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专论与综述

球孢子菌和组织胞浆菌感染的实验室诊断研究进展

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摘　要：球孢子菌属(*Coccidioides*)和组织胞浆菌属(*Histoplasma*)致病性强，其孢子经空气播散引发感染，属于潜在的重要真菌生物战剂。尽管这 2 个属的真菌多在美洲等地区被检出，但其在全球的流行范围正在不断扩大。这 2 种真菌引发的感染在早期阶段的症状包括咳嗽、胸痛、呼吸困难和发热等，特异性不高，与细菌或病毒感染引起的社区获得性肺炎、结核等症状相似，因此，对这 2 种真菌感染的快速灵敏诊断具有重要意义和挑战性。本文对这 2 种高致病性真菌感染的实验室诊断方法进行了综述，重点描述了目前实验室诊断方法的特点和局限性。
关键词：球孢子菌属；球孢子菌病；组织胞浆菌属；组织胞浆菌病；实验室诊断

Advances in laboratory diagnosis of *Coccidioides* and *Histoplasma* infections

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Abstract: *Coccidioides* and *Histoplasma* are highly pathogenic fungi that cause infections through airborne dissemination of spores and are potential candidates for fungal biological warfare agents. Although the two genera of fungi are mainly detected in America, their global prevalence is constantly expanding. The early-stage symptoms of infections induced by them

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include cough, chest pain, dyspnea, and fever, which have no specific clinical manifestations and are similar to those of community-acquired pneumonia, tuberculosis, and other diseases caused by bacterial or viral infections. Therefore, the rapid and sensitive diagnosis of infection by the two genera of fungi is of great importance and challenging. This paper reviews the laboratory diagnostic methods of *Coccidioides* and *Histoplasma* infections and particularly describes the advantages and limitations of the current laboratory diagnostic methods.
Keywords: *Coccidioides*; coccidioidomycosis; *Histoplasma*; histoplasmosis; laboratory diagnosis

球孢子菌属(*Coccidioides*)和组织胞浆菌属(*Histoplasma*)均为高致病性双相真菌，危害程度较高，被视为潜在的生物战剂。它们可通过空气传播，感染人体后可引起球孢子菌病和组织胞浆菌病[1]，症状轻重不一，严重时可导致肺外播散性疾病[2-3]。这 2 种真菌主要在美洲地区流行[4]，近年来在非流行区的病例数量也呈上升趋势，国内时有本土病例报道[5-6]，表明这 2 种病原菌的分布范围可能远超预期。

1 球孢子菌病和组织胞浆菌病的实验室诊断

球孢子菌病和组织胞浆菌病早期均无特异性临床表现，易误诊为结核病、社区获得性肺炎等疾病[7]，误诊和延迟诊断会导致治疗不当和治疗延迟[8]，部分患者直到死亡才明确诊断为球孢子菌病或组织胞浆菌病[9-10]。球孢子菌病和组织胞浆菌病的死亡率很高，快速、准确的诊断方法对于降低患者的病死率和改善预后效果有着非常重要的意义。实验室目前常用的诊断方法主要有培养法、镜检法、免疫学检测和分子诊断等。本文分析了球孢子菌病和组织胞浆菌病不同诊断方法之间的优势和局限性(表 1)，并重点介绍了免疫学检测方法和分子诊断技术在这 2 种疾病检验诊断中的应用以及最新研究进展。

1.1 培养法和镜检法

培养法和镜检法是诊断球孢子菌病和组织胞浆菌病的金标准。球孢子菌和组织胞浆菌的培养要求并不高，普通培养基 28−30 ℃培养 2−3 周即可见丝状菌落生长，显微镜下可观察到明显的关节孢子[4,11]。通过钙荧光白处理或使用六胺银、过碘酸-希夫等染料对病理组织切片等临床样本进行染色后，可在显微镜下清晰地观察到直径为 20−70 μm、双层膜结构(内部含有大量 2−5 μm 分生孢子)的球孢子菌以及特征为小而圆的窄芽形态的组织胞浆菌[1]。痰液、血液、脑脊液、胸水等临床标本均可用于培养，但总体敏感性低于 50%[12-13]，在我国球孢子菌和组织胞浆菌感染病例的诊断中，70%以上的病例通过镜检法检出[5-6]。

