Global Guideline for the Diagnosis and Management of Cryptococcosis

Nicholas Parham, Product Manager, Alpha Laboratories Ltd.

Cryptococcosis is a fungal infection of worldwide importance, with its most lethal manifestation being cryptococcal meningitis. Indeed, the WHO listed *Cryptococcus neoformans* as a top fungal priority pathogen in 2022.[1] Management of cryptococcal infections is complicated by the diversity of syndromes, at-risk patient groups, and clinical resources available. Hence, new guideline recommendations have been developed by ECMM and ISHAM in cooperation with the ASM[2]. The aim is to facilitate optimal clinical decision making on cryptococcosis and address the myriad of clinical complications that are known to exist.

Cryptococcosis often involves the CNS or the lungs, with cryptococcal meningoencephalitis having high mortality, ranging from 24 to 47% at 10 weeks. Although the burden of disease is highest among those with HIV and AIDS, other immunocompromised and immunocompetent risk groups are increasingly being reported. Hence, it is important for physicians to have the necessary tools to facilitate clinical decision making in identification and management of cryptococcosis.

The recent paper by Chang et al.covers clinical assessment, diagnostic strategies, and treatment recommendations for various cryptococcosis syndromes (central nervous system [CNS], disseminated, pulmonary and skin).[2] The guidelines emphasise the importance of accurate syndrome classification (through the use of diagnostics such as the Cryptococcal Antigen [CrAg] Lateral Flow assay [LFA]) to guide therapy, recommend optimal antifungal regimens tailored to resource settings, and stress the need for monitoring and managing drug toxicity and relapse. Some of the key diagnostic points include:

Screening in People Living with HIV:

CrAg LFA is used globally for screening and diagnosis in individuals with HIV, particularly those with CD4 counts <200 cells/mm^3 or interruptions in antiretroviral therapy [ART].

CrAg LFA is recommended for initial screening, diagnosis, and risk stratification within this population.

Patients Without HIV:

In non-HIV patients, routine screening with the lateral flow assay is not advised, but is used when infection is suspected in high-risk groups (e.g. solid organ transplant).

Diagnosis in All Patients:

Microscopy and culture of cerebrospinal fluid (CSF), accompanied by CSF and blood (i.e. serum, plasma, or whole blood) CrAg testing and imaging, are central to the diagnosis of cryptococcosis.

TABLE 1 *Cryptococcus* species and their detection by four CE/IVD cryptococcal antigen lateral flow assays

Cryptococcal species and genotype	Detection (*n* [%]) with: IMMY Diagnostics	FungiXpert	Dynamiker	Biosynex
Cryptococcus neoformans, serotype A; genotypes AFLP1/VNI, AFLP1A/VNB/VNII, AFLP1B/VNII	7/7 (100)	7/7 (100)	7/7 (100)	7/7 (100)
Cryptococcus deneoformans , serotype D; genotype AFLP2/VNIV	6/6 (100)	6/6 (100)	6/6 (100)	6/6 (100)
Cryptococcus gattii sensu stricto, serotype B; genotype AFLP4/VGI	4/4 (100)	4/4 (100)	4/4 (100)	4/4 (100)
Cryptococcus bacillisporus, serotype B and C; genotype AFLP5/VGIII	4/4 (100)	4/4 (100)	**3/4 (75)**[a]	**3/4 (75)**[a]
Cryptococcus deuterogattii, serotype B; genotype AFLP6/VGII	5/5 (100)	5/5 (100)	5/5 (100)	**4/5 (80)**
Cryptococcus tetragattii, serotype C; genotype AFLP7/VGIV	6/6 (100)	6/6 (100)	**4/6 (66.6)**	**0/6 (0)**
Cryptococcus decagattii, serotype B; genotype AFLP10	2/2 (100)	2/2 (100)	2/2 (100)	2/2 (100)
Cryptococcus deneoformans × *Cryptococcus neoformans* hybrid, serotype AD; genotype AFLP3/VNIII	4/4 (100)	4/4 (100)	4/4 (100)	4/4 (100)
Cryptococcus deneoformans × *Cryptococcus gattii* hybrid, serotype BD; genotype AFLP8	1/1 (100)	1/1 (100)	1/1 (100)	1/1 (100)
Cryptococcus gattii × *Cryptococcus neoformans* interspecies, serotype AB; genotype AFLP9	1/1 (100)	1/1 (100)	1/1 (100)	1/1 (100)

[a]The Dynamiker and Biosynex LFAs could not detect a serotype C strain of *C. bacillisporus*. The boldfaced values indicate the presence of false-negative test results.

Limitations in C. *gattii* Disease:

Not all commercial lateral flow assays are able to detect C. *gattii* disease. However, this is not the case for IMMY's CrAg LFA, which has good reactivity across all serotypes.[3]

The IMMY Cryptococcal Antigen Lateral Flow Assay (CrAg) is a qualitative or semi-quantitative test for detection of capsular polysaccharide antigens of Cryptococcus species (*Cryptococcus neoformans* and *Cryptococcus gattii*) in serum, plasma, whole blood, and cerebral spinal fluid (CSF). It is highly sensitive and specific, with a rapid turnaround time of just 10 minutes. The CrAg LFA is a professional-use, laboratory assay which can be used as an aid in the diagnosis of cryptococcosis.

Find out more, please visit:
alphalabs.co.uk/cr2003

References: 1.WHO. WHO fungal priority pathogens list to guide research, development and public health action. Geneva: World Health Organization, 2022.
2.Chang CC, et al. Global guideline for the diagnosis and management of cryptococcosis: an initiative of the ECMM and ISHAM in cooperation with the ASM. Lancet Infect Dis. 2024 Aug;24(8):e495-e512. doi: 10.1016/S1473-3099(23)00731-4. Epub 2024 Feb 9. Erratum in: Lancet Infect Dis. 2024 Aug;24(8):e485. doi: 10.1016/S1473-3099(24)00426-2. PMID: 38346436; PMCID: PMC11526416.
3.Shi D, et al. Neglecting Genetic Diversity Hinders Timely Diagnosis of Cryptococcus Infections. J Clin Microbiol. 2021 Mar 19;59(4):e02837-20. doi: 10.1128/JCM.02837-20. PMID: 33472900; PMCID: PMC8092738.

