Clinical Infectious Diseases

BRIEF REPORT

Clinical Testing Guidance for Coccidioidomycosis, Histoplasmosis, and Blastomycosis in Patients With Community-Acquired Pneumonia for Primary and Urgent Care Providers

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Coccidioidomycosis, histoplasmosis, and blastomycosis are underrecognized and frequently misdiagnosed fungal infections that can clinically resemble bacterial and viral community-acquired pneumonia. This guidance is intended to help outpatient clinicians test for these fungal diseases in patients with community-acquired pneumonia to reduce misdiagnoses, unnecessary antibacterial use, and poor outcomes.

Keywords. coccidioidomycosis; histoplasmosis; blastomycosis; community-acquired pneumonia; diagnostic algorithms.

Coccidioidomycosis, histoplasmosis, and blastomycosis are caused by environmental fungi with geographical niches in the United States and globally [1, 2]. These infections often clinically resemble community-acquired pneumonia (CAP) caused by bacterial or viral pathogens [3]. Patients with these fungal diseases frequently seek initial care in primary care, emergency department, and urgent care settings; are prescribed empiric antibiotics, which are ineffective against fungal infections; and experience long delays in diagnosis, leading to prolonged symptoms and poor outcomes [4].

Clinicians infrequently test for coccidioidomycosis, histoplasmosis, and blastomycosis, even in areas of the United States where these infections are most common [5]. Guidelines for CAP diagnosis do not explicitly recommend testing for fungal pathogens, and existing guidance for diagnosing fungal pneumonia is aimed at specialists in acute care hospital settings rather than outpatient healthcare providers [6]. Diagnosing coccidioidomycosis, histoplasmosis, and blastomycosis is challenging for multiple reasons, including the availability of multiple test types (eg, antibody, antigen, culture, histopathology); lack of standardization in serologic test methodology among laboratories; the potentially invasive nature, low sensitivity, or long turnaround time; and challenges with test interpretation [7].

METHODS

A literature review was completed to assess the sensitivity and specificity of diagnostic tests for coccidioidomycosis, histoplasmosis, and blastomycosis. The following terms were searched using Google Scholar and PubMed: "Coccidioides," "Blastomyces," "Histoplasma," and "antigen," "antibody," "culture," "histopathology," "cytology," "β-D-glucan," "polymerase chain reaction (PCR)," and "lateral flow assays (LFA)". (Supplementary Table 1). Initial algorithms were developed based on these data and individual feedback from 6 clinicians during routine partner meetings regarding availability and feasibility of different test methodologies.

Twelve infectious diseases physicians who specialize in fungal diseases from the Mycoses Study Group Education and Research Consortium (a group of experts in medical mycology who focus on advancing understanding and treatment of invasive fungal diseases (https://msgerc.org/page-18120)) or the Coccidioidomycosis Study Group and three primary care or emergency medicine physicians provided individual feedback during meetings and text review of the algorithms during January–July 2022.

RESULTS

Testing Guidance for Outpatients With Community-Acquired Pneumonia

For all 3 diseases, testing is suggested in patients with CAP who have (1) lived in or visited known endemic areas and (2) symptoms that did not improve following empiric antibiotics. However, testing can be considered at the initial visit based on features that increase the pretest likelihood of these diseases. These considerations are intended to be simple and feasible ways to balance test accuracy.

Coccidioidomycosis

Consider coccidioidomycosis testing (Figure 1*A*) at initial presentation of CAP (or erythema nodosum in the setting of recent respiratory symptoms) in patients who have:

