CNS Infection II

Fungal and Parasitic Infection of CNS

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Main Pathogens that cause fungal infection of CNS

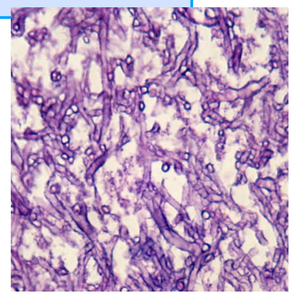
- Cryptococcus species
- Aspergillus species
- Candida species
- Mucormycosis

Advances in the diagnosis and treatment of fungal infections of the CNS, Schwartz, Stefan et al. The Lancet Neurology Vol 17 April 2018

Fungal infection of CNS : Morphological Classifications

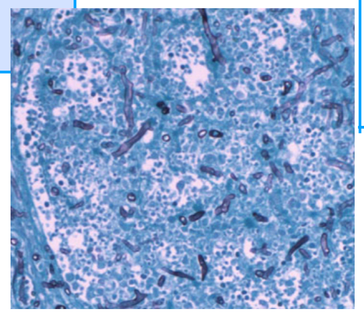
MOLDS

Septate hyphae
: Aspergillus spp.



Weisenberg E. Aspergillus. PathologyOutlines.com

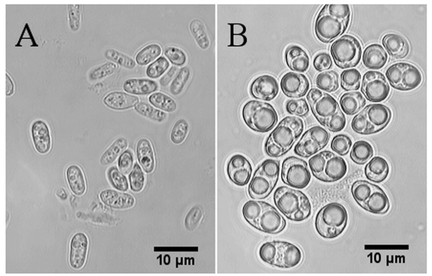
Aseptate hyphae
: Mucor spp.



A.J. Layon et al. (eds.), Central Nervous System Infection Textbook of Neurointensive Care, DOI 10.1007/978-1-4471-5226-2_22,

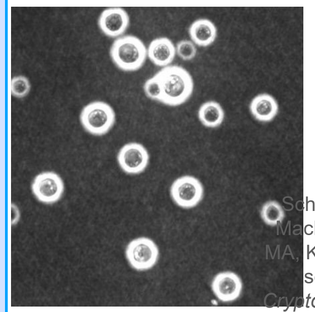
YEAST

Candida
: C.albicans



Funk, Irina & Sieber, Volker & Schmid, Jochen. (2017). Effects of glucose concentration on 1,18-cis-octadec-9-enedioic acid biotransformation efficiency and lipid body formation in Candida tropicalis. Scientific Reports.

Cryptococcus
: C.neoforman
C.gattii



Schein JE, Tangen KL, Chiu R, Shin H, Lengeler KB, MacDonald WK, Bosdet I, Heitman J, Jones SJ, Marra MA, Kronstad JW. Physical maps for genome analysis of serotype A and D strains of the fungal pathogen *Cryptococcus neoformans*. Genome Res. 2002;12: 1445-53.

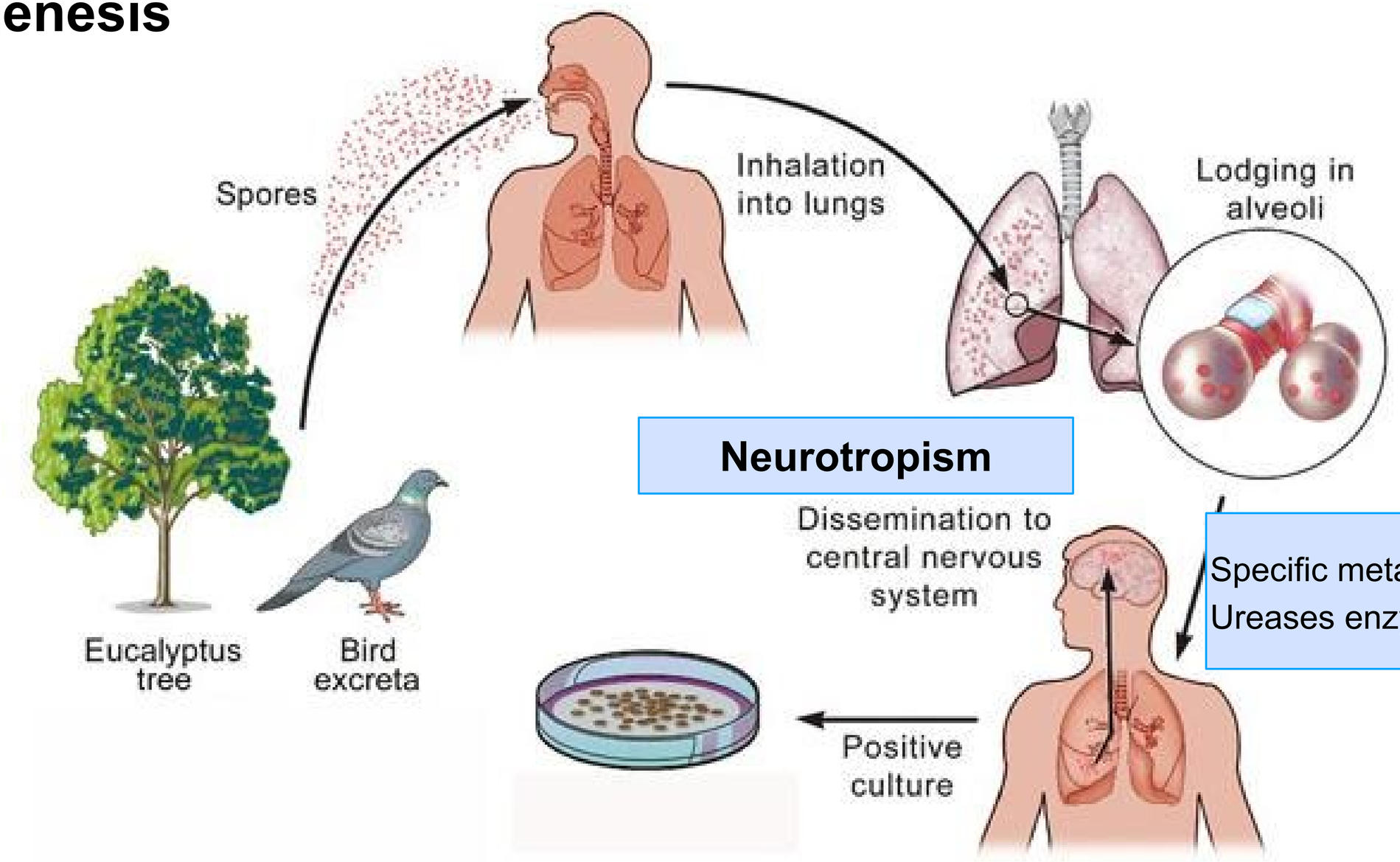
Dimorphic Fungi

Histoplasma capsulatum

Cryptococcal Meningitis

Cryptococcal Meningitis

Pathogenesis



Raksha, Gurjeet & Singh, & Singh, Gurjeet. (2013). CRYPTOCOCCAL MENINGITIS: EPIDEMIOLOGY AND LABORATORY DIAGNOSIS. International Journal of Universal Pharmacy and Bio Sciences. 2. 234-241.

Pathogenic cryptococci

- ***Cryptococcus neoformans***
  - Reservoir - Bird excreta
  - Infected mainly in Immunocompromised host

CNS > LUNGS

More susceptible to fluconazole

- ***Cryptococcus gatti***
  - Reservoir - Eucalyptus tree
  - Infected mainly in immunocompetent host

LUNGS > CNS

Less susceptible to fluconazole

Cryptococcal Meningitis

Epidemiology

- **HIV associated cryptococcal infection**
  - Patients at risk : CD4+ T cell counts <100 cells/μl and not on effective antiretroviral therapy (ART)
- Infection in **HIV-negative** individuals : transplant recipients and other patients with defects in cell-mediated immunity

Williamson PR, Jarvis JN, Panackal AA, Fisher MC, Molloy SF, Loyse A, Harrison TS. Cryptococcal meningitis: epidemiology, immunology, diagnosis and therapy. Nat Rev Neurol. 2017 Jan;13(1):13-24. doi: 10.1038/nrneurol.2016.167. Epub 2016 Nov 25. PMID: 27886201.

Cryptococcal Meningitis

Box 2 | Predisposing genetic and other conditions in non-HIV CM

Syndromes and autoantibodies

- Idiopathic $CD4^+$ lymphopenia[22,23]
- Pulmonary alveolar proteinosis with autoantibodies to GM-CSF[24–26]
- Autoantibodies to IFN-γ[27]

Monogenic disorders

- Primary immunodeficiency owing to *GATA2* mutations[28–30]
- Chronic granulomatous disease
- Hyperimmunoglobulin E recurrent infection syndrome (also known as Job syndrome)[31,32]
- X-Linked CD40L deficiency (also known as hyper-IgM syndrome)[33,34]

Polygenetic modifiers

- FCg receptor II polymorphism[35]

Comorbidities[18,19]

- Sarcoidosis, autoimmune disease, steroid treatment
- Hepatic disease
- Solid organ transplant conditioning

CM, cryptococcal mengitis; GM-CSF, granulocyte-macrophage colony stimulating factor.

Williamson PR, Jarvis JN, Panackal AA, Fisher MC, Molloy SF, Loyse A, Harrison TS. Cryptococcal meningitis: epidemiology, immunology, diagnosis and therapy. Nat Rev Neurol. 2017 Jan;13(1):13-24. doi: 10.1038/nrneurol.2016.167. Epub 2016 Nov 25. PMID: 27886201.

Cryptococcal Meningitis

Clinical Features

- **Subacute meningoencephalitis**

: most typically headache and altered mental status, fever, nausea and vomiting

- The median duration from symptom onset to presentation
  - 2 weeks in patients with HIV infection
  - 6–12 weeks in non-HIV CM cases

Many patients develop visual symptoms, such as diplopia and, later in the disease, reduced acuity secondary to high CSF pressure and/or involvement of the optic nerve and tracts

Williamson PR, Jarvis JN, Panackal AA, Fisher MC, Molloy SF, Loyse A, Harrison TS. Cryptococcal meningitis: epidemiology, immunology, diagnosis and therapy. Nat Rev Neurol. 2017 Jan;13(1):13-24. doi: 10.1038/nrneurol.2016.167. Epub 2016 Nov 25. PMID: 27886201.

Cryptococcus Meningitis

Diagnosis and Investigation

- Characteristic CSF :
  - Elevated white cell count
  - Lymphocyte predominance
  - Elevated CSF protein
  - Low CSF glucose

1/2 of HIV-infected patients with CM have a CSF opening pressure of >25 cmH2O,High pressure is associated with worse symptoms, including headache, nausea, diplopia secondary to 6th nerve palsies, and altered mental status

In HIV- associated cryptococcal meningitis

CSF white cell count is lower (median 15 × 106 cells/l) and can often be normal

Jarvis JN, Bicanic T, Loyse A, Namarika D, Jackson A, Nussbaum JC, Longley N, Muzoora C, Phulusa J, Taseera K, Kanyembe C, Wilson D, Hosseinipour MC, Brouwer AE, Limmathurotsakul D, White N, van der Horst C, Wood R, Meintjes G, Bradley J, Jaffar S, Harrison T. Determinants of mortality in a combined cohort of 501 patients with HIV-associated Cryptococcal meningitis: implications for improving outcomes. Clin Infect Dis. 2014 Mar;58(5):736-45.

Williamson PR, Jarvis JN, Panackal AA, Fisher MC, Molloy SF, Loyse A, Harrison TS. Cryptococcal meningitis: epidemiology, immunology, diagnosis and therapy. Nat Rev Neurol. 2017 Jan;13(1):13-24. doi: 10.1038/nrneurol.2016.167. Epub 2016 Nov 25. PMID: 27886201.

