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Oral Manifestations and Clinical Management of Coccidioidomycosis: A Systematic Review

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Introduction: *Coccidioidomycosis* is a systemic fungal infection caused by *Coccidioides immitis* and *C. posadasii*, transmitted through the inhalation of arthroconidia from the soil. It predominates in arid regions of the Americas, including Brazil. Although it primarily affects the lungs, it can manifest in the oral cavity, causing lesions such as ulcers, nodules, and verrucous plaques, often mistaken for other oral diseases.
Methodology: The systematic literature search was conducted in January 2025 in the databases PubMed, Web of Science, and LILACS, included studies were those published in Portuguese and English from 1964 to 2024, and case reports relating coccidioidomycosis to the oral cavity. Diagnosis requires clinical examination, epidemiological history, and laboratory tests, including biopsy, serology, and PCR. Treatment is based on antifungal agents such as fluconazole and itraconazole, with amphotericin B used in severe cases. Diabetic patients are more vulnerable to infection. This literature review analyzed studies, identifying two relevant cases.
Results: The research highlighted the importance of early diagnosis and individualized treatment management. Additionally, awareness and prevention are essential, especially in endemic areas. The relationship between diabetes and coccidioidomycosis reinforces the need for an integrated clinical approach. Early recognition of these lesions significantly influenced therapeutic decision-making and improved clinical outcomes, highlighting their prognostic value.
Conclusion: Further studies are needed to enhance the understanding of the disease, its diagnosis, and therapeutic approach, with a focus on oral manifestations. Emphasizing the importance of early diagnosis through oral findings can lead to timely treatment and better patient prognosis.

Keywords: Coccidioidomycosis; infections; etiology; Coccidioides posadasii; oral cavity.

ABBREVIATIONS

PCR : Polymerase Chain Reaction
IDSA : Infectious Diseases Society of America

1. INTRODUCTION

Coccidioidomycosis, also known as valley fever, is a fungal infection caused by the etiological agents Coccidioides immitis and C. posadasii, which infect humans after the inhalation of spores. These fungal structures can be found in the soil of endemic areas, such as the southwestern United States and Latin America, particularly in Argentina, Paraguay, Venezuela, and Brazil. Although cases are rarely documented, they have been reported in the states of Piauí, Ceará, Bahia, and Maranhão, with transmission associated with activities involving soil handling and exposure to fungal arthroconidia (Wang et al., 2022; Eulálio et al., 2024). In particular, people who engage in animal hunting in underground burrows, as well as agricultural workers, construction workers, gardeners, or individuals exposed to large amounts of dust in associated regions, are among the most affected (Eulálio et al., 2024).

The genus Coccidioides has the potential to cause a slowly progressing infection, with the onset of symptoms usually occurring between 1 and 3 weeks after exposure. Clinical manifestations of coccidioidomycosis are predominantly asymptomatic, occurring in about 60% of cases (Valdivia et al., 2006). When symptomatic, the disease presents similarly to bacterial pneumonia, including fever, cough, chest pain, dyspnea, and prolonged fatigue. In more severe cases, especially in immunocompromised patients, the infection can evolve into extrapulmonary forms, affecting the skin, bones, oral cavity, and joints (Eulálio et al., 2024; Galgiani et al., 2005).

Diagnosing coccidioidomycosis requires clinical evaluation and a history of contact with soil in endemic regions. Confirmation involves a combination of clinical history, laboratory tests (serologies, cultures, skin or histopathological biopsies), and imaging of the affected tissue or lesion (Galgiani et al., 2016).

Treatment varies depending on the severity and location of the infection, as well as the patient's immune status. According to the guidelines of the Infectious Diseases Society of America (IDSA), azole antifungals are the cornerstone of treatment (Galgiani et al., 2016). Fluconazole and itraconazole are generally considered first-line choices, especially in uncomplicated

pulmonary infections and in immunocompetent patients. In more severe or disseminated cases, or when there is intolerance or therapeutic failure with first-line azoles, second-line antifungals such as voriconazole, posaconazole, or isavuconazole may be used due to their broader spectrum of action (Méndez et al., 2017).