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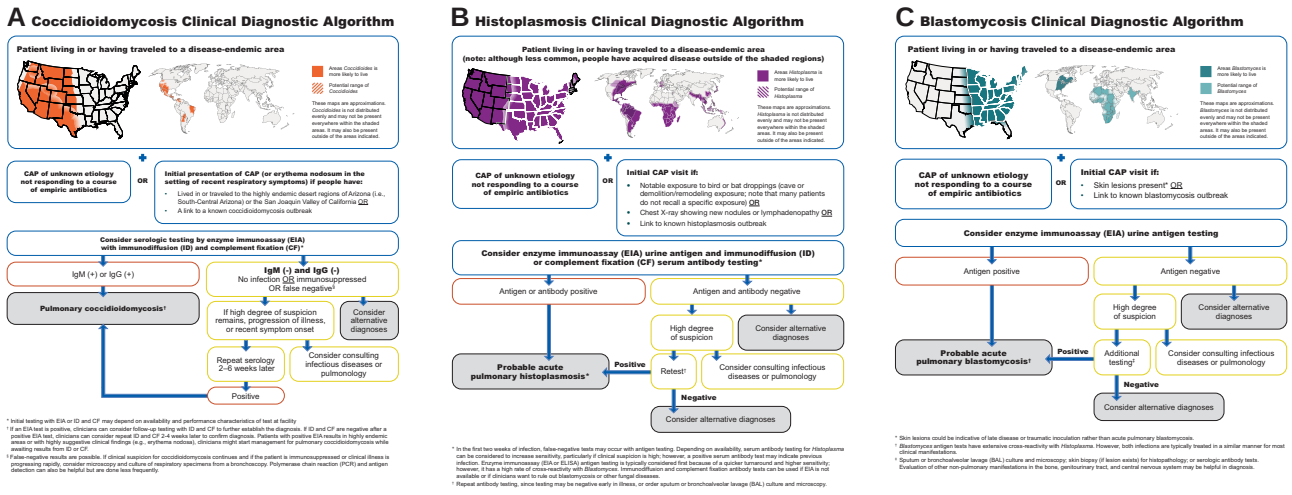

Figure 1. *A*, Coccidioidomycosis clinical diagnostic algorithm. *Initial testing with enzyme immunoassay (EIA) or immunodiffusion (ID) and complement fixation (CF) may depend on availability and performance characteristics of test at facility. †If an EIA test is positive, clinicians can consider follow-up testing with ID and CF to further establish the diagnosis. If ID and CF are negative after a positive EIA test, clinicians can consider repeat ID and CF 2–4 wks later to confirm diagnosis. Patients with positive EIA results in highly endemic areas or with highly suggestive clinical findings (eg, erythema nodosa), clinicians might start management for pulmonary coccidioidomycosis while awaiting results from ID or CF. §False-negative results are possible. If clinical suspicion for coccidioidomycosis continues and if the patient is immunosuppressed or clinical illness is progressing rapidly, consider microscopy and culture of respiratory specimens from a bronchoscopy. Polymerase chain reaction (PCR) and antigen detection can also be helpful but are done less frequently. *B*, Histoplasmosis clinical diagnostic algorithm. *In the first 2 weeks of infection, false-negative tests may occur with antigen testing. Depending on availability, serum antibody testing for *Histoplasma* can be considered to increase sensitivity, particularly if clinical suspicion is high; however, a positive serum antibody test may indicate previous infection. Enzyme immunoassay (EIA or enzyme-linked immunosorbent assay) antigen testing is typically considered first because of a quicker turnaround and higher sensitivity; however, it has a high rate of cross-reactivity with *Blastomyces*. Immunodiffusion and complement fixation antibody tests can be used if EIA is not available or if clinicians want to rule out blastomycosis or other fungal diseases. †Repeat antibody testing because testing may be negative early in illness, or order sputum or bronchoalveolar lavage (BAL) culture and microscopy. *C*, Blastomycosis clinical diagnostic algorithm. *Skin lesions could be indicative of late disease or traumatic inoculation rather than acute pulmonary blastomycosis. †*Blastomyces* antigen tests have extensive cross-reactivity with *Histoplasma*. However, both infections are typically treated in a similar manner for most clinical manifestations. ‡ Sputum or BAL culture and microscopy; skin biopsy (if lesion exists) for histopathology; or serologic antibody tests. Evaluation of other nonpulmonary manifestations in the bone, genitourinary tract, and central nervous system may be helpful in diagnosis. Abbreviation: CAP, community-acquired pneumonia.

- Lived in or traveled to the highly endemic desert regions of Arizona (ie, south-central Arizona) or the San Joaquin Valley of California OR
- An epidemiologic link to a coccidioidomycosis outbreak.