1.2 免疫学检测

免疫学检测凭借其高灵敏度和精确性，已广泛应用于球孢子菌病和组织胞浆菌病高发地区的临床诊断中，克服了传统培养法和镜检法在诊断上可能存在的低灵敏度和易误诊等问题。目前最常用的免疫学检测包括酶联免疫法(enzyme immunoassays method, EIA)、免疫扩散(immunodiffusion, ID)、补体结合(complement fixation, CF)、侧向层析测定(lateral flow assay, LFA)和抗原检测[11,14]等。然而，免疫学检测在球孢子菌病和组织胞浆菌病流行地区诊断方面的应用存在明显的差异，这些差异通常由病原体的生物学特性、流行病学特点及地区资源等因素决定，本文详细介绍了免疫学检测在这 2 种真菌感染诊断中的应用情况，并简要概述了其优势和局限性(表 2)。

表 1 球孢子菌病和组织胞浆菌病的实验室诊断方法优势及局限性

Table 1 Advantages and limitations of laboratory diagnostic methods for coccidioidomycosis and histoplasmosis

实验室诊断方法 Laboratory diagnostics methods	球孢子菌病和组织胞浆菌病 Coccidioidomycosis and histoplasmosis	
	优势 Advantage	局限性 Limitation
培养 Culture	金标准，培养出球孢子菌属、组织胞浆菌属即可确诊 Gold-standard, culturing the presence of *Coccidioides* spp. and *Histoplasma* spp. can confirm the diagnostics	耗时长，敏感性低，需要生物安全 III 级实验室 Time-consuming, low sensitivity, biosafety level III needed
镜检 Microscopy	金标准，操作简单，无需复杂的设备，成本低 Gold-standard, simple operation, no complex equipment, low cost	敏感性低，易误诊，对临床医生的技术水平要求较高 Low sensitivity, easily misdiagnosed, require high technical level of clinicians
免疫学检测 Immunological detection	敏感性和特异性高于培养法和镜检法，操作简便，检测速度快 Sensitivity and specificity are higher than culture and microscopy, simple operation, fast detection speed	假阳性率高，成本高，感染早期可能检测不到抗体，不适合疾病的非流行或相对落后的地区 High false positive rate, high cost, antibodies may not be detected in the early stage of infection, not suitable for areas where diseases are not prevalent or relatively backward
分子诊断 Molecular diagnostics	高敏感性和特异性，快速，高通量，定性或定量检测 High sensitivity and specificity, fast, high throughput, qualitative or quantitative detection	需要专业的设备和熟练的技术人员，成本高，可能出现假阴性和假阳性结果，标准化程度低 Professional equipment and skilled technicians are required, high cost, false negative and false positive results may occur, low degree of standardization

1.2.1 球孢子菌病的抗体检测

抗体检测是球孢子菌病最主要的检测方法，其敏感性和特异性普遍高于培养法和镜检法，但有时需要多种抗体检测方法结合才能得出准确的检测结果。

EIA 是检测球孢子菌属免疫球蛋白 M 和 G (IgM 和 IgG)抗体最便宜也是最敏感的方法，几个小时内即可获得结果。根据 Kassis 等[15]的研究，EIA 检测 IgM 的敏感性为 36.2%–61.2%，特异性为 95.3%–97.7%；检测 IgG 的敏感性为 80.9%–87.4%，特异性为 90.0%–93.2%，在 EIA 抗体检测中增加抗原检测能进一步提高检测的敏感性。

ID 检测抗体的灵敏度为 84.2%，诊断的准确率为 93.6%，当增加抗原检测后，敏感性会提高到 93.0%，诊断的准确率会提升至 95.4%，如果未进行抗原检测，可能会导致漏诊[16]。

CF 可定量检测 IgG 抗体，McHardy 等[17]分析了球孢子菌病患者接受抗真菌治疗期间的血清动力学，CF 滴度与疾病的严重程度存在强相关性。Bryan 等[18]的研究表明，CF 和 ID 的检测结果具有高度一致性。因此，应对 EIA 筛查为阳性结果的人群进行 ID 和 CF 检测，在提高检测结果可信度的同时，也可以定量监测患者病情程度，为临床医生用药提供参考。

LFA 操作简单、快速、对设备的要求低，可用于即时检测。Donovan 等[19]开发的 LFA 试纸可在 1 h 内完成检测，但相较于 EIA，LFA 在早期球孢子菌病患者中的敏感度仅为 31%，特异度为 92%，需进一步改进。Viale 等[20]评

表 2 免疫学检测在球孢子菌病和组织胞浆菌病诊断中的优势和局限性

Table 2 Advantages and limitations of immunological tests in the diagnosis of coccidioidomycosis and histoplasmosis