Cryptococcus Meningitis

Diagnosis and Investigation : Cryptococcus capsular polysaccharide antigen

- Cryptococcus capsular polysaccharide antigen (CrAg) in CSF, serum, plasma or whole blood is key to rapid diagnosis of cryptococcal meningitis

- CrAg lateral flow assay (LFA) **Sensitivity and Specificity 99%** with whole blood, serum and plasma, being nearly as accurate for diagnosis of meningitis

Poplin, V., Boulware, D. R., & Bahr, N. C. (2020). Methods for rapid diagnosis of meningitis etiology in adults. *Biomarkers in medicine*, *14*(6), 459–479.

Cryptococcus Meningitis

Cryptococcus capsular polysaccharide antigen titer

Both latex agglutination and CrAg LFA can be semiquantified using titers

Titer between the Immy latex agglutination test and Immy LFA are **not** comparable

CrAg titer is predictive of meningitis and death

Plasma CrAg titers of 1:80 by Immy CrAg have an exceedingly low probability of meningitis

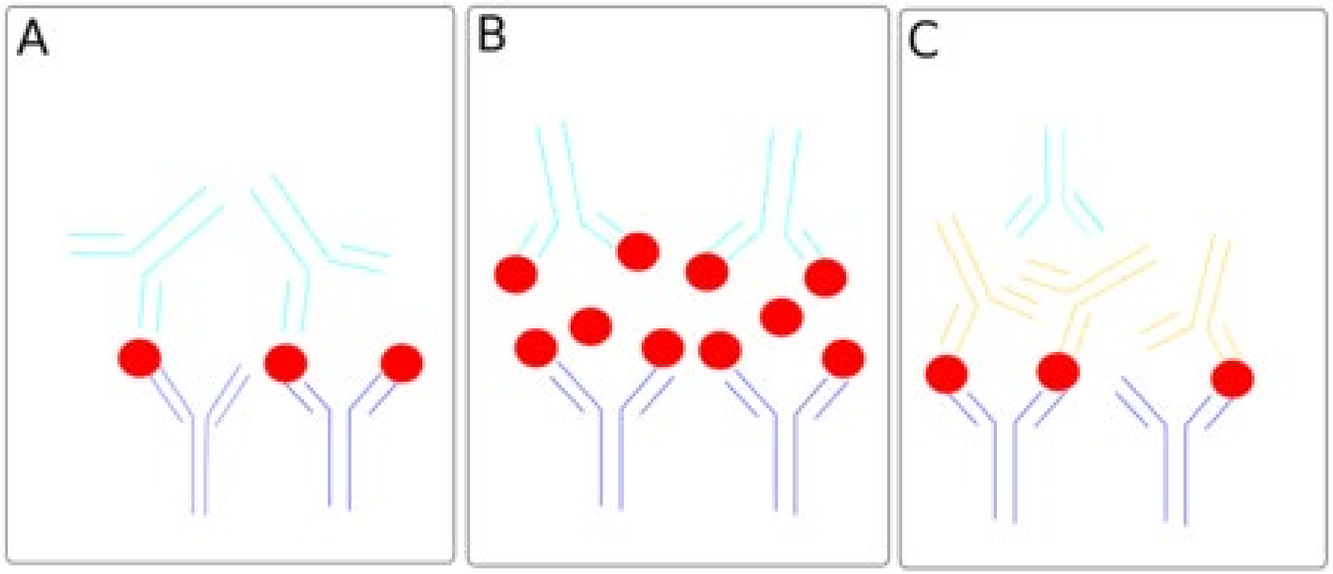
CrAg titers of 1:1,280 have near-universal CNS involvement

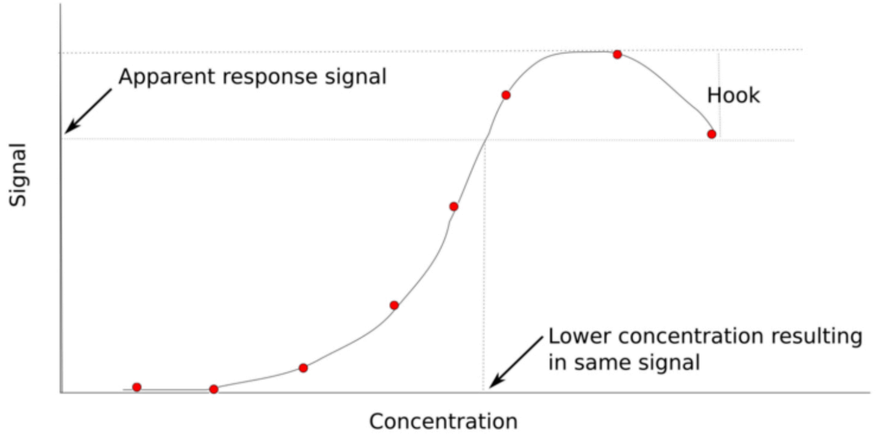
Rajasingham R, Wake RM, Beyene T, Katende A, Letang E, Boulware DR. 2019. Cryptococcal meningitis diagnostics and screening in the era of point-of-care laboratory testing. J Clin Microbiol 57:e01238-18. https:// doi.org/10.1128/JCM.01238-18.

Cryptococcus Meningitis

Diagnosis and Investigation : Cryptococcus capsular polysaccharide antigen

- **Lower sensitivity (91%)** has been noted with **high fungal burdens** due to the **pro-zone or hook effect :** High cryptococcal load interfering with antigen–antibody complex of the assay resulting in a false negative) >>>> this issue resolves **with dilution (sensitivity 100%)**





A dose response assay illustrating the hook effect. At high concentrations of analyte, a lower signal is observed. This shows that using this assay to determine the concentration of analyte in a sample containing very high levels would produce a lower signal. Since this signal normally correlates to a lower concentration, an inaccurately low result is recorded.

Schiettecatte, Johan; Anckaert, Ellen; Smitz, Johan (2012-03-23). "Interferences in Immunoassays". *Advances in Immunoassay Technology*. InTech. doi:10.5772/35797. ISBN 978-953-51-0440-7.

Poplin, V., Boulware, D. R., & Bahr, N. C. (2020). Methods for rapid diagnosis of meningitis etiology in adults. *Biomarkers in medicine*, *14*(6), 459–479.

Cryptococcus Meningitis

Diagnosis and Investigation

- India Ink , sensitivity is as low as 42% when fungal burden is <1000 CFU/ml, and the best case is 85% sensitivity
- Fungal culture, growth can take up to 10 days and false- negative results can occur with a low fungal burden

Poplin, V., Boulware, D. R., & Bahr, N. C. (2020). Methods for rapid diagnosis of meningitis etiology in adults. *Biomarkers in medicine*, *14*(6), 459–479.

Cryptococcus Meningitis

Diagnosis and Investigation

- Quantitative culture, useful for
  - Monitoring response to treatment
  - **Differentiating relapse** of cryptococcal meningitis from **IRIS**

A paired comparison : Quantitive CSF culture and CSF Cr Ag

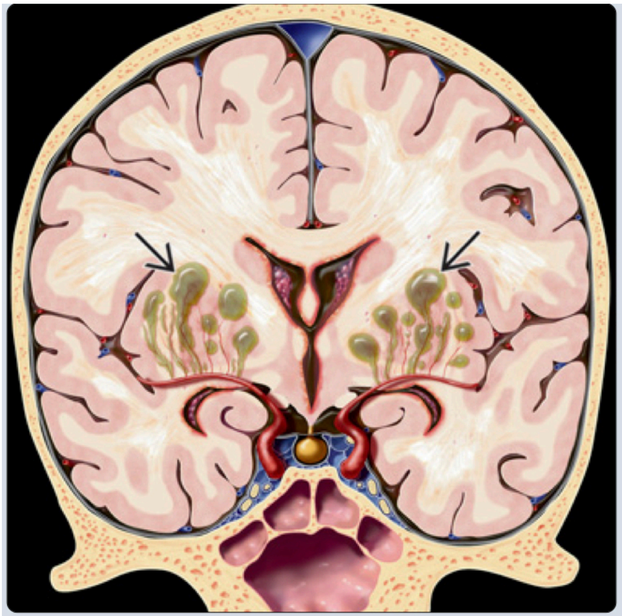
no significant difference between their results of the two assays (P = .09 by paired t-test)

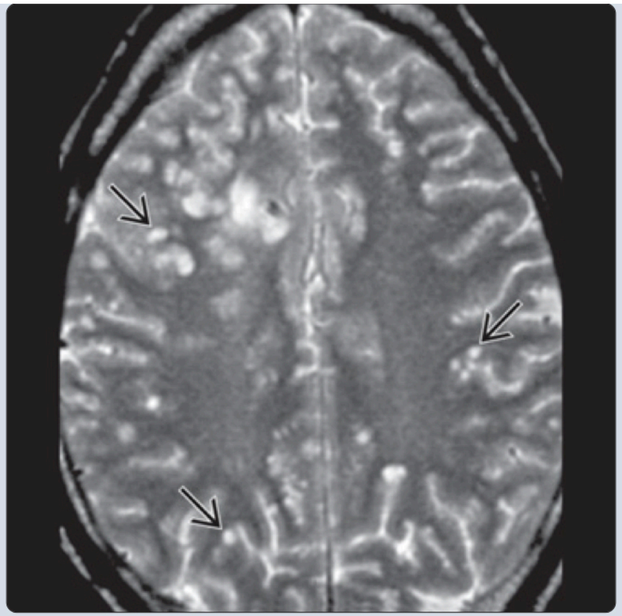
Reproducibility of CSF quantitative culture methods for Cryptococcus neoformans April 2014, International Journal of Infectious Diseases 21(S1):286

Poplin, V., Boulware, D. R., & Bahr, N. C. (2020). Methods for rapid diagnosis of meningitis etiology in adults. *Biomarkers in medicine*, *14*(6), 459–479.

Cryptococcus Meningitis

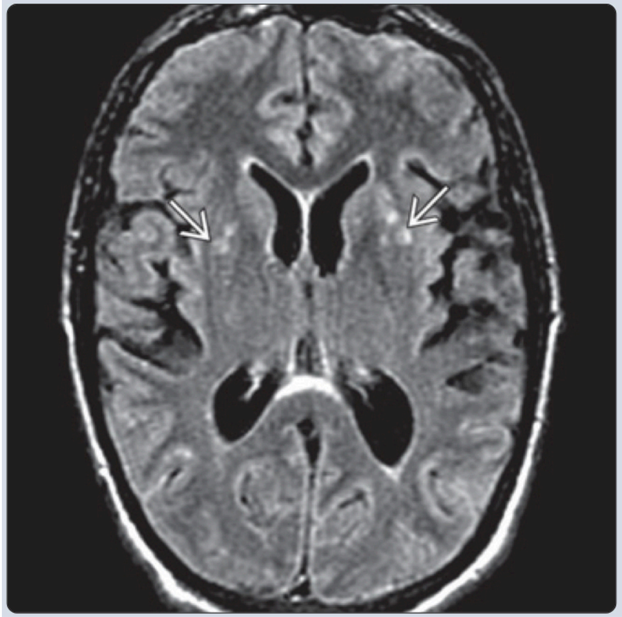
Features on Neuroimaging

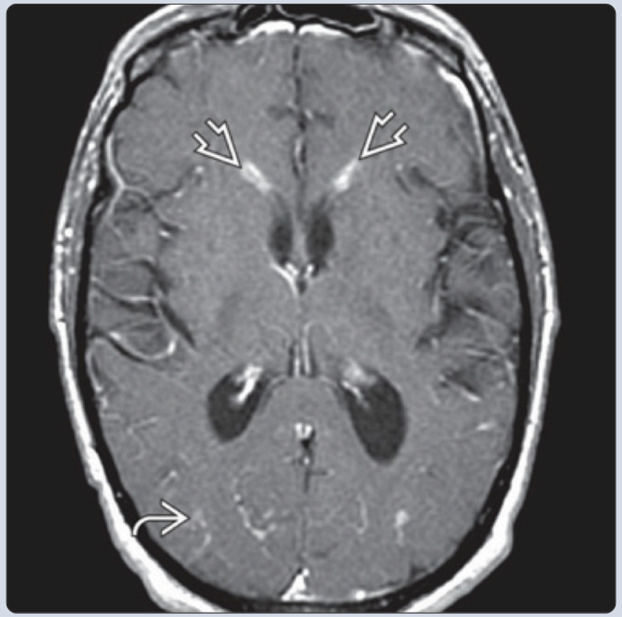




(Left) Coronal graphic shows multiple dilated perivascular (Virchow-Robin) spaces , filled with fungi and mucoid material, resulting in **gelatinous pseudocysts** which are characteristic of cryptococcal infection in AIDS

(Right) Axial T2WI MR shows multiple **dilated perivascular spaces** in this immunocompromised patient with cryptococcal meningitis. **Gelatinous pseudocysts are most commonly located in the basal ganglia and thalami** but may be seen in the brainstem, cerebellum, and cerebral hemispheres.