Also consider coccidioidomycosis testing in all patients with CAP who:

- Have symptoms that did not improve following empiric antibiotics AND
- Live in or have traveled to known endemic areas (Arizona, California, Nevada, New Mexico, Texas, Utah, Washington State, and Central and South America) [2,8].

Initial test selection includes an enzyme immunoassay (EIA) antibody test with immunodiffusion (ID) and complement fixation (CF) testing are suggested. EIAs often have faster turnaround time, usually a lower cost, and generally higher sensitivity than ID and CF, with some variability by test manufacturer and laboratory. ID and CF antibody tests exhibit greater specificity than EIAs, although they are typically available only at reference laboratories and high-volume academic clinical centers.

Guidance Based on Initial *Coccidioides* Serologic Results

- If the EIA is positive, consider follow-up testing with ID or CF to rule out a false positive because these tests are more specific than EIA. For patients in highly endemic areas or with highly suggestive clinical findings (eg, erythema nodosum), clinicians might start treatment for pulmonary coccidioidomycosis based on positive EIA while awaiting ID and CF results. CF testing also provides a quantitative value that is useful prognostically during longitudinal care.
- If the EIA is negative, consider alternative diagnoses. If a high degree of suspicion remains, progression of illness occurs, or if symptom onset was recent, consider:
  - Obtaining infectious diseases or pulmonology consultation.
  - Repeating serology 2–6 weeks after initial EIA. Antibody testing can be negative early in the illness course.
  - Obtaining sputum or bronchoalveolar lavage (BAL) culture and microscopy, although these have low sensitivity.

- Performing antigen testing; however, this has primarily been studied in immunocompromised patients with moderately severe or disseminated disease, including meningitis [7]. It can be considered as an adjunctive test when there is a high suspicion for coccidioidomycosis in immunocompromised patients who cannot mount an antibody response.
- Performing polymerase chain reaction (PCR) and lateral flow assay testing. PCR can have a low sensitivity and requires an invasive sample, whereas lateral flow assay has a lower sensitivity and specificity than other serologic methods [9].

Histoplasmosis

Consider histoplasmosis testing (Figure 1*B*) in all patients with CAP who:

- Have symptoms that did not improve following empiric antibiotics AND
- Live in or have traveled to endemic areas (eg, Central and Eastern United States and Central Canada, predominantly in areas around the Ohio and Mississippi River Valleys and the Great Lakes region, Puerto Rico, Latin America, Central Africa, and Southeast Asia) [2,8]. *Histoplasma* distribution is likely nationwide; living in or travel to the Western United States may warrant *Histoplasma* testing.

Testing can also be considered on initial presentation of CAP in patients who have:

- Extensive exposure to bird or bat droppings (eg, entered a cave, participated in the demolition or remediation of building with droppings) [10] OR
- A chest x-ray demonstrating new nodules or lymphadenopathy consistent with histoplasmosis [11] OR
- An epidemiologic link to a histoplasmosis outbreak [10].

An EIA urine antigen test is suggested. Consider obtaining a concurrent ID or CF antibody test to increase sensitivity; false positives from previous infection can occur, but ID antibody positivity typically wanes within a few years after infection [12]. Ordering *Histoplasma* serum and urine antigen tests together may increase sensitivity but is associated with increased cost versus ordering just 1 of these tests [12].

Guidance based on *Histoplasma* Antigen Results

- A positive antigen test almost always indicates active infection, although cross-reactivity with other fungal diseases, particularly blastomycosis, is possible. Cross-reactivity is unlikely to change therapy; clinicians should avoid ordering a *Blastomyces* antigen test after ordering a *Histoplasma* antigen test. Antigen tests can be negative early in disease.
- If the initial test (antigen, ID, or CF) is negative, consider alternative diagnoses. If a high degree of suspicion remains despite negative initial testing, consider:
  - Obtaining infectious diseases or pulmonology consultation.
  - Ordering (or repeating) ID and CF antibody testing because tests can be negative early in the illness course.
  - Obtaining sputum or BAL culture and microscopy, although these have low sensitivity [13].
  - PCR testing is not widely available; however, it can be performed on serum, tissue, or BAL fluid.