免疫学检测 Immunological detection	球孢子菌病 Coccidioidomycosis		组织胞浆菌病 Histoplasmosis	
	优势 Advantage	局限性 Limitation	优势 Advantage	局限性 Limitation
抗原检测 Antigen detection	在疾病的早期阶段或免疫缺陷患者中可作为辅助诊断 In the early stage of the disease or patients with immunodeficiency, it can be used as an auxiliary diagnosis	敏感性和特异性显著低于抗体检测，存在交叉反应的可能 Sensitivity and specificity are significantly lower than antibody detection, and there is the possibility of cross reaction	尿液样本的敏感性和特异性高，尤其是在播散性组织胞浆菌病的患者中 Urine samples have high sensitivity and specificity, especially in patients with disseminated histoplasmosis	易与其他真菌发生交叉反应 Easy to cross-react with other fungi
抗体检测 Antibody detection	高敏感性和特异性，EIA 可用于疾病的大规模筛查；ID 可用于疾病的确诊；CF 可用于疾病的分期、预后和评价治疗的效果；LFA 可快速得到诊断结果 High sensitivity and specificity, EIA can be used for large-scale screening of diseases; ID can be used to confirm the diagnostics of disease; CF can be used for disease staging, prognosis and evaluation of treatment effect; LFA can quickly get the diagnostics result	仅使用一种抗体检测方法易误诊或漏诊，EIA 假阳性率高；ID 和 CF 操作复杂标准化的程度低，需要训练有素的专业人员；LFA 敏感性低； Using only one antibody detection method may lead to misdiagnosis or missed diagnosis, EIA has a high false positive rate; ID and CF are complex to operate; low sensitivity of LFA; have a low degree of standardization, and require trained professionals	在慢性和急性肺型组织胞浆菌病患者中的敏感性较高 Sensitivity is higher in patients with chronic and acute pulmonary histoplasmosis	敏感性和特异性远低于抗原检测，免疫抑制患者中的诊断能力较差 Sensitivity and specificity are much lower than antibody detection, diagnostics ability in immunosuppressed patients is poor

估了一款市售的 LFA 检测试剂盒，结果显示灵敏度为 88%，特异度和准确性为 87%，与其他抗体检测方法有着高度一致性，有助于辅助球孢子菌病的诊断。而 Grill 等[21]最近开发了一种针对抗几丁质酶-1 (chitinase-1, CTS1)抗体的 LFA 方法，该技术在与 ID 和 CF 测定结果的对比中，表现出了 92.9%的阳性一致率和 97.7%的阴性一致率；在保持近乎相同的检测性能的同时，此方法将检测时间大幅缩短至 10 min。

1.2.2 球孢子菌病的抗原检测

抗原检测的敏感性低于抗体检测，但在部分患者尤其是在人类免疫缺陷病毒/获得性免疫缺陷综合征(human immunodeficiency virus/acquired immunodeficiency syndrome, HIV/AIDS)患者的临床样本中，仅能检测到抗原，只使用抗体检测可能会导致误诊或者漏诊[22]。抗原检测的重点是在患者血清或者尿液中检测到球孢子菌抗原如(1,3)-β-D-葡聚糖、CTS1 等。但多篇文献报道了球孢子菌抗原检测与其他侵袭性真菌(皮炎芽生菌、组织胞浆菌等)出现交叉反应的情况[23-24]，需进一步开发敏感性和特异性更高的抗原检测方法。Grill 等[25]最近开发了一种球孢

子菌 CTS1 定量检测方法，该方法具有高临床敏感性(89.74%)和特异性(94.90%)，有望成为一种用于球孢子菌病诊断的有力工具。

1.2.3 组织胞浆菌病的抗原检测

抗原检测是诊断组织胞浆菌病的首选方法，可使用尿液、血清、支气管肺泡灌洗液、脑脊液等多种液体样本，其中尿液样本以其高敏感性、无创性等优势，广泛应用于抗原检测[26-27]。Marin 等[28]评估了尿 EIA 抗原检测与其他实验室检测方法在检测播散性组织胞浆菌病患者中的性能，结果显示，抗原检测的敏感性为 94%，明显优于血培养(70%)和抗体检测(26%)，特异性也达到了 96%，验证了 EIA 抗原检测的有效性。Martínez-Gamboa 等[29]又进一步评估了播散性组织胞浆菌病的抗原和核酸检测方法的性能，证实了抗原检测比分子检测的性能更强。Medina 等[30]比较了 HIV 患者中抗原检测、血培养和 PCR 的阳性率，其结果分别是 72.3%、36.3%和 62.7%，抗原检测的敏感性最高。近年来，不断有新的抗原检测方法被开发出来，其敏感性和特异性也通常高于商业试剂盒[31]。