(Left) Axial FLAIR MR shows bilateral dilated perivascular spaces with hyperintense rims in this AIDS patient with Cryptococcus meningitis. **Hydrocephalus** is a common complication of this infection

(Right) Axial T1WI C+ MR in the same patient shows subependymal enhancement **along the frontal horns of the lateral ventricles as well as nodular leptomeningeal enhancement**
Enhancement in Cryptococcus infection is dependent on the cell-mediated immunity of the host.

Diagnostic Imaging Brain Third edition Elsevier

Stage	Pharmacological treatment regimen	Duration
Induction	L-AmB 3–6 mg/kg daily or D-AmB 0.7–1.0 mg/kg daily (L-AmB preferred in organ transplant patients and when >2-week induction is needed) in combination with flucytosine 100 mg/kg daily (75 mg/kg daily if intravenous formulation is used)	• HIV+ patients: 2 weeks • Transplant recipients:* ≥2 weeks • For all other patients, including patients with *Cryptococcus gatti* infection:* 4–6 weeks
Consolidation	• Fluconazole 400–800 mg daily‡ • In HIV+ patients, start ART at 4 weeks	8 weeks
Maintenance therapy	• Fluconazole 200 mg daily • In HIV+ patients, consider discontinuing maintenance after a minimum of 1 year if $CD4^+$ cell count is >100 cells/μL and HIV viral load is suppressed	≥1 year
Induction therapy in resource-limited settings	• If flucytosine is not available: • D-AmB 0.7–1 mg/kg daily intravenously in combination with fluconazole 800–1200 mg daily	2 weeks (1 week is better than no D-AmB)
	• If D-AmB is not available: • Fluconazole 1,200 mg daily§ in combination with flucytosine 100 mg/kg daily orally (if available)	2 weeks

ART, antiretroviral therapy; D-AmB, amphotericin B deoxycholate; L-AmB, liposomal amphotericin B. *see IDSA guidelines[78]. ‡800 mg daily preferred if second line induction regimens used. §Fluconazole increases nevirapine levels, and safety of high-dose fluconazole with nevirapine is unknown. Alternative antiretrovirals are preferred.

Williamson PR, Jarvis JN, Panackal AA, Fisher MC, Molloy SF, Loyse A, Harrison TS. Cryptococcal meningitis: epidemiology, immunology, diagnosis and therapy. Nat Rev Neurol. 2017 Jan;13(1):13-24.

Amphotericin B deoxycholate (D-AmB)

Amphotericin B deoxycholate (D-AmB) associated with

- Renal impairment
- Hypokalaemia
- Hypomagnesaemia
- Anaemia

- Saline and fluid loading equivalent to giving 1 l of regular saline per day in addition to usual fluid requirements, has been shown to reduce renal impairment

- Liposomal amphotericin B (L-AmB) is equally as effective as D-AmB, and is better tolerated

The rate of clearance of infection derived from quantitative cultures of CSF from **serial lumbar punctures** over the **first 2 weeks of treatment** provides a statistically powerful and clinically relevant endpoint

Williamson PR, Jarvis JN, Panackal AA, Fisher MC, Molloy SF, Loyse A, Harrison TS. Cryptococcal meningitis: epidemiology, immunology, diagnosis and therapy. Nat Rev Neurol. 2017 Jan;13(1):13-24.

Cryptococcal Meningitis

Treatment

Therapeutic LP are recommended to control high CSF pressure

The safe maximum volume of CSF that can be drained at one lumbar puncture is unclear, but up to 30 ml are frequently removed in patients with high pressure, with checking of pressure after each 10 ml removed

Williamson PR, Jarvis JN, Panackal AA, Fisher MC, Molloy SF, Loyse A, Harrison TS. Cryptococcal meningitis: epidemiology, immunology, diagnosis and therapy. Nat Rev Neurol. 2017 Jan;13(1):13-24. doi: 10.1038/nrneurol.2016.167. Epub 2016 Nov 25. PMID: 27886201.

Cryptococcal Meningitis

Treatment

CSF opening pressure of >25 cmH2O

: LP to reduce OP 50% or to normal [20 cmH2O]

Persistent pressure >25 cmH2O with symptoms

: Repete LP daily until stabilized for > 2 days

Consider temporary percutaneous lumbar drains or ventriculostomy

Permanent VP shunts when Fail conservative measures

PG, Powderly WG, Singh N, Sobel JD, Sorrell TC. Clinical practice guidelines for the management of cryptococcal disease: 2010 update by the infectious diseases society of america. Clin Infect Dis. 2010 Feb 1;50(3):291-322.

Cryptococcal Meningitis

Treatment

- In patients **without HIV**, the clinical response depends on **control** of aberrant **immune responses** as much as it depends on control of the initial infection
- Initial therapy with amphotericin B and flucytosine is similar to that for HIV-related disease, but the **induction phase is longer** (4–6 weeks)

Lipid formulations have been favoured over the deoxycholate preparation because of reduced renal toxicity

Post-transplant cryptococcosis : **Discontinuation of calcineurin agents** (Tacrolimus, reducing IL-2 production and receptor expression, leading to reduction in T-cell activation) has been associated with clinical **deterioration and IRIS**

Williamson PR, Jarvis JN, Panackal AA, Fisher MC, Molloy SF, Loyse A, Harrison TS. Cryptococcal meningitis: epidemiology, immunology, diagnosis and therapy. Nat Rev Neurol. 2017 Jan;13(1):13-24. doi: 10.1038/nrneurol.2016.167. Epub 2016 Nov 25. PMID: 27886201.

Cryptococcal IRIS

Paradoxical IRIS

: 1–2 months after ART initiation

Risk factors for CM-IRIS

Low pre-ART CD4+ cell count that rises rapidly after ART initiation

A low initial CSF white cell count

Low markers of inflammation and IFN-γ responses on initial presentation

High fungal burden at baseline and day 14

Unmasking IRIS

Lower fungal burden compared with ART-naive cases

Unmasking CM-IRIS are treated with the **same antifungal regimens** used for those who are ART-naive

Williamson PR, Jarvis JN, Panackal AA, Fisher MC, Molloy SF, Loyse A, Harrison TS. Cryptococcal meningitis: epidemiology, immunology, diagnosis and therapy. Nat Rev Neurol. 2017 Jan;13(1):13-24. doi: 10.1038/nrneurol.2016.167. Epub 2016 Nov 25. PMID: 27886201.

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Cryptococcal Optimal ART Timing (COAT) study

Patients given early ART (median initiation at 8 days)

Higher CSF WBC and CSF markers of macrophage and/or microglial activation than patients not yet started on ART

suggesting the excess deaths in the early ART arm may have been immune mediated

Current guidelines suggest that ART is initiated at 4–6 weeks

Boulware, D. R. et al. Timing of antiretroviral therapy after diagnosis of cryptococcal meningitis. N. Engl. J. Med. 370, 2487–2498 (2014).

Williamson PR, Jarvis JN, Panackal AA, Fisher MC, Molloy SF, Loyse A, Harrison TS. Cryptococcal meningitis: epidemiology, immunology, diagnosis and therapy. Nat Rev Neurol. 2017 Jan;13(1):13-24. doi: 10.1038/nrneurol.2016.167.

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Patients who re-present (worsening) after the start of ART should

- LP to screening for ongoing infection + C/S
- Re-induction anti fungal therapy
  L-AmB 3-6 mg/kg/day or D-AmB 0.7-1 mg/kg/day
- **Short course corticosteroid**

Boulware, D. R. et al. Timing of antiretroviral therapy after diagnosis of cryptococcal meningitis. N. Engl. J. Med. 370, 2487–2498 (2014).

Williamson PR, Jarvis JN, Panackal AA, Fisher MC, Molloy SF, Loyse A, Harrison TS. Cryptococcal meningitis: epidemiology, immunology, diagnosis and therapy. Nat Rev Neurol. 2017 Jan;13(1):13-24. doi: 10.1038/nrneurol.2016.167.

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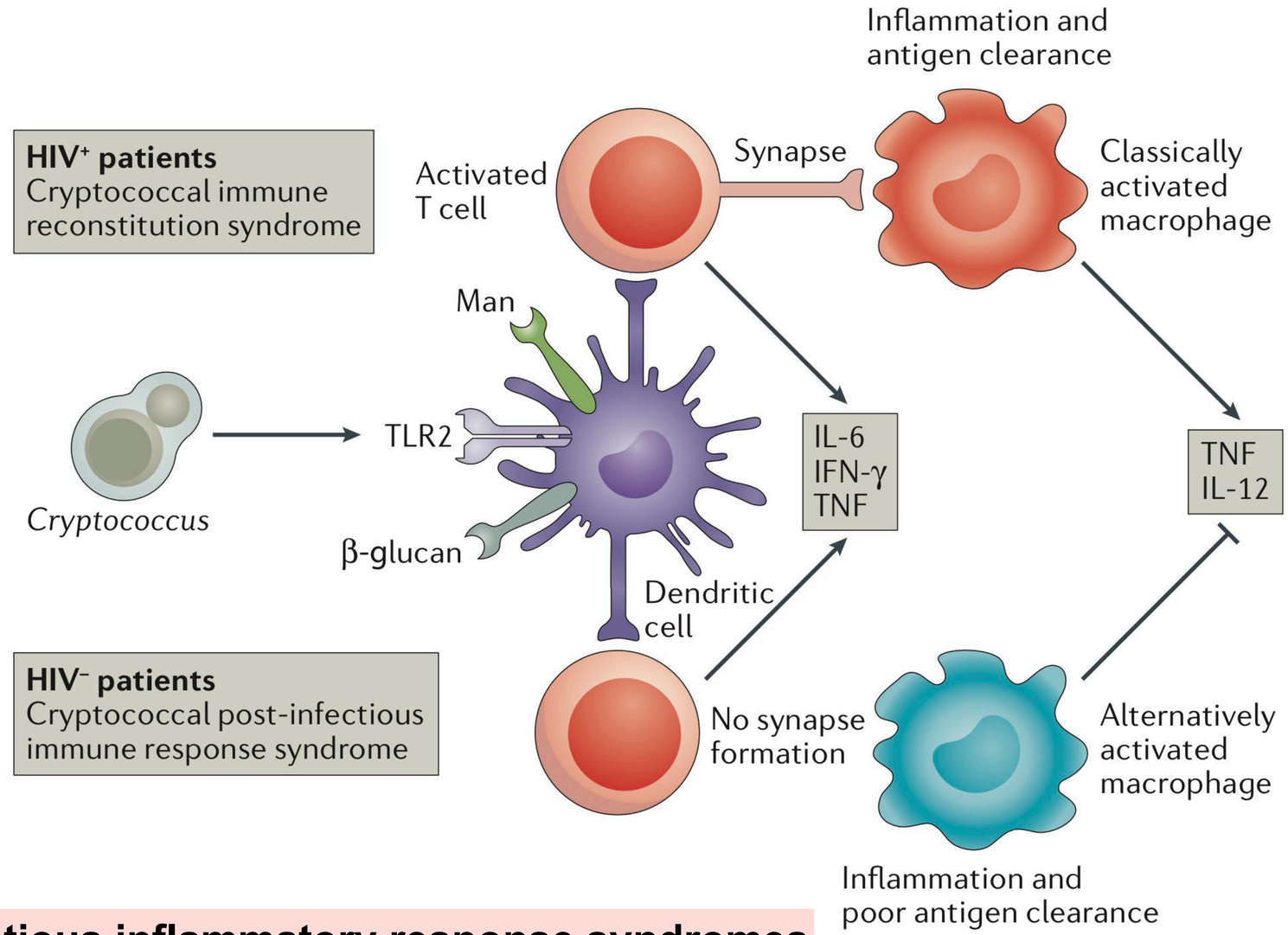
Host damage from infection-related inflammatory syndromes in HIV-positive and in HIV-negative cryptococcal meningitis