Rheumatologic symptoms (eg, myalgias, arthralgias) and dermatologic findings (eg, erythema nodosum, erythema multiforme) can present in pulmonary histoplasmosis and may increase clinical suspicion [11]. Pulmonary histoplasmosis, particularly in immunocompromised persons, may disseminate and cause hepatosplenomegaly; lymphadenopathy; and skin ulcers, nodules, or molluscum-like papules. These findings may also prompt increased clinical suspicion [11].

Blastomycosis

Consider blastomycosis testing (Figure 1*C*) in all patients with CAP who:

- Have symptoms that did not improve following empiric antibiotics AND
- Live in or have traveled to endemic areas (Midwestern, South Central, and Southeastern United States, particularly around the Ohio and Mississippi River Valleys, the Great Lakes, and the Saint Lawrence River. Northern Wisconsin and Minnesota may be hyperendemic.) [2,8].

Testing can also be considered on initial presentation of CAP in patients who have:

- Abnormal skin lesions consistent with blastomycosis [14] OR
- An epidemiologic link to a blastomycosis outbreak.

An EIA urine antigen test is suggested first because of its high sensitivity and quick turnaround time.

Guidance Based on *Blastomyces* Antigen Results

- A positive antigen test almost always indicates active infection, although cross-reactivity with other fungal diseases, particularly histoplasmosis, is possible. Cross-reactivity is unlikely to change therapy; clinicians should avoid ordering a *Histoplasma* antigen test after ordering a *Blastomyces* antigen test.
- If the EIA urine antigen test is negative, consider alternative diagnoses. If a high degree of suspicion remains despite negative initial testing, consider:

- Obtaining infectious diseases or pulmonology consultation.
- Obtaining sputum, BAL, or tissue culture and microscopy.
- Performing a skin biopsy (if a lesion is present) for microscopy and culture.
- Ordering serologic antibody tests; however, antibody tests are reported to have low sensitivity but may be useful when an antigen test is negative or when trying to differentiate blastomycosis from histoplasmosis.
- Evaluating for potential disease manifestations in bone, genitourinary tract, and central nervous system.

DISCUSSION

These diagnostic algorithms were developed based on available evidence and expert opinion and are intended to help clinicians in outpatient settings consider when and how to test for coccidioidomycosis, histoplasmosis, and blastomycosis in patients with CAP. These algorithms might help increase testing and reduce misdiagnoses, unnecessary antibacterial use, and poor outcomes. This guidance can be adapted based on local laboratory capacity. This guidance addresses diagnostic approaches to coccidioidomycosis, histoplasmosis, and blastomycosis in CAP but does not address other clinical presentations (eg, fatigue alone, focal infection, disseminated disease). For treatment considerations, clinicians can refer to the IDSA's treatment guidelines (Coccidioidomycosis Infectious Disease Society of America (IDSA) treatment guidelines: 2016 Infectious Diseases Society of America (IDSA) Clinical Practice Guideline for the Treatment of Coccidioidomycosis [oup.com]; histoplasmosis IDSA treatment guidelines: Clinical Practice Guidelines for the Management of Patients with Histoplasmosis: 2007 Update by the Infectious Diseases Society of America [oup.com]; blastomycosis IDSA treatment guidelines: Clinical Practice Guidelines for the Management of Blastomycosis: 2008 Update by the Infectious Diseases Society of America [oup.com]).

Approaches to diagnosing coccidioidomycosis, histoplasmosis, and blastomycosis could be further refined by (1) assessing the uptake and impact of this guidance, (2) incorporating new diagnostic methods into these algorithms as they become available, (3) quantifying the proportion and geographic distribution of CAP and other lower respiratory infections attributable to coccidioidomycosis, histoplasmosis, and blastomycosis, (4) further assessing test sensitivity and specificity, including inter-laboratory and inter-manufacturer assessments, and (5) considering developing guidelines for diagnosing CAP of various etiologies that does not respond to initial antibiotics.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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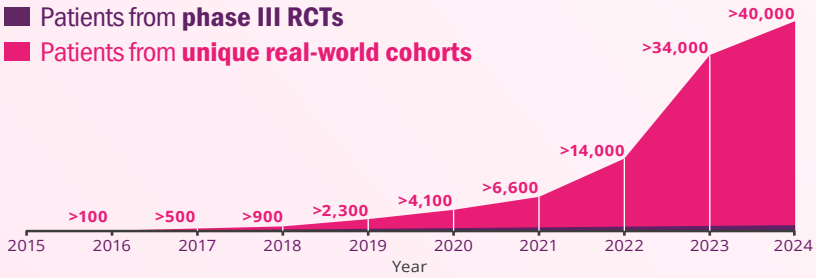

