agentes. *Veterinary Microbiology*, 166, 690-693. https://doi.org/10.1016/j.vetmic.2013.07.024.

Tondolo, J. S. M., Loreto, E. S., Jesus, F. P. K., Dutra, V., Nakazato, L., Alves, S. H., & Santurio, J. M. (2018). *In Vitro* assessment of antifungal drugs and sulfamethoxazole-trimethoprim against clinical isolates of *Conidiobolus lamprauges*. *Antimicrobial Agents and Chemotherapy*, 62(4), 1-4. https://doi.org/10.1128/aac.01685-17

Ubiali, D. G., Cruz, R. A. S., De Paula, D. A. J., Silva, M. C., Mendonça, F.S., Dutra, V., Nakazato, L., Colodel E.M., & Pescador, C. A. (2013). Pathology of nasal infection caused by *Conidiobolus lamprauges* and *Pythium insidiosum* in sheep. *Journal of Comparative Pathology*, 149(2-3), 137-145. https://doi.org/10.1016/j.jcpa.2013.01.001

Vilela, R., Silva, S. M. S., Riet-Correa, F., Dominguez, E., & Mendoza, L. (2010). Morphologic and phylogenetic characterization of *Conidiobolus lamprauges r*ecovered from infected sheep. *Journal of Clinical Microbiology*, 48(2), 427-432. https://doi.org/10.1128/JCM.01768-09

Ximenes, F. H. B., Pereira, C. S., Leite, C. R., Gontijo, L. A., Mustafa, V. S., Gouvêa, L. V., Godoy, R. F., Castro, M. B., & Borges, J. R. J. (2007). Effect of sodium iodide by intravenous rout in the treatment of Zygomycosis in sheeps. *Archives of Veterinary Science*, 12, 242-243. https://revistas.ufpr.br/veterinary/article/view/11153/7651

Xu, Y., *Sheng, C., Wang, W., Che, X., Cao, Y., Dong, G., Wang, S., Ji, H., Miao, Z., Yao, J., Zhang, W.* (2010). Structure-based rational design, synthesis and antifungal activity of oxime-containing azole derivatives. *Bioorganic & Medicinal Chemistry Letters*, 20(9), 2942-2945. https://doi.org/10.1016/j.bmcl.2010.03.014

Weiblen, C., Pereira, D. I. B., Dutra, V., Godoy, I., Nakazato, L., Sangioni, L. A., Santurio, J. M., & Botton, S. A. (2016). Epidemiological, clinical and diagnostic aspects of sheep conidiobolomycosis in Brazil. *Ciência Rural*, 46(5), 839-846. https://doi.org/10.1590/0103-8478cr20150935

Wüppenhorst, N., Lee, M.K., Rappold, E., Kayser, G., Beckervordersandforth, J., de With, K., Serr, A. (2010). Rhino-orbitocerebral zygomycosis caused by *Conidiobolus incongruus* in an immunocompromised patient in Germany. *Journal of Clinical Microbiology*, 48(11), 4322-4325, 2010. https://doi.org/10.1128/JCM.01188-10