Oral manifestations of coccidioidomycosis are rarely reported in the literature but represent an important diagnostic challenge, as they often resemble malignant neoplasms, traumatic ulcers, or other deep fungal infections. In this context, it becomes necessary to gather and analyze the available scientific literature documenting oral lesions caused by coccidioidomycosis, with the aim of expanding knowledge about its clinical, diagnostic, and therapeutic aspects (Rodriguez & Konia, 2005).

Given this gap and the clinical relevance of the topic, this study aims to investigate and analyze, through a systematic review of the literature, cases of coccidioidomycosis with clinical manifestations in the oral cavity, with emphasis on the characterization of lesions, diagnostic methods used, and therapeutic approaches applied.

2. METHODOLOGY

This study is a systematic literature review that investigated evidence regarding signs, symptoms, diagnosis, and treatment of coccidioidomycosis in the oral cavity. The search strategy was developed based on the PICO method, which stands for: POPULATION (P): coccidioidomycosis; INTERVENTION (I): oral cavity; COMPARISON (C): there was no; OUTCOME (O): Identification of oral clinical manifestations of coccidioidomycosis.

2.1 Literature Search Strategy

The systematic literature search was conducted in January 2025 in the databases PubMed, Web of Science, and LILACS (Latin American and Caribbean Literature on Health Sciences). Three search strategies (A, B, and C) were established, one for each database, using keywords registered in Health Sciences Descriptors (DeCS) and Medical Subject Headings (MeSH) (Table 1).

2.2 Inclusion and Exclusion Criteria

Included studies were those published in Portuguese and English from 1964 to 2024, and case reports relating coccidioidomycosis to the oral cavity. Exclusion criteria included studies not directly related to the topic, duplicate articles, literature reviews, preclinical studies, and infections caused by other species of dimorphic fungi.

2.3 Data Analysis

Data were collected, including author, year, type of study, materials and methods used in the study, and results.

2.4 Database Search Strategy Output

The search yielded a total of 27 studies from the analyzed databases. Duplicates were removed, and titles and abstracts were reviewed, resulting in 11 studies. Of these, 5 did not meet the inclusion and exclusion criteria. Thus, 6 studies were selected for full-text reading.

To assess the methodological quality of the included studies, a risk of bias analysis was performed using the RoB 2 (Risk of Bias 2.0) tool, recommended by Cochrane for randomized clinical trials. Although the analyzed studies were

Table 1. Search keys, organized according to DeCS and MeSH descriptors and specific to each database

Database	Keywords
A) PubMed	("Coccidioidomycosis"[MeSH Terms] OR "Valley Fever" OR "Coccidioidomycosis" OR "Coccidioidomicosis") AND ("Mouth Diseases"[MeSH Terms] OR "Oral Manifestations" OR "Oral Cavity" OR "Mouth Lesions" OR "Oral Symptoms") AND ("Case Reports"[Publication Type] OR "Clinical Presentation" OR "Diagnosis")
B) Web of Science	("Coccidioidomycosis" OR "Valley Fever" OR "Coccidioidal infection") AND ("Mouth Diseases"[MeSH Terms] OR "Oral Manifestations" OR "Oral Cavity" OR "Mouth Lesions" OR "Oral Symptoms")
C) Lilacs	("Coccidioidomicose" OR "Coccidioidomycosis" OR "Valley Fever") AND ("Mouth" OR " Mouth Diseases " OR "Oral Cavity" OR "Oral Manifestastions")

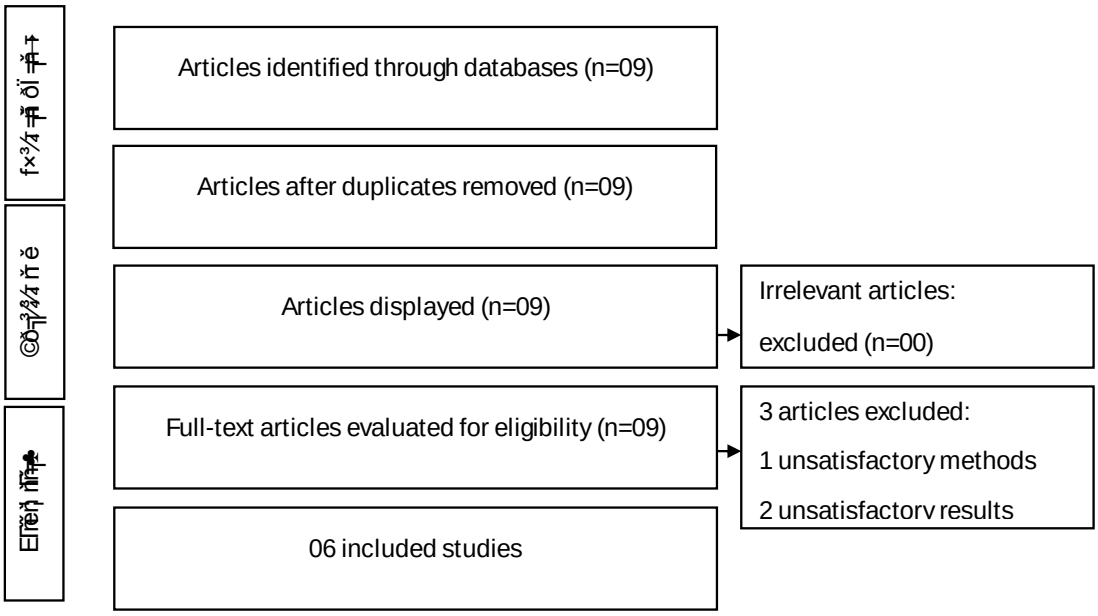

Fig. 1. Flowchart adapted from the PRISMA model, showing the steps of identification, screening, eligibility, and inclusion of the studies analyzed in this review

not randomized clinical trials but rather case reports, the RoB 2 structure was adapted to allow for a systematic and transparent evaluation of potential biases.

3. FINDING AND DISCUSSION

After applying the selection criteria, six studies were deemed eligible. The reviewed studies highlight the diversity of clinical manifestations of the infection, as well as the importance of histopathological, serological, and imaging examinations for accurate diagnostic clarification and appropriate therapeutic management. Table 2 presents a summary of the main case reports found in the literature regarding coccidioidomycosis, with emphasis on the diagnostic methods used, the clinical findings described, and the outcomes observed.

The table presents the main methods used in the diagnosis of coccidioidomycosis in case reports, including biopsy, serological, histopathological, and imaging exams. Additionally, relevant clinical findings and patient outcomes after treatment are highlighted.

Table 3 summarizes the risk of bias assessment for the included case reports, based on the domains proposed for methodological appraisal.

Based on the analysis of the six included studies, 33.3% (n=2) were classified as having a low risk of bias in the overall assessment, while 33.3% (n=2) raised some concerns, and the remaining 33.3% (n=2) were considered to have a high risk of bias. These results highlight the methodological heterogeneity among studies on coccidioidomycosis, underscoring the importance of caution when interpreting findings and extrapolating inferences from clinical outcomes.

Coccidioidomycosis, a fungal infection caused by dimorphic fungi, although more commonly associated with pulmonary infections, can, in rare cases, manifest in the oral cavity, resulting in various lesions such as ulcers, nodules, or plaques (Rodriguez & Konia, 2005; Nagler et al., 2014). These lesions may be painful or asymptomatic and are often mistaken for other oral pathologies, such as carcinomas, tuberculosis, or other fungal infections, complicating differential diagnosis (Gabriel & Mu, 2019). The most frequently affected areas in the mouth include the buccal mucosa, gums, lips, and tongue, which can significantly impact the patient's quality of life (Nagler et al., 2014; Kaur et al., 2023).

Diagnosis of oral coccidioidomycosis requires a multifactorial approach, including a detailed clinical examination of the oral cavity, assessment of lesion characteristics (such as ulceration, nodularity, or verrucous appearance), lymph node inspection, investigation of associated systemic signs,

Table 2. Diagnostic methods and main clinical findings of the reviewed studies

Author/Year	Type of study and country	Title	Materials and Methods	Results (Outcome and case)
Rodriguez, R. A.; Konia, T. 2005	Case report, United States.	*Coccidioidomycosis of the Tongue.*	Lingual biopsy, special staining serology, imaging examinations.	Ulcerated lesion on the tongue due to C. immitis; improvement with itraconazole.
Nagler, A. R. et al, 2014.	Case report, United States.	Verrucous Nodule on the Upper Lip The Diagnosis: Disseminated *Coccidioidomycosi.*	Histopathology, serology, clinical review	Labial nodule due to disseminated coccidioidomycosis; differential diagnosis discussed.
Mendez, L. A. et al, 2017	Case report, Mexico.	Ulcerated Lesion of the Tongue as Manifestation of Systemic Coccidioidomycosi.	Biopsy, histopathological examinations, chest X-ray.	Lingual lesion due to C. immitis with pulmonary involvement; itraconazole for another year.
Araújo, P.S.R, et al, 2018.	Case report, Brazil.	Coccidioido-mycosis: first cases reported in Pernambuco, Brazil.	Bronchoalveolar lavage, induced sputum, KOH; clinical and radiological examinations.	Three farmers with pneumonia due to Coccidioides spp.; clinical improvement with fluconazole.
Gabriel, A.; MU, A, 2019.	Case report, United States.	A 42-Year-Old Man With Lingual Nodules and a Headache.	Biopsies, PCR, culture, serology, lumbar puncture.	Disseminated coccidioidomycosis with meningitis and oral lesions; fluconazole 800 mg/day.
KAUR, H. et al, 2023	Case report, United States.	"It's Not Just Bacteria": A Cavitary Lung Lesion in a Patient Living in the Coachella Valley.	Fungal cultures, lung biopsy, bronchoscopy, chest tomography, serologies.	Pulmonary cavity coccidioidomycosis caused by C. posadasii; improvement with fluconazole after lobectomy.

Table 3. Risk of bias analysis of the reviewed studies

Study (Author/Year)	Domain 1 (Randomization)	Domain 2 (Deviations from Intended Interventions)	Domain 3 (Absent outcomes)	Domain 4 (Outcome measurement)	Domain 5 (Selection of results)	Global Judgment
Rodriguez & Konia, 2005	Not applicable	Low risk	Low risk	Low risk	Moderate risk	Moderate risk
Nagler et al., 2014	Not applicable	Low risk	Low risk	Low risk	Moderate risk	Moderate risk
Mendez et al., 2017	Not applicable	Moderate risk	Low risk	Low risk	High risk	High risk
Araújo et al., 2018	Not applicable	Low risk	Low risk	Low risk	Low risk	Low risk
Gabriel & MU, 2019	Not applicable	Low risk	Low risk	Moderate risk	High risk	High risk
Kaur et al., 2023	Not applicable	Low risk	Low risk	Low risk	Low risk	Low risk

epidemiological history, and laboratory tests. Biopsy of the oral lesions is essential for identifying fungal structures, while serological tests and cultures can confirm the presence of Coccidioides immitis and posadasii (Araújo et al., 2018; Lacaz et al., 2002). Molecular methods have also shown promise for faster and more accurate identification of the infection (Kaur et al., 2023).

Treatment of oral coccidioidomycosis varies depending on the severity and extent of dissemination. In mild cases, oral antifungals such as fluconazole or itraconazole are usually effective. In more severe or disseminated infections, amphotericin B is recommended (Wanke et al., 1996). The therapeutic regimen is typically prolonged, potentially lasting for months, to ensure complete fungal eradication and minimize the risk of recurrence (Rodriguez & Konia, 2005).

The prognosis of oral coccidioidomycosis depends on how quickly the diagnosis is made and the treatment's effectiveness. Early identification and proper management are crucial to avoid complications and prevent the spread of the infection (Araújo et al., 2018). Immunocompromised patients may face greater therapeutic challenges and have a more guarded prognosis. Prevention involves avoiding inhalation of spores, especially in endemic areas, which may include using protective masks in dusty environments and raising awareness of environmental risks such as contaminated soil (Macêdo, 2006).

The studies selected in this review highlight the clinical heterogeneity of oral manifestations, with a predominance of ulcerated and nodular lesions on the tongue, lips, and buccal mucosa. The time to definitive diagnosis varied among cases, possibly indicating both a lack of awareness about the disease and limited diagnostic resources, especially in non-endemic regions (Stevens, 1995; Chiller et al., 2003). From a diagnostic standpoint, the combination of detailed medical history, biopsy with histopathological staining, and serological testing was essential for identifying the infection. The advancement of molecular methods, such as PCR, is promising, as it enables rapid and sensitive detection of the etiological agent, supporting early initiation of treatment (Fisher et al., 2002; Wanke et al., 2000).

Prolonged antifungal treatment, particularly with fluconazole or itraconazole, was most frequently reported, with variable clinical responses. In more severe cases or immunosuppressed patients, such as those with meningeal coccidioidomycosis, continuous suppressive antifungal therapy was required, demonstrating the complexity of clinical management (Neves et al., 2019).

The average duration of antibiotic therapy varied between 7 to 14 days, primarily as empirical treatment before the fungal etiology was confirmed. Oral manifestations typically resolved within 2 to 6 weeks after the initiation of antifungal therapy. The most commonly used antifungal agents were fluconazole and amphotericin B, administered either orally or intravenously, with dosages ranging from 200 to 400 mg/day for fluconazole, depending on the severity of the case (Wanke et al., 2000; Neves et al., 2019).

Additionally, diabetes mellitus can worsen the periodontal condition associated with coccidioidomycosis. Diabetic patients exhibit compromised immune responses and increased susceptibility to fungal infections, including coccidioidomycosis. Diabetes mellitus significantly exacerbates periodontal disease, which may contribute to heightened vulnerability and worsening of other opportunistic infections, such as coccidioidomycosis (Neves et al., 2019). Chronic hyperglycemia promotes fungal growth, hinders infection control, and delays healing of oral lesions. Therefore, proper diabetes management is essential to improve antifungal treatment response and reduce periodontal complications in these patients (Chiller et al., 2003; Neves et al., 2019).

Finally, the findings of this review reinforce the need for greater clinical vigilance regarding atypical oral lesions, particularly in patients from endemic areas or those with a history of travel to such regions.

4. CONCLUSION

Although more frequently associated with pulmonary infections, coccidioidomycosis can also manifest in the oral cavity, representing a significant diagnostic challenge. Oral lesions caused by this fungal infection may be mistaken for more common pathologies, potentially delaying accurate diagnosis and treatment.

The analysis of the studies revealed a diversity of oral manifestations of coccidioidomycosis, with a

predominance of ulcerated and nodular lesions, and the necessity of a comprehensive diagnostic approach, including history-taking, biopsy, histopathological staining, and serological testing. Advances in molecular techniques such as PCR have proven promising for quicker and more precise diagnosis.

Despite these diagnostic advances, the findings underscore the need for increased vigilance regarding atypical oral lesions, especially in patients from endemic areas. The limited literature on the subject restricts current knowledge, highlighting the urgency of further studies to deepen understanding and improve the clinical management of oral coccidioidomycosis. Given the potential severity of these manifestations, early recognition is essential to reduce morbidity and prevent delayed diagnoses.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of this manuscript.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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