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ABBREVIATIONS

3TC, lamivudine; **CD4,** cluster of differentiation 4; **DTG,** dolutegravir; **FDA,** United States Food and Drug Administration; **FTC,** emtricitabine; **HIV,** human immunodeficiency virus; **ITT-E,** intention-to-treat exposed; **NRTI,** nucleoside/nucleotide reverse transcriptase inhibitor; **RCT,** randomised controlled trial; **RNA,** ribonucleic acid; **TAF,** tenofovir alafenamide fumarate; **TDF,** tenofovir disoproxil fumarate; **XTC,** emtricitabine.

FOOTNOTES

*Data extracted from a systematic literature review of DTG+3TC real-world evidence. Overlap between cohorts cannot be fully excluded.

**The reported rate reflects the sum-total of resistance cases calculated from GEMINI I and II (n=1/716, through 144 weeks), STAT (n=0/131, through 52 weeks), and D2ARLING (n=0/106, through 24 weeks).[5–7]

†GEMINI I and II are two identical 148-week, phase III, randomised, double-blind, multicentre, parallel-group, non-inferiority, controlled clinical trials testing the efficacy of DTG/3TC in treatment-naïve patients. Participants with screening HIV-1 RNA ≤500,000 copies/mL were randomised 1:1 to once-daily DTG/3TC (n=716, pooled) or DTG + TDF/FTC (n=717, pooled). The primary endpoint of each GEMINI study was the proportion of participants with plasma HIV-1 RNA <50 copies/mL at Week 48 (ITT-E population, snapshot algorithm).[13]

‡STAT is a phase IIIb, open-label, 48-week, single-arm pilot study evaluating the feasibility, efficacy, and safety of DTG/3TC in 131 newly diagnosed HIV-1 infected adults as a first line regimen. The primary endpoint was the proportion of participants with plasma HIV-1 RNA <50 copies/mL at Week 24.[6]

§D2ARLING is a randomised, open-label, phase IV study designed to assess the efficacy and safety of DTG/3TC in treatment-naïve people with HIV with no available baseline HIV-1 resistance testing. Participants were randomised in a 1:1 ratio to receive DTG/3TC (n=106) or DTG + TDF/XTC (n=108). The primary endpoint was the proportion of participants with plasma HIV-1 RNA <50 copies/mL at Week 48.[7] Results at week 24 of the study.

||The reported rate reflects the sum-total of resistance cases calculated from TANGO (n=0/369, through 196 weeks) and SALSA (n=0/246, through 48 weeks).[8,9]

¶TANGO is a randomised, open-label, trial testing the efficacy of DOVATO in virologically suppressed patients. Participants were randomised in a 1:1 ratio to receive DOVATO (n=369) or continue with TAF-containing regimens (n=372) for up to 200 weeks. At Week 148, 298 of those on TAF-based regimens switched to DOVATO. The primary efficacy endpoint was the proportion of subjects with plasma HIV-1 RNA ≥50 copies/mL (virologic non-response) as per the FDA Snapshot category at Week 48 (adjusted for randomisation stratification factor).[8,13]

#SALSA is a phase III, randomised, open-label, non-inferiority clinical trial evaluating the efficacy and safety of switching to DTG/3TC compared with continuing current antiretroviral regimens in virologically suppressed adults with HIV. Eligible participants were randomised 1:1 to switch to once-daily DTG/3TC (n=246) or continue current antiretroviral regimens (n=247). The primary endpoint was the proportion of subjects with plasma HIV-1 RNA ≥50 copies/mL at Week 48 (ITT-E population, snapshot algorithm).[9]

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