CM-IRIS



PIIRS : Post-infectious inflammatory response syndromes

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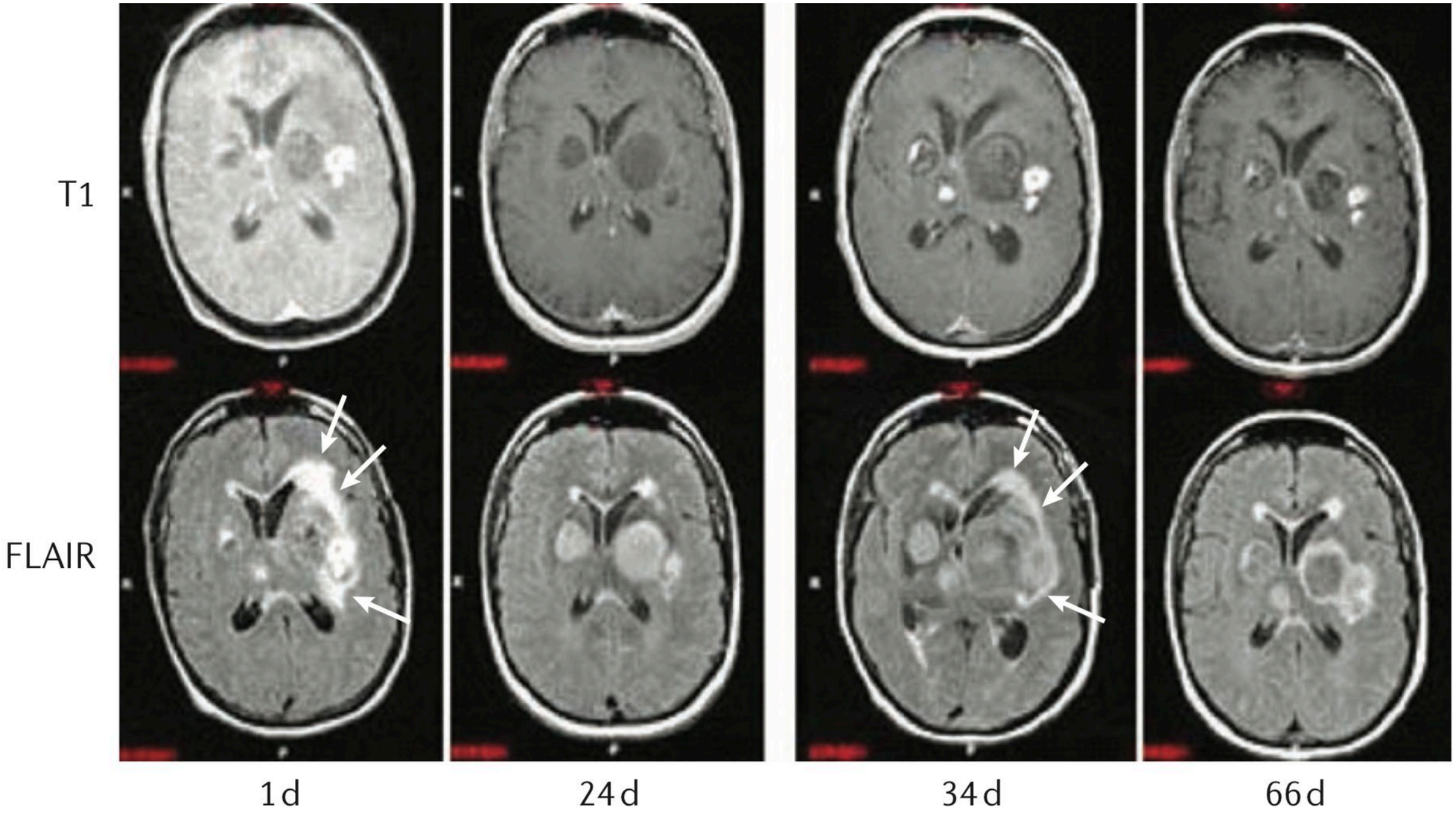

Corticosteroid treatment can reduce brain oedema in patients with HIV-negative cryptococcal meningitis

MRI scans demonstrate reduced brain oedema (arrows) after treatment with corticosteroids in an HIV-negative patient with CM and PIIRS

T1 and FLAIR weighted MRI scans of a patient with Cryptococcus gattii infection and autoantibody against granulocyte-macrophage colony stimulating factor treated with ampho

Corticosteroid therapy was stopped on day 24, but then reinstituted at day 34–66 after clinical deterioration.

Panackal, A. A. et al. Paradoxical immune responses in non-HIV cryptococcal meningitis. PLoS Pathog. 11, e10047884 (2015)

Screening and Prevention

- Antigen was detectable in the blood at a median of 22 days before development of CNS symptoms
- Retrospective cohort study of over 700 prospectively monitored patients in Cape Town, South Africa, blood samples were taken before initiation of ART
- None of the 661 patients who were cryptococcal antigen negative (93%) went on to develop CM in the first year of ART
- By contrast, at least 7 of 25 patients (28%) who were antigen- positive with no prior history of CM developed CM during this time

French, N. et al. Cryptococcal infection in a cohort of HIV-1-infected Ugandan adults. AIDS 16, 1031–1038 (2002).

Jarvis, J. N. et al. Screening for cryptococcal antigenemia in patients accessing an antiretroviral treatment program in South Africa. Clin. Infect. Dis. 48, 856–862 (2009).

Screening and Prevention

Pre-emptive therapy strategy
Patients at risk (with CD4+ T cell counts <100 cells/µl) are tested for antigen and those who tested positive are given pre-emptive therapy with the widely available and safe oral fluconazole

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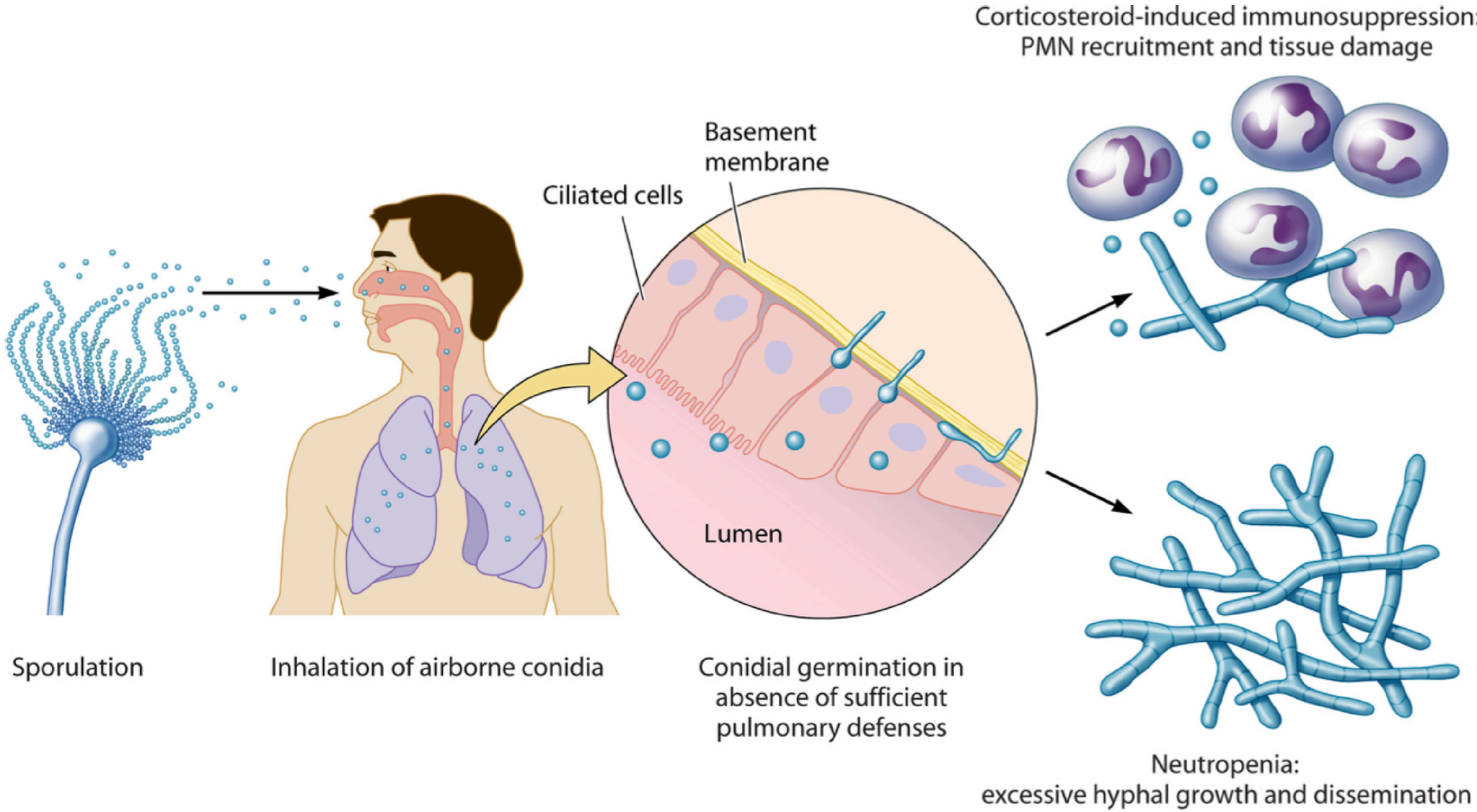
CNS Aspergillosis

Invasive Aspergillosis

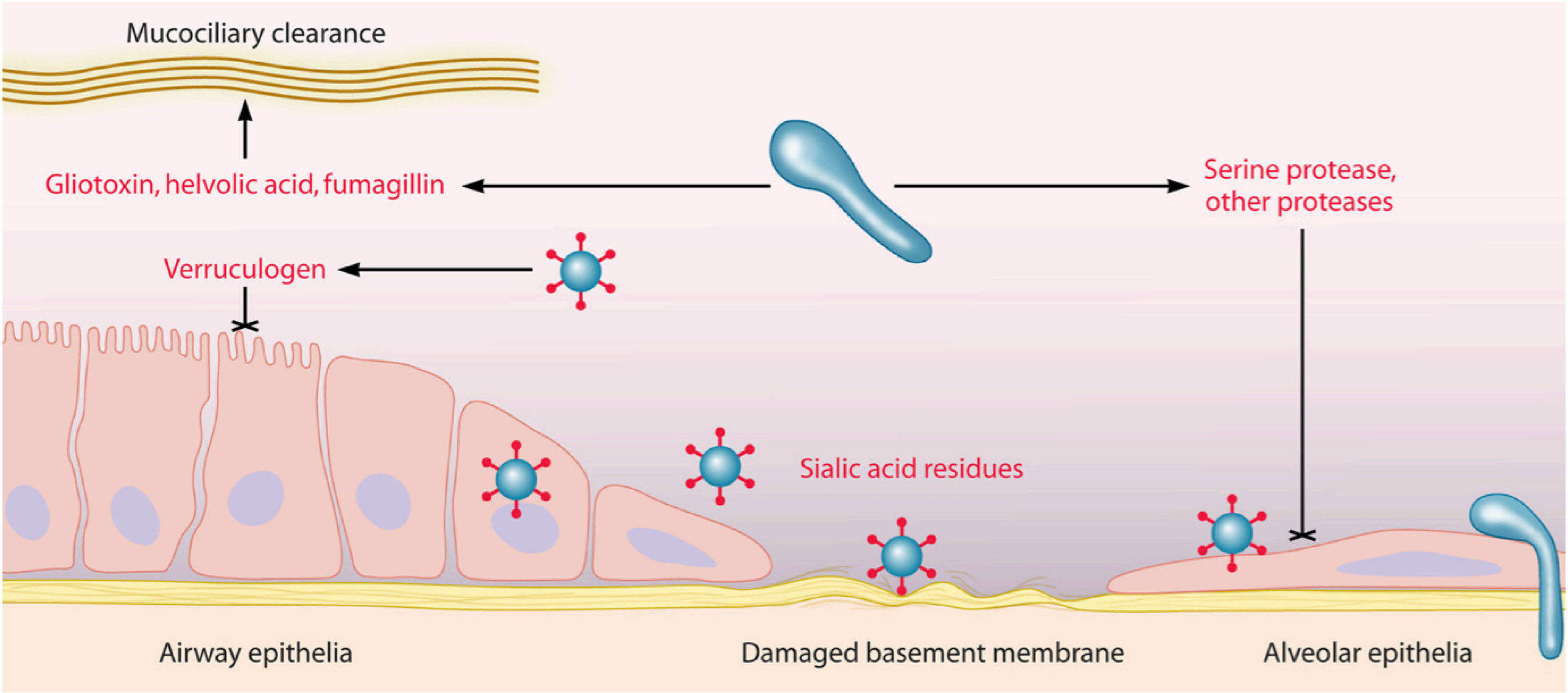
Pathogenesis



Pathogenesis of *Aspergillus fumigatus* in Invasive Aspergillosis Taylor R. T. Dagenais, Nancy P. Keller Clinical Microbiology Reviews Jul 2009, 22 (3) 447-465;

Invasive Aspergillosis

Pathogenesis



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Invasive Aspergillosis

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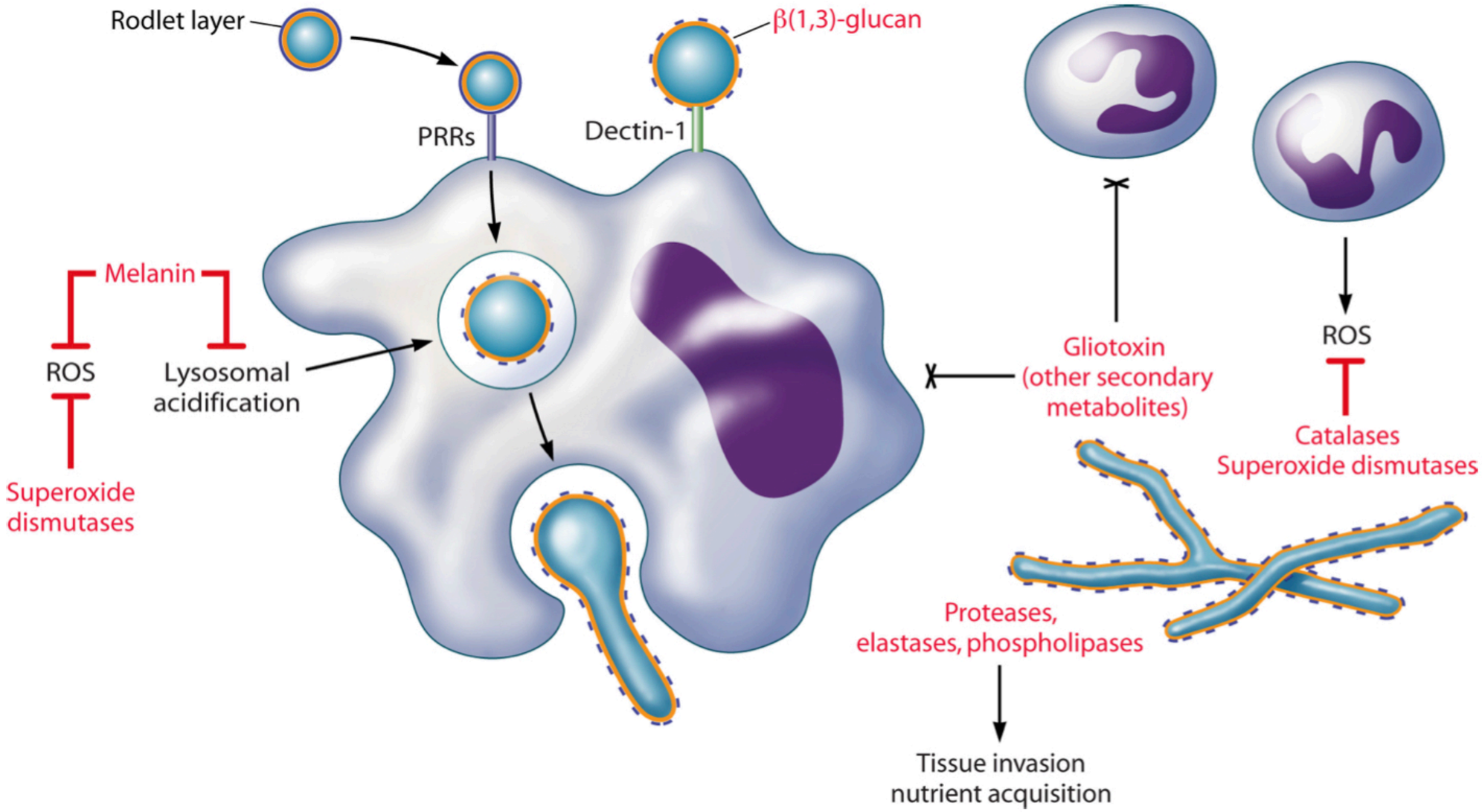

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Invasive Aspergillosis

- 70% of invasive mold infection
- Commonly caused by *Aspergillus fumigatus*
- Risk Factors
  - Neutropenia
  - Chemotherapy
  - Corticosteroid use
  - Transplants (Stem cell or solid organ)

Aspergillus species

Clinical Symptoms

Immunosuppressive gliotoxin and enzymes (proteases, elastases and phospholipases) which hinder the host immune response and facilitate tissue penetration

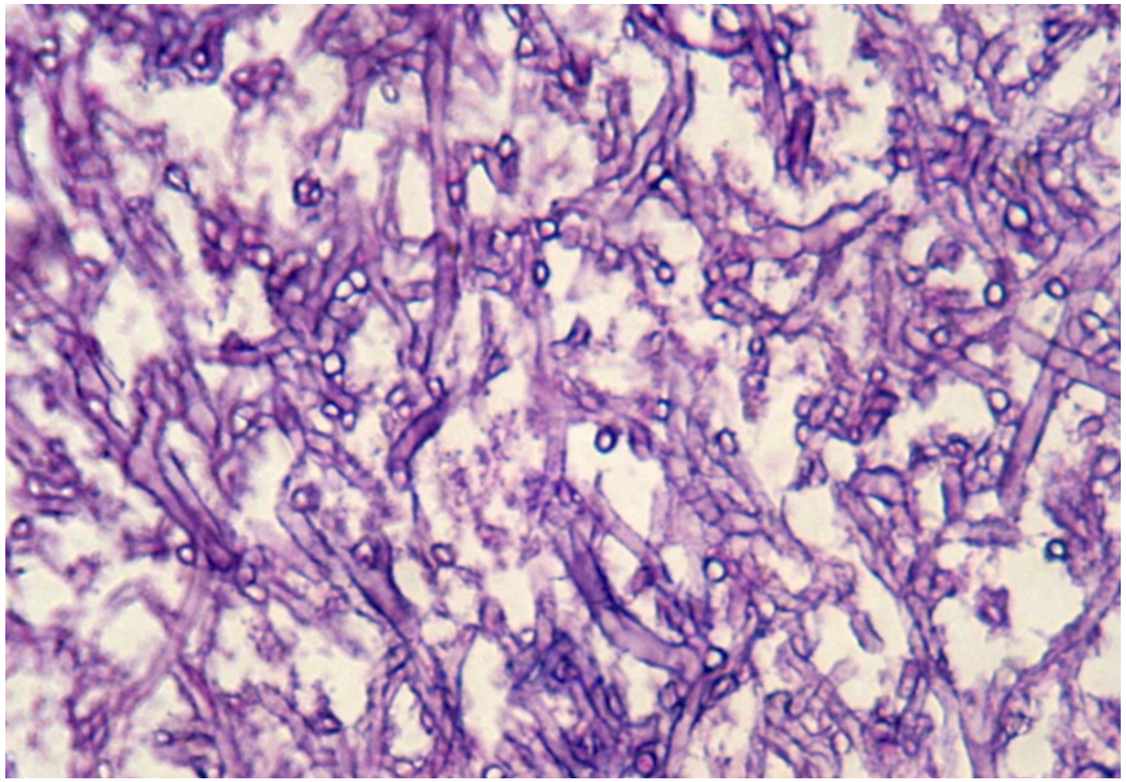
- Aspergillosis is **angioinvasive**, and neurologic manifestations most frequently involve a **CNS vasculitis** of small and medium-sized arteries
- Meningeal involvement is a less common complication and, when present, is typically associated with vasculitis and brain abscesses
- Invasive CNS aspergillosis involving the meninges may also result from **direct invasion** from **adjacent sinonasal structures**, although this occurs much more rarely than hematogenous spread

CONTINUUM (MINNEAP MINN) regarding diagnostic procedures. 2018;24(5, NEUROINFECTIOUS DISEASE):1298 –1326.

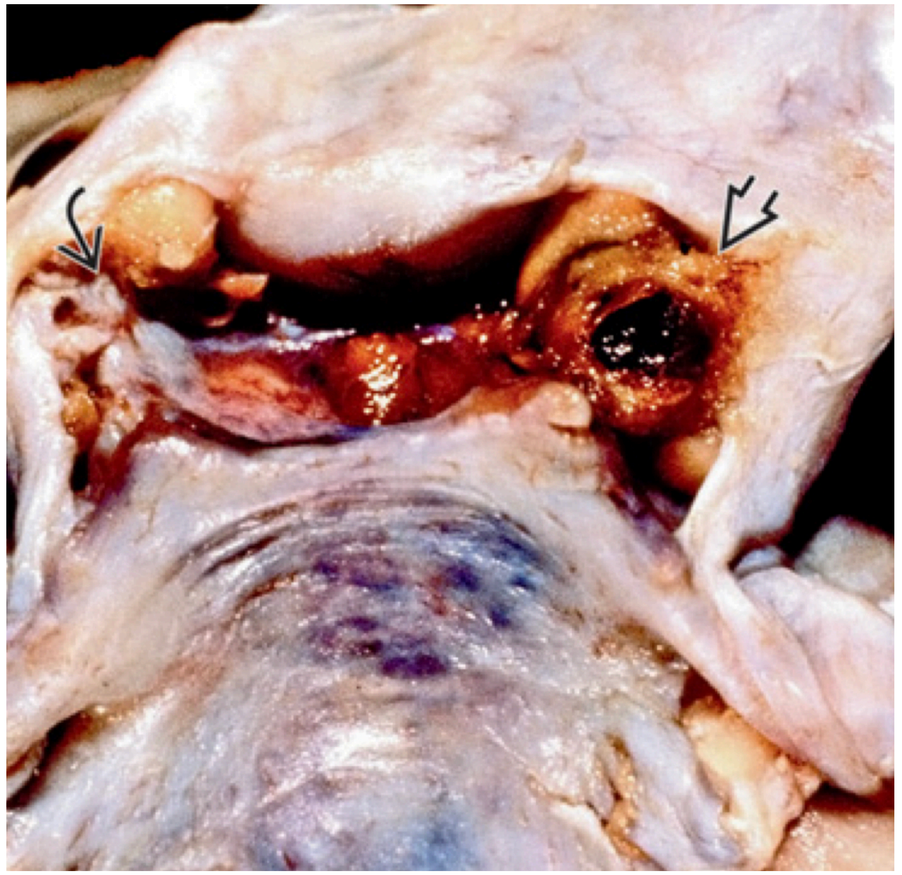
Diagnosis of Invasive Aspergillosis

Definite case

Histopathology : Septate hyphae with acute angle branching



PAS stains Contributed by Dr. Claudia Mendez, Bogota, Columbia.



Autopsy specimen shows aspergillosis invading the paranasal sinuses and skull base. One internal carotid artery is encased by fungus while the other has been occluded . (Courtesy R. Hewlett, MD.)

Diagnosis of Invasive Aspergillosis

CSF fungal culture is only 31% sensitive among all hosts, and 18% in immunocompromised hosts

Galactomannn antigen is a cell wall polysaccharide released by Aspergillus that can be detected in body fluids including CSF,

CSF galactomannan sensitivity is 70–90% and specificity 70–100%

CSF Aspergillus PCR was 75% sensitive

although larger studies are needed to establish the utility of CSF PCR for diagnosis of CNS aspergillosis

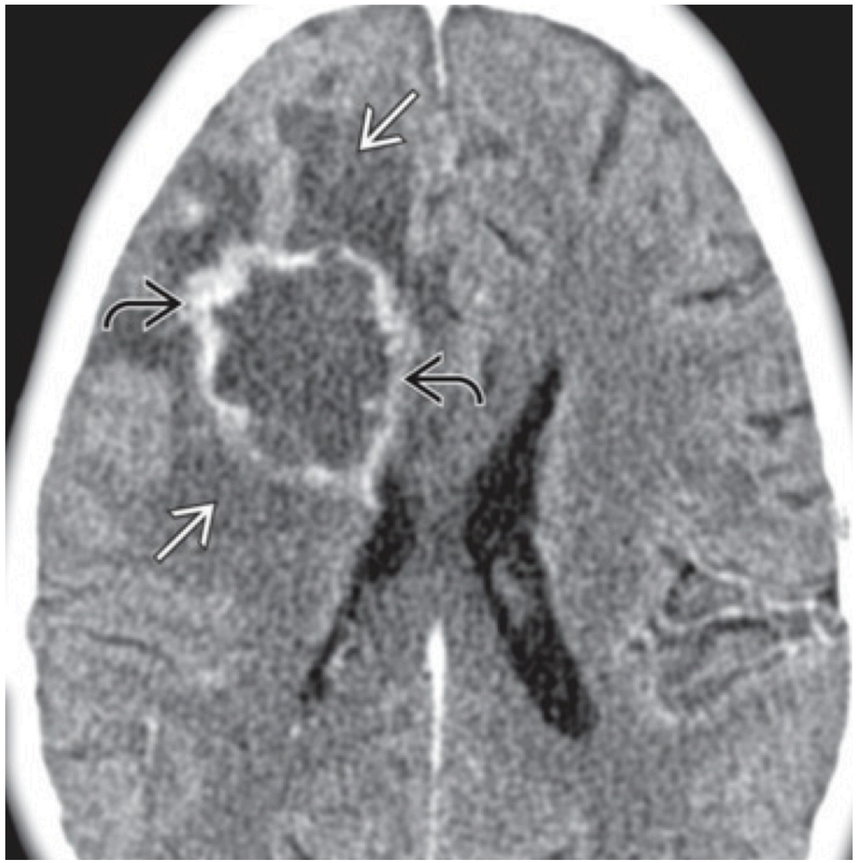
Aspergillus antibody detection in CSF is possible but performance is unreliable

CONTINUUM (MINNEAP MINN) regarding diagnostic procedures. 2018;24(5, NEUROINFECTIOUS DISEASE):1298 –1326.

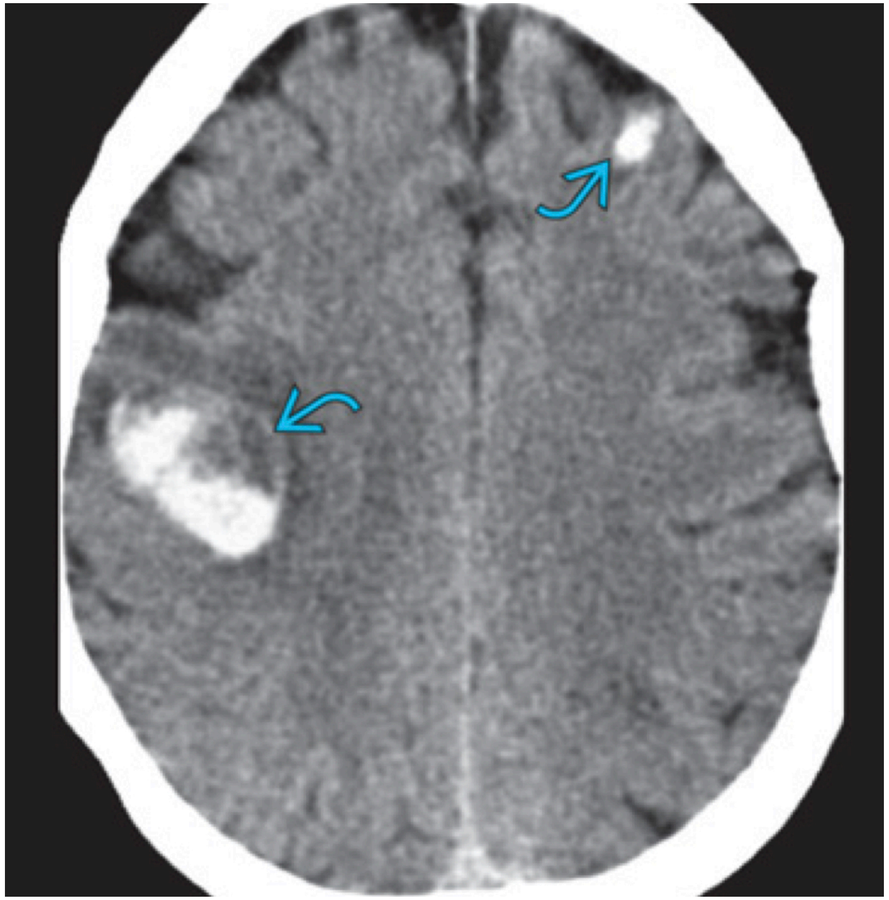
Poplin, V., Boulware, D. R., & Bahr, N. C. (2020). Methods for rapid diagnosis of meningitis etiology in adults. *Biomarkers in medicine*, *14*(6), 459–479.

CNS Aspergillosis

Features on Neuroimaging



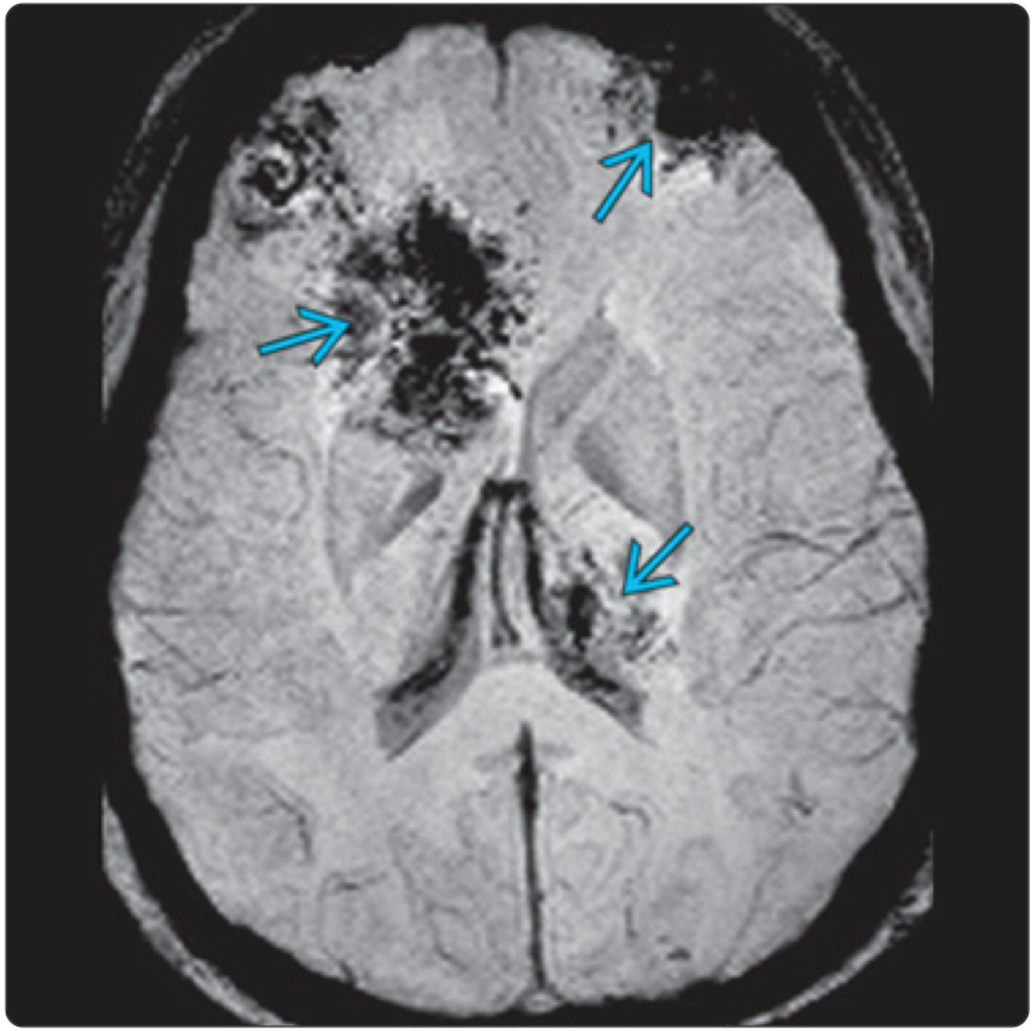
Axial CECT in an immunosuppressed patient shows a large, low-density mass in the right frontal lobe and deep basal ganglia with irregular rim enhancement and surrounding edema ſt with local mass effect. Aspergilloma abscess was found at surgery.

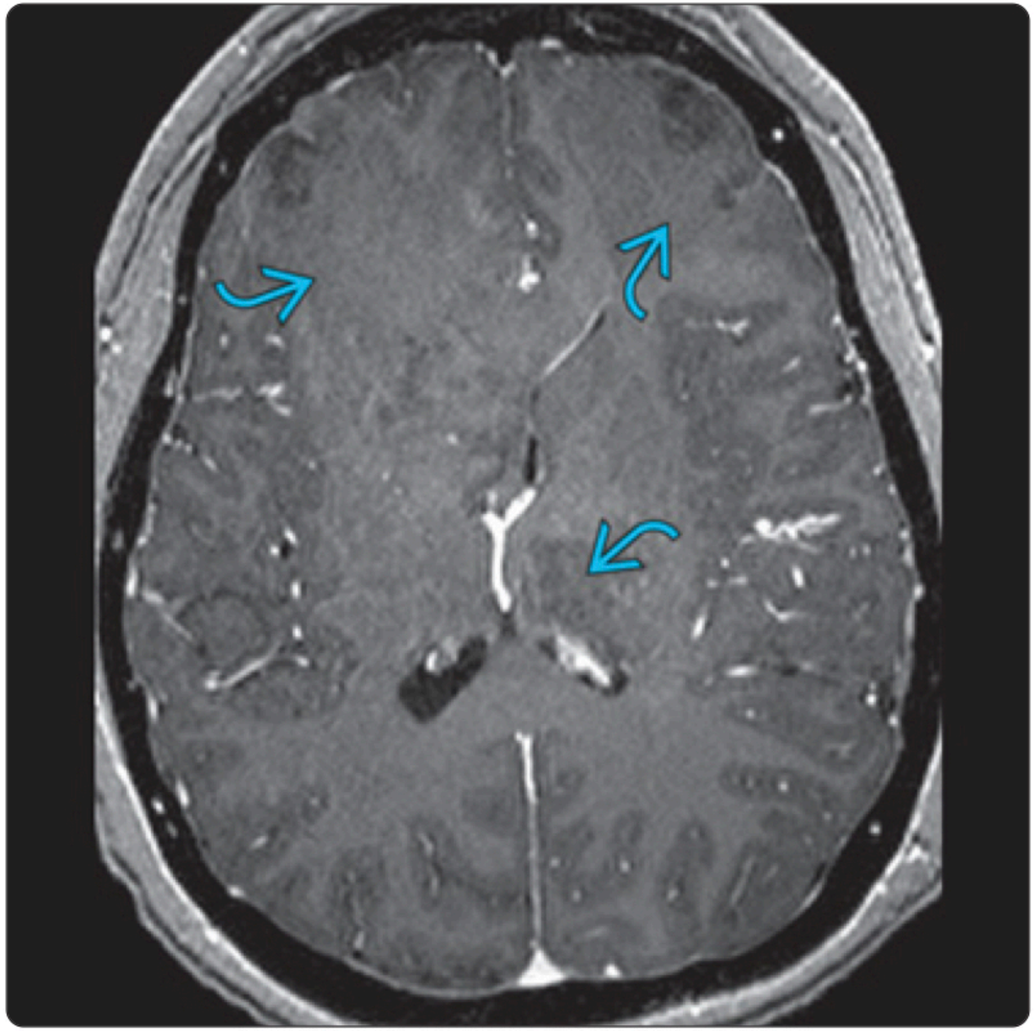


Axial NECT in an immunosuppressed patient shows multifocal parenchymal hemorrhages at the gray- white matter interface. Hemorrhagic mycetomas from angioinvasive aspergillosis were documented at surgery.

Diagnostic Imaging Brain Third edition Elsevier

CNS Aspergillosis





(Left) Axial SWI image in the same patient shows areas of hemorrhage in the regions of diffusion abnormality. (Right) Axial T1+C MR in the same patient does **not** demonstrates any abnormal enhancement in the frontal lobes or left thalamus. Biopsy of the right frontal lobe lesion revealed invasive aspergillosis. Aspergillus infections leads to an infectious vasculopathy resulting in acute infarction, hemorrhage, and cerebritis/abscess.

Diagnostic Imaging Brain Third edition Elsevier

2016 IDSA Guidelines for Management of Invasive Aspergillosis

Primary Treatment

Voriconazole for CNS aspergillosis (strong recommendation)

Duration : at least 6-12 weeks

Alternative Treatment

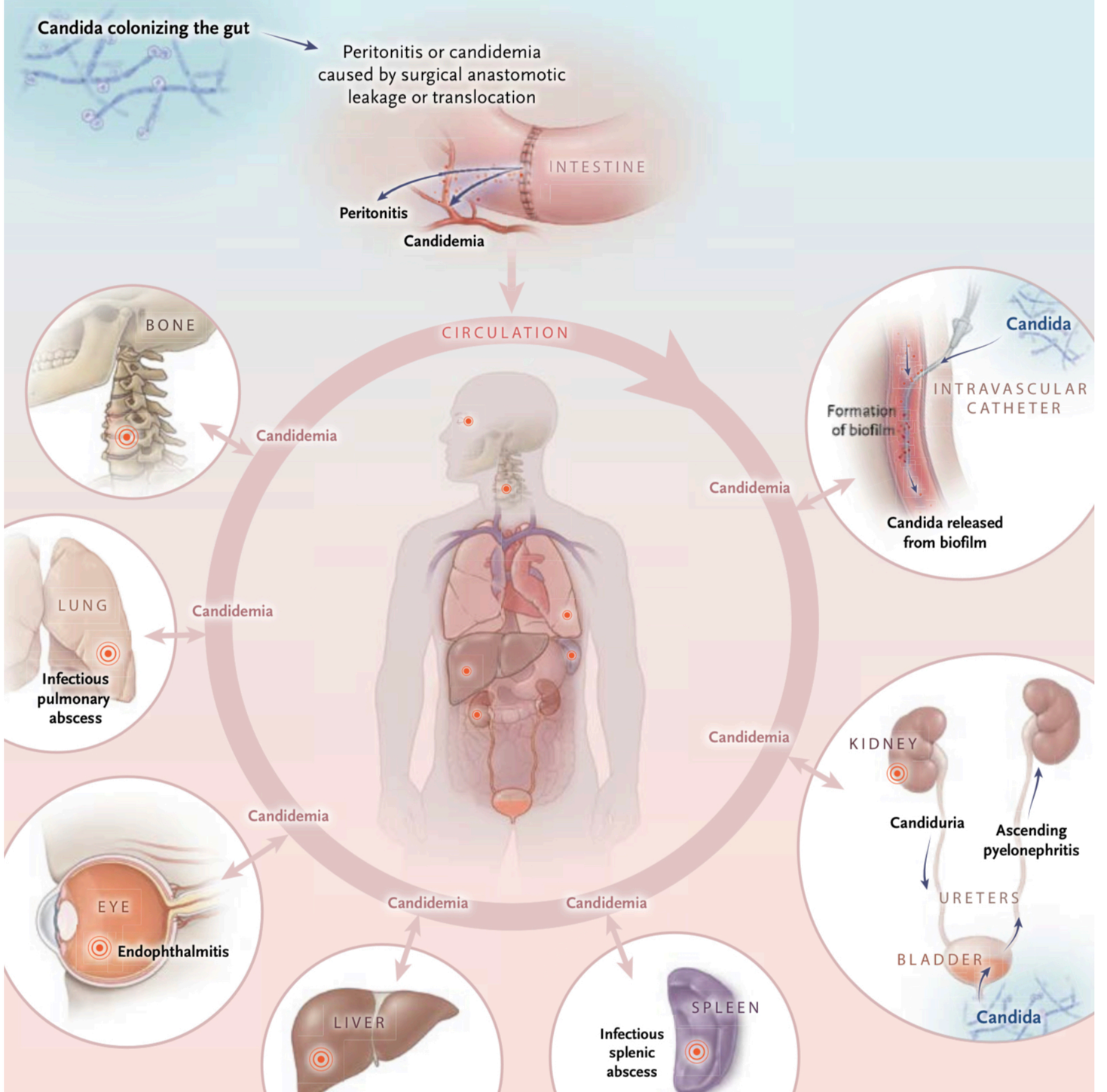
Lipid formulations of AmB are reserved for those intolerant or refractory to voriconazole (strong recommendation; moderate-quality evidence)

Patterson TF, Thompson GR 3rd, Denning DW, Fishman JA, Hadley S, Herbrecht R, Kontoyiannis DP, Marr KA, Morrison VA, Nguyen MH, Segal BH, Steinbach WJ, Stevens DA, Walsh TJ, Wingard JR, Young JA, Bennett JE. Practice Guidelines for the Diagnosis and Management of Aspergillosis: 2016 Update by the Infectious Diseases Society of America. Clin Infect Dis. 2016 Aug 15;63(4):e1-e60

Candida species

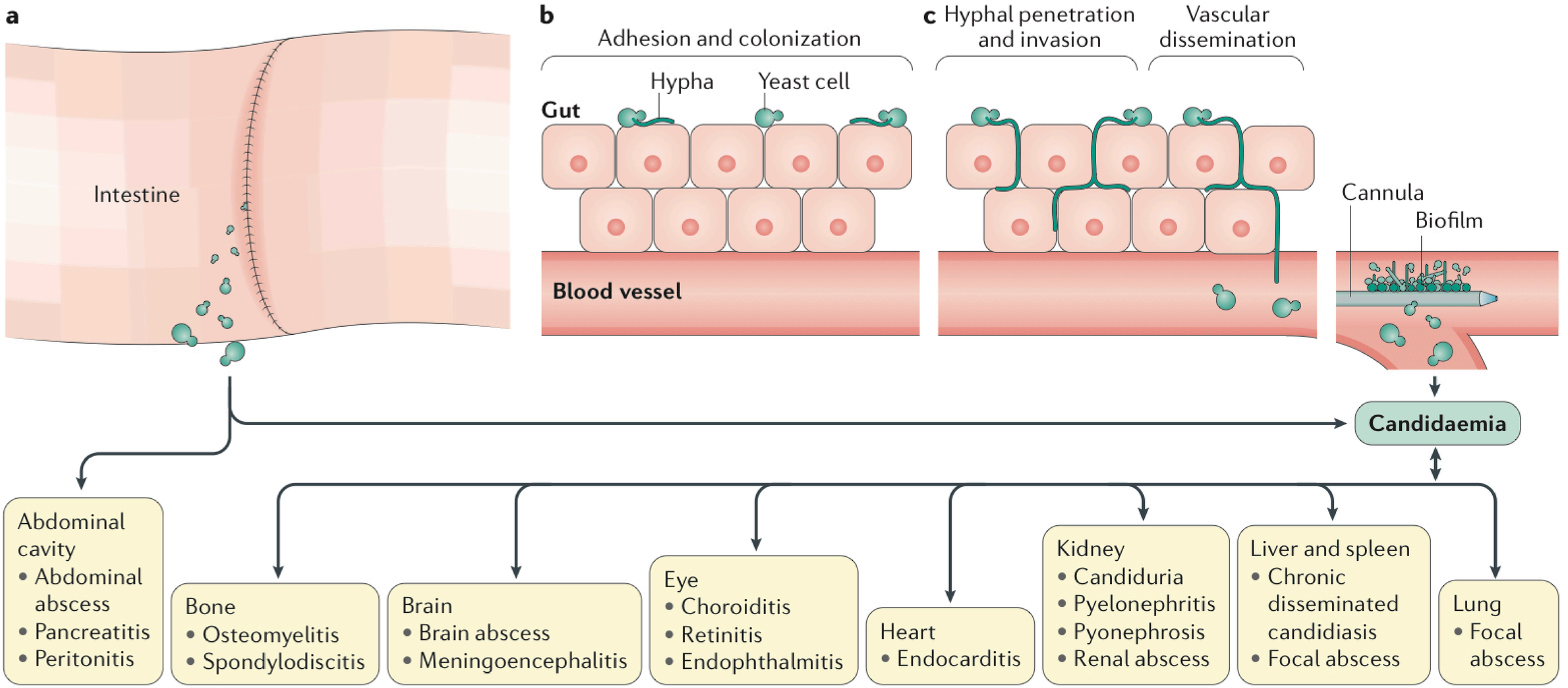
Invasive Candidiasis

Pathogenesis



Kullberg BJ, Arendrup MC. Invasive Candidiasis. N Engl J Med. 2015 Oct 8;373(15):1445-56. doi: 10.1056/NEJMra1315399. PMID: 26444731.

Pathogenesis



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Invasive Candidiasis

is most often caused by *C. albicans*

Risk Factors

Long-term Use of Broad-Spectrum Antibiotics

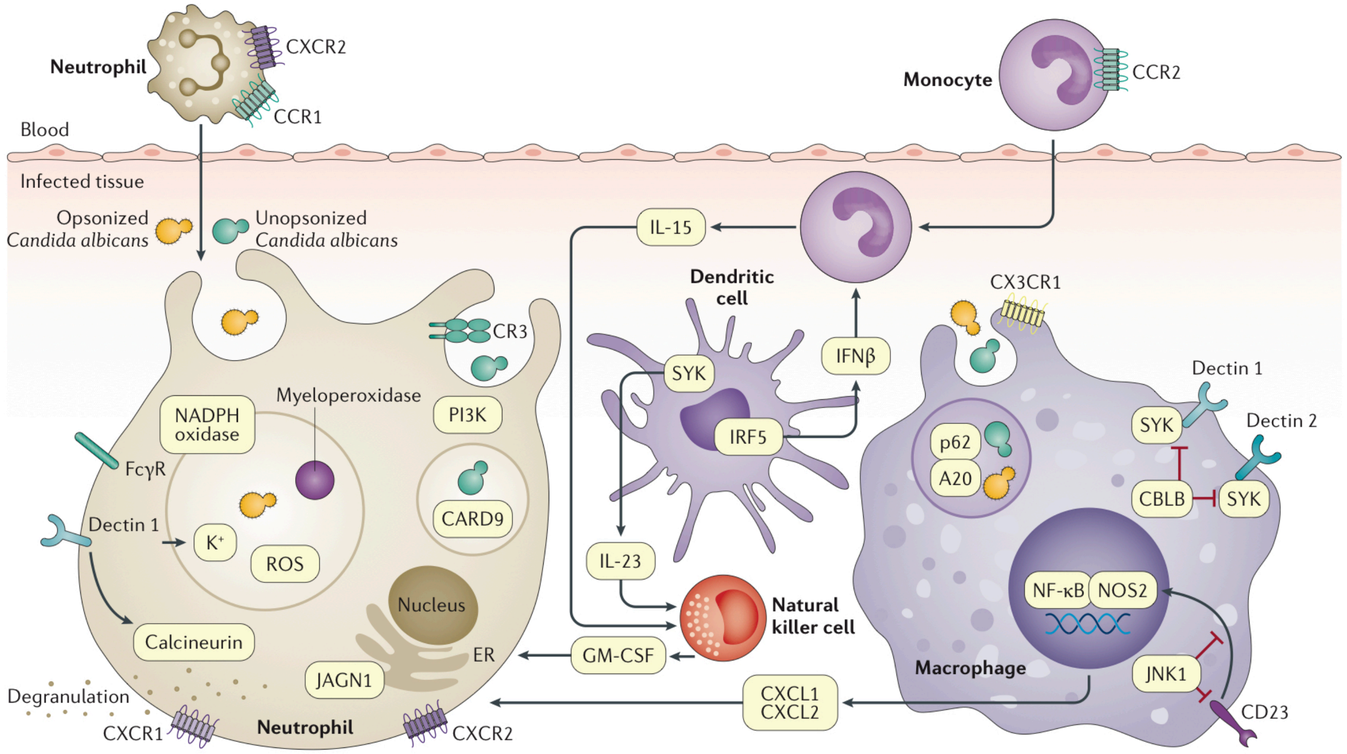
Breach of GI and Cutaneous barriers : Infalmmation/Perforation

Central Vascular Catheters : TPN, HD

Immunosuppression : Chemotherapy-induced neutropenia, Steroid therapy

Hematologic malignancy disease

Solid-organ tumors



Effector mechanisms of myeloid phagocytes for control of invading Candida spp. in infected tissue.

Kullberg BJ, Arendrup MC. Invasive Candidiasis. N Engl J Med. 2015 Oct 8;373(15):1445-56. doi: 10.1056/NEJMra1315399. PMID: 26444731.

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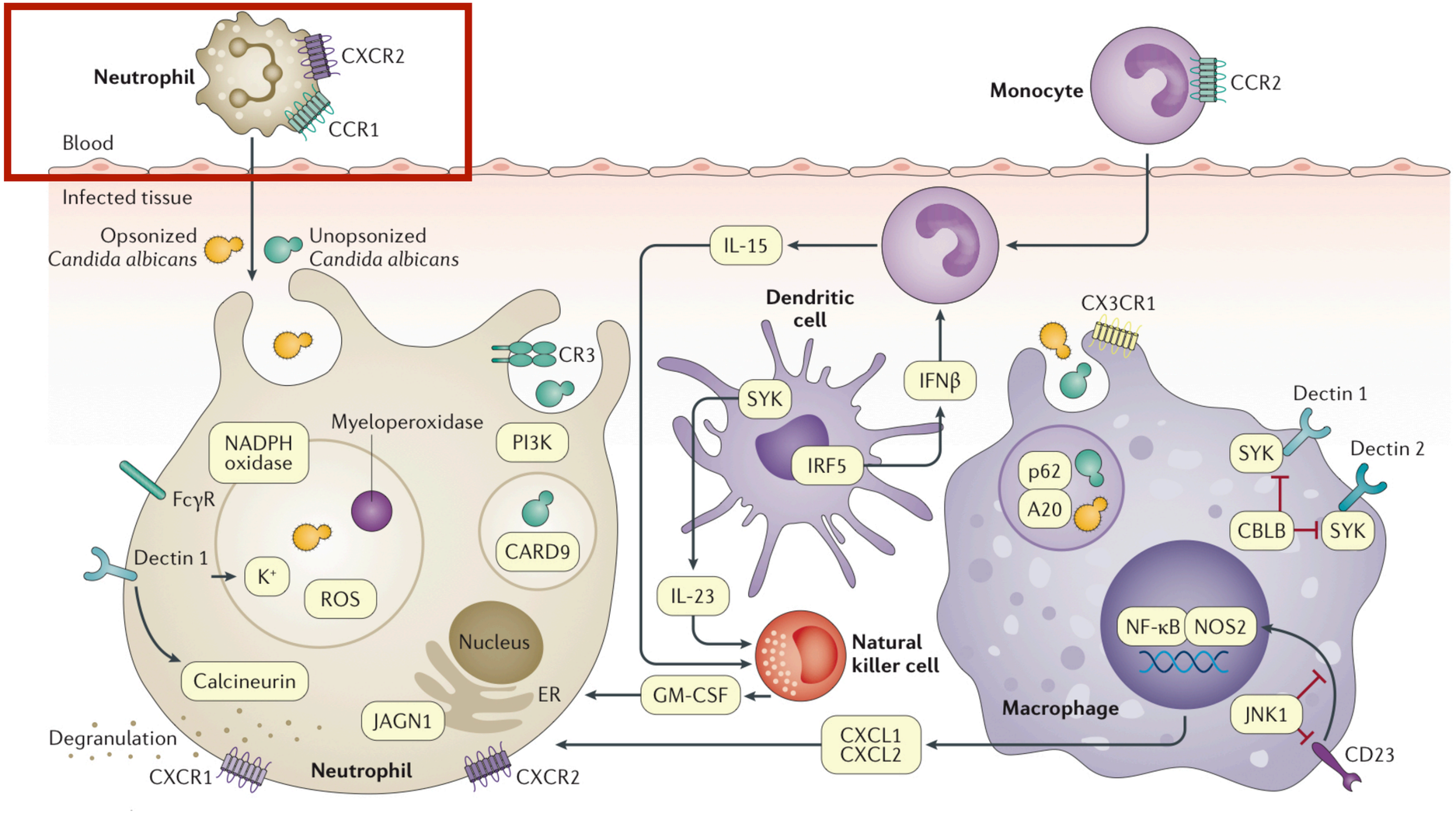

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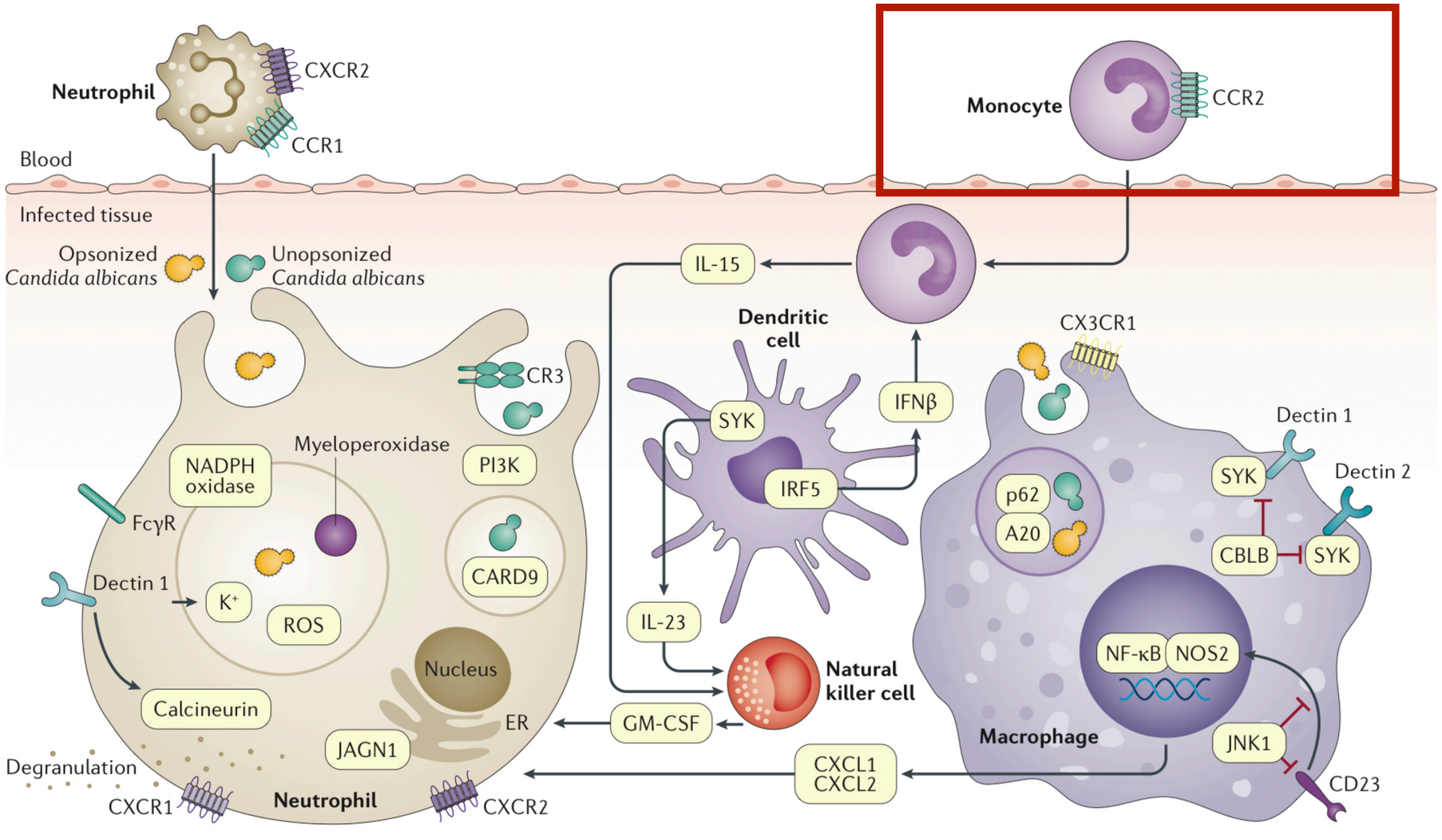

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