然而，抗原检测也有其局限性，因其常与其他真菌(球孢子菌、皮炎芽生菌等)发生交叉反应[32]，导致对阳性结果难以解释，需要与其他检测方法结合作出明确诊断。当抗原检测与其他诊断方法结合使用时，诊断的敏感性和准确性会进一步提高[28]。

1.2.4 组织胞浆菌病的抗体检测

Toscanini 等[31]比较了抗体检测和抗原检测在 HIV/AIDS 组织胞浆菌病患者中的敏感性，抗体检测的敏感性和特异性均低于抗原检测。Fida 等[33]评估了 ID 和 CF 在组织胞浆菌病确诊患者中的检测性能，敏感性分别为 65.7%和 62.7%，总体敏感性提高到 70.1%。而 Richer 等[34]评估了 4 种检测方法(3 种抗体检测和 1 种抗原检测)在急性组织胞浆菌病患者中的灵敏度，其中 EIA、ID、CF 和抗原检测的灵敏度分别为 88.8%、55.0%、73.1%和 67.5%；抗原和抗体检测相结合灵敏度提高到 96.3%。

1.3 球孢子菌病和组织胞浆菌病的分子诊断技术

分子诊断技术相较于传统真菌诊断方法，检测的敏感度和特异性显著提高，极大地缩短了检测所需的时间[35]。目前临床应用的分子诊断技术有 PCR、等温扩增技术(isothermal amplification technology)、宏基因组新一代测序(metagenomics next generation sequencing, mNGS)技术等[36]。本文主要介绍比较成熟的 PCR 相关分子诊断技术在这 2 种病原真菌检测方面的应用。

Yang 等[37]通过内转录间隔区(internal transcribed spacer, ITS)片段的巢式 PCR 方法，在不可培养的石蜡包埋组织中成功识别出了球孢子菌属。相较于培养法，实时荧光定量聚合酶链式反应(quantitative real-time polymerase chain reaction, qPCR)展现出更高的敏感性和特异性，Dizon 等[38]基于 ITS2 序列对临床标本进行 qPCR 检测，发现其总体敏感性为 74%，特异性为 100%。Chaturvedi 等[39]根据抗原-2/脯氨酸-富集抗原(antigen-2/proline-rich antigen, *Ag2/PRA*)靶基因设计的引物和 TaqMan 探针，成功地在培养物和临床标本中检测并区分了粗球孢子菌(*Coccidioides immitis*)和波萨达斯球孢子菌(*Coccidioides posadasii*)，其检测下限达到 10 个基因拷贝的水平。

Martínez-Gamboa 等[29]研究者对不同临床样本中的荚膜组织胞浆菌蛋白 100 (*H. capsulatum* protein 100, *Hcp100*)和序列特征性扩增区域(sequence characterized amplified region, *SCAR*)靶基因巢式 PCR 的检测性能进行了比较；在敏感性相近的情况下，巢式 *Hcp100* PCR 在血液、骨髓和组织样本中的特异性(82.6%−89.5%)显著优于 *SCAR* PCR 的特异性(40.4%−58.8%)，但这 2 种巢式 PCR 的检测性能均不及抗原检测。特异靶基因的筛选是提升 PCR 相关技术在诊断领域应用能力的关键，代表了未来研究的重要

方向。López 等[40-41]先后在小鼠模型和临床样本中评估了靶向 *Hcp100*、*H* 和 *M* 抗原基因的 qPCR 方法的性能，认为基于 *Hcp100* 和 *H* 抗原基因的 qPCR 分子检测是诊断组织胞浆菌病的一种有前途的方法。本实验室设计了基于组织胞浆菌 *Hcp100* 基因的 qPCR 引物和探针，开发出包含荚膜组织胞浆菌、烟曲霉(*Aspergillus fumigatus*)、镰刀菌属(*Fusarium*)、根霉属(*Rhizopus*)在内的四重 qPCR 真菌检测体系，检出限均达到 100 拷贝的高灵敏度，特异性达到 100%，彼此间不发生交叉反应[42]。

基于等温扩增检测组织胞浆菌也有相关的报道。研究者根据 ITS 序列开发的环介导等温扩增(loop-mediated isothermal amplification, LAMP)检测方法，可检测到低至 1 fg/μL 的组织胞浆菌 DNA，相较于 *Hcp100* 巢式 PCR，灵敏度和特异度可分别达到 83%和 92%[43]。Scheel 等[44]开发的 LAMP 方法在培养分离出的菌株中敏感性和特异性均为 100%，但在抗原检测阳性的尿液样本中敏感性仅为 67%。本文汇总了当前实验室诊断中常用的分子检测靶标。同时，根据敏感性和特异性这 2 个关键指标，对这些检测方法的性能进行了初步评估，具体内容详见表 3。

