### **Cryptococcus**

#### **1. Taxonomy & Nomenclature**

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| **Species complex** | **Varieties / Serotypes** | **Usual host status** | **Key points for exam** |
| **C. neoformans** | var. *grubii* (A) — 95 % of isolates; var. *neoformans* (D) | Opportunist | Worldwide; pigeon guano & decaying wood reservoirs |
| **C. gattii** | Serotypes B & C | “Primary” pathogen | Tropical/sub-tropical (Eucalyptus) but emergent in Canada & PNW USA temperate regions |
| **Other spp.**  (*C. albidus,*  *C. laurentii,* etc.) | — | Rare opportunists | Often device-associated or profound T-cell immunodeficiency |

*► Exam tip*: C. *neoformans* vs C. *gattii* separation on **CGB agar** (blue colour = *gattii*).

Extra point :

Animal reservoir & (rare) zoonosis – dogs, cats, koalas; animal-to-human transmission documented, though exceptional.

#### **2. Morphology & Basic Lab Features**

* Encapsulated, round/oval basidiomycete yeasts; narrow-necked budding.
* **Urease-positive**, non-fermentative; produce melanin on bird-seed agar.
* Mucicarmine / Alcian blue stain capsule in tissue; **India ink** gives clear halo in CSF.

#### **3. Virulence Factors (memorise capsule-melanin-laccase pentad)**

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| **Factor** | **Function / exam pearl** |
| **Polysaccharide capsule (GXM & GXMGal)** | Anti-phagocytic, anti-oxidative, prevents desiccation |
| **Melanin** (via laccase) | UV protection, drug resistance, environmental survival |
| **Proteinases & phospholipases** | Tissue invasion, nutrient acquisition |
| **Urease** | Aids blood–brain crossing |
| **MATα mating type** | More common & more virulent than MATa |

#### **4. Epidemiology & Risk Factors**

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| **Species** | **Geography** | **Classic host** | **Emerging risks** |
| *C. neoformans* var. *grubii* | Global | Advanced HIV, transplant | DM, malignancy |
| var. *neoformans* | Europe (≈30 % isolates) | As above | — |
| *C. gattii* | Tropics/Sub-tropics, Vancouver Isl., PNW USA | Immunocompetent adults | Cancer, idiopathic CD4 lymphopenia, chronic steroids, smoking |
| Non-neoformans/gattii | Worldwide | Profound CD4 depression, catheters | — |

*Global burden*: ≈1 million cases/yr cryptococcal meningitis in HIV (>70 % sub-Saharan Africa).

Disease in children is very uncommon (≈ 1 % of AIDS cases)

#### **5. Pathogenesis & Disease Spectrum**

* Acquired by **inhalation** → pulmonary infection ± latent foci.
* **Dissemination** (especially to CNS) during cell-mediated immunosuppression or via urease-mediated BBB transit.
* *C. gattii*: tendency to form large **cryptococcomas** in lung/brain; morbidity high, mortality lower vs *neoformans*.

#### **6. Clinical Presentation (species-independent)**

1. **CNS** – meningitis/meningo-encephalitis, raised ICP.
2. **Pulmonary** – nodules, mass lesions, pneumonia.
3. **Bloodstream** – fungaemia in severe immunosuppression.
4. **Other** – skin, bone, prostate, ocular.

#### **7. Diagnostic Approach**

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| **Step** | **Key tests** | **FRCPath nuances** |
| **Direct microscopy** | India ink (CSF, urine), tissue histology stains | Less sensitive in low-burden disease |
| **Antigen detection** | Serum/CSF **CrAg LFA** (IMMY) – rapid, high Sn/Sp for *neoformans/gattii* | False + rare; NOT reliable for other species |
| **Culture** | Sabouraud agar; bird-seed (melanin) & **CGB** for speciation | gatii = blue |
| **Identification** | rDNA ITS / D1-D2 sequencing or **MALDI-TOF-MS** (database-dependent) |  |
| **Susceptibility** | CLSI broth microdilution; all intrinsically **echinocandin-resistant** |  |

#### **8. Treatment & Prophylaxis**

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| **Setting** | **Induction (2 weeks)** | **Consolidation / Maintenance** | **Notes** |
| *C. neoformans* / *C. gattii* meningitis | **Liposomal amphotericin B** 5mg/kg + flucytosine 25mg/kg PO QDS | Fluconazole 400mg OD ≥8 wks then 200mg ≥12 m maintenance (lifelong if relapse risk) | Monitor ICP; HAART integration @ 2 wks improves outcome in HIV |
| Non-neoformans/gattii | Amphotericin B until improvement → step-down fluconazole *if susceptible* | Tailor to site/severity; device removal may suffice in mild disease | Higher MICs to 5-FC & azoles reported |

*Resistance alerts*: emerging fluconazole, amphotericin B, 5-FC resistance after prolonged therapy or prophylaxis.

#### **9. High-Yield Exam Pearls**

1. **CGB agar blue = *gattii*** (g for *gattii* and **g**lycine).
2. Urease positivity plus encapsulation distinguishes Cryptococcus from other yeasts.
3. **CrAg LFA** is validated for serum/CSF/urine; limited for non-neoformans/gattii.
4. Always consider raised opening pressure (>25 cm H₂O) in cryptococcal meningitis → serial lumbar punctures.
5. Intrinsic **echinocandin resistance**—never suitable for treatment.
6. *C. gattii* outbreaks linked to non-Eucalyptus trees in Canada (Douglas Fir).
7. MATα isolates predominate in clinical disease.
8. Mortality without therapy ~100 %; early induction therapy critical.

**Mnemonic for virulence factors** – **“CLaMPU”**: **C**apsule, **La**ccase (melanin), **M**elanin, **P**hospholipase/proteinase, **U**rease.