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Progressive disseminated histoplasmosis: a systematic review on the performance of non-culture-based diagnostic tests

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ABSTRACT

The diagnosis of progressive disseminated histoplasmosis is often a challenge to clinicians, especially due to the low sensitivity and long turnaround time of the classic diagnostic methods. In recent years, studies involving a variety of non-culture-based diagnostic tests have been published in the literature. We performed a systematic review by selecting studies evaluating non-culture-based diagnostic methods for progressive disseminated histoplasmosis. We searched for articles evaluating detection of antibody, antigens, as well as DNA-based diagnostic methods. A comprehensive PUBMED, Web of Science, and Cochrane Library search was performed between the years 1956 and 2016. Case reports, review articles, non-human models and series involving less than 10 patients were excluded. We found 278 articles and after initial review 18 articles were included: (12) involved antigen detection methods, (4) molecular methods, and (2) antibody detection methods. Here we demonstrate that the pursuit of new technologies is ultimately required for the early and accurate diagnosis of disseminated histoplasmosis. In particular, urinary antigen detection was the most accurate tool when compared with other diagnostic techniques.

Introduction

Histoplasmosis is a fungal disease caused by the thermally dimorphic fungus *Histoplasma capsulatum*.[1] Humans develop histoplasmosis by inhaling *H. capsulatum* spores from the environment, usually in the context of acid and moist nitrogen-rich soils containing excrement from poultry, bats, or birds. Even though histoplasmosis may be a self-limiting disease, disseminated infection may occur particularly in the immunocompromised host. Diagnosis of

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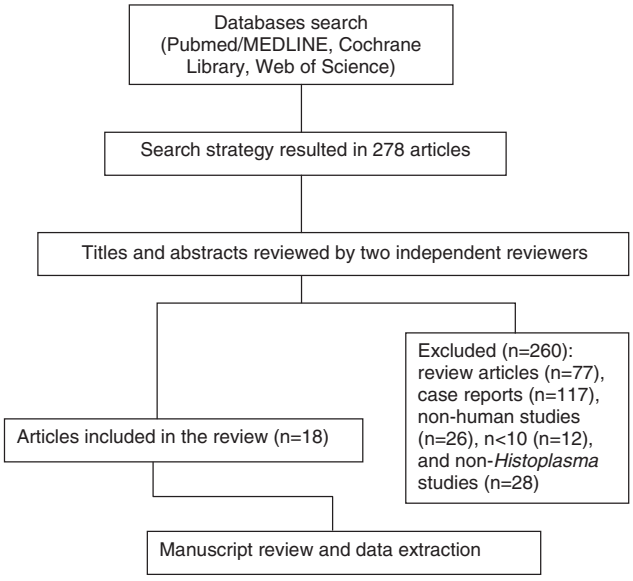

Fig. 1 – Finding evidence for comparing diagnostic studies for progressive disseminated histoplasmosis.

progressive disseminated histoplasmosis (PDH) has historically been made by combination of fungal culture and histopathology. However, these may require invasive medical procedures to obtain tissues, and cultures may take up to six weeks to reveal fungal growth.[2,3] Moreover, in recent years a variety of non-culture-based diagnostic methods have been developed to diagnose PDH aiming for an early and more sensitive diagnosis.[2] In this study we performed a systematic review of the available data on these novel technologies, summarizing their performance.

Methods

A computerized search without language restrictions was conducted in Pubmed/MEDLINE, Web of Science, and Cochrane Library, for articles published up to June 2016 combining the following terms ((DISSEMINATED HISTOPLASMOSIS) AND (ANTIBODY OR MOLECULAR OR "POLYMERASE CHAIN REACTION"[MH] OR ANTIGEN OR IMMUNODIFFUSION OR "COMPLEMENT FIXATION TESTS/METHODS"[MAJR] OR "LATEX FIXATION TESTS"[MH]) AND (DIAGNOSIS)). Only original articles dealing with non-culture-based diagnostic tests for PDH were studied. References from selected articles were also screened for review. Publications describing case reports, review articles, case series involving <10 patients, and histoplasmosis in non-humans were not included in the review (Fig. 1).

This systematic review aimed to summarize the performance of non-culture-based diagnostic methods for the detection of *H. capsulatum*, focusing on three distinct test groups: (i) antibody detection tests, including immunodiffusion, complement fixation and latex agglutination; (ii) antigen detection tests, including enzyme immunoassays (EIAs); and (iii) molecular methods. A total of eighteen studies were included in the review (Table 1).

Results

Serological tests: immunodiffusion, complement fixation, and latex agglutination test

Currently, two main serological tests are used for the detection of *H. capsulatum* antibodies: immunodiffusion and complement fixation.[2] Although these methods have the advantage of being non-invasive, but enclose several limitations, including (i) marked intra-patients variation in results; (ii) long time for positive results (up to six weeks are required after exposure for antibody production); (iii) potential cross-reactivity with antibodies produced by other fungi such as *Blastomyces dermatitidis*.[1–5]

The immunodiffusion method is widely used in clinical practice and it is based on the precipitation of the anti-M and anti-H antibodies. This method is more specific than the complement fixation[2,3] and presents the following strengths: (i) it is based on simple and reliable methodology; (ii) it has a low cost; (iii) specificity is close to 70–100%.[2,4] Test sensitivity is unacceptably low in the immunocompromised population, particularly in individuals with AIDS.

The complement fixation method is more sensitive than the immunodiffusion test and presents variable test sensitivity, depending on the antigen phase, ranging from 72.8% in mycelial to 94.3% in yeast phase. The specificity varies between 70% and 80%; cross-reactions may occur with blastomycosis, candidosis, and paracoccidioidomycosis. Antibody titers of 1:8 and 1:16 are frequently seen in individuals with past infections or living in endemic regions and these are considered weakly positive results. Test sensitivity is reduced in the presence of hemolytic and lipemic samples.[2,3]

H. capsulatum may also be detected by the means of latex agglutination test. The test is based on latex connection with histoplasmin for the detection of the antibody anti-*Histoplasma*. Studies conducted in mid to late 1970s demonstrated that the latex test was not well-suited for diagnosis of PDH due to low sensitivity (64%) and cross-reactivity with tuberculosis, in a comparison with the gel immunodiffusion.[5] Main test advantages are low cost and better specificity, as compared to the complement fixation test, despite of false-positives observed with *M. tuberculosis* infection.[2,5]

Immunological tests: enzyme immunoassays (EIAs)

EIAs are based on the detection of the *H. capsulatum* polysaccharide antigen (HPA) on various biological materials such as urine, serum, and bronchoalveolar washing fluid. Different EIAs have been used as surrogate of PDH by reference laboratories.[6–9] Two commercial EIA tests to detect *H. capsulatum* are currently available in the United States of America: *MVista* in Indianapolis, IN, and *IMMY* in Norman, OK. Both laboratories provide similar and robust EIA tests with minor differences in terms of test performance. However, there has been a strong debate in the literature on difference between them, which seems to be influenced by a marked commercial bias.[8,10–13]

In 1989, Wheat and other researchers from Miravista Diagnostics (Indianapolis, IN) developed a rapid and promising