1.4 其他检测技术的最新应用情况

除免疫学和 PCR 相关分子学诊断技术之外，mNGS、基质辅助激光解吸电离飞行时间质谱(matrix-assisted laser desorption ionization-time of flight mass spectrometry, MALDI-TOF MS)等技术也不断应用于这 2 种疾病的检测中。近年来，国内不断有球孢子菌病和组织胞浆菌病的患者通过 mNGS 方法进行诊断[5,45-47]的报道。mNGS 可作为球孢子菌病和组织胞浆菌病的辅助诊断工具，提高诊断的敏感性。但受到采样标准、检测成本及方法本身的限制，无法取代传统的微生物检测方法。MALDI-TOF MS 方法也可用于快速检测球孢子菌和组织胞浆菌[48-49]，但对参考数据库的质量有一定要求。Rana 等[50]开发了一种基于 DNA 杂交原理的核酸传感器，可快速识别全血或肺泡灌洗液中的

表 3 球孢子菌病和组织胞浆菌病分子检测常用靶标

Table 3 Common targets for molecular detection of coccidioidomycosis and histoplasmosis

疾病类型 Disease types	靶标 Target	检测方法 Detection method	敏感性 Sensitivity (%)	特异性 Specificity (%)	参考文献 Reference
球孢子菌病 Coccidioidomycosis	ITS2	qPCR	Cerebrospinal fluid: 59	100	[38]
			Bronchioalveolar lavage fluid: 91	100	[38]
			Lung tissue: 44	100	[38]
			Sputum: 94	100	[38]
			Pleural fluid: 86	100	[38]
	Ag2/PRA		Clinical isolates: 100	100	[39]
组织胞浆菌病 Histoplasmosis	*Hcp100*	nPCR	Blood: 62.9	89.5	[29]
			Bone marrow: 65.9	89.0	[29]
			Tissue: 62.1	82.6	[29]
			Urine: 34.9	67.3	[29]
			82.0	97.0	[28]
		qPCR	93.9	93–100	[40]
		LAMP	67	100	[44]
	H antigen	qPCR	91	100	[40]
	M antigen		57	100	[40]
	ITS	LAMP	83	92	[43]

组织胞浆菌，并可检测低至 100 aM 的 DNA，足以满足临床诊断的需求。Yang 等[37]巧妙地将激光捕获显微切割技术与 PCR 技术相结合，在组织病理学检查呈阳性但无法进行培养的样本中，成功鉴定出了球孢子菌属。而 Tsai 等[51]研究者则运用生物传感器技术，实现了对球孢子菌的快速、高灵敏度检测，能够精确识别低至 2.5 pg/mL 的菌体。Gu 等[52]采用的靶向液相色谱-串联质谱的代谢分析手段，对球孢子菌的检测表现出较高的灵敏度(89.7%–94.4%)和特异度(88.1%–94.4%)。

2 问题与展望

本文通过对目前实验室常用的球孢子菌病和组织胞浆菌病诊断方法进行综述，发现以下问题：(1) 在疾病流行区域，为了提高诊断的敏感性和准确性，多种免疫学检测方法联用已成为一种趋势，但这也导致了检测时间延长，有时可达 3 d 以上，检测成本也随之增加。(2) 我国目前最主要的临床诊断技术为镜检法，敏感性低，远远无法满足临床诊断需求。(3) 分子诊断技术操作相对复杂、标准化程度低，目前尚未在临床诊断中普及。

分子诊断是一种有前景的检测方法，用于检测球孢子菌、组织胞浆菌及其他真菌的相关专利和试剂盒也已陆续报道，为病原菌的诊断提供了强有力的技术支持[53-57]。病原菌的检测正向着快速化、简单化、一体化的方向发展，灵敏、特异、快速和多重的分子诊断技术是未来病原菌感染检测的趋势。因此，为提高我国对这 2 种疾病的诊断能力，未来的工作应着重考虑以下几个方面：(1) 提高我国临床医生对这 2 种真菌感染的认知，以降低误诊和漏诊的风险。(2) 筛选敏感性更高、特异性更强的靶基因，提升分子检测的技术水平。(3) 将分子诊断与传统检测方法联合使用，进一步提高诊断的准确性。(4) 建立并优化多重病原菌分子检测体系，推广其在临床诊断中的应用。目前，本课题组正在研究构建含球孢子菌和组织胞浆菌在内的高致病性真菌多重 qPCR 和液滴数字 PCR 检测体系，下一步工作重点和难点是进一步简化操作流程、规范质量控制和提高其标准化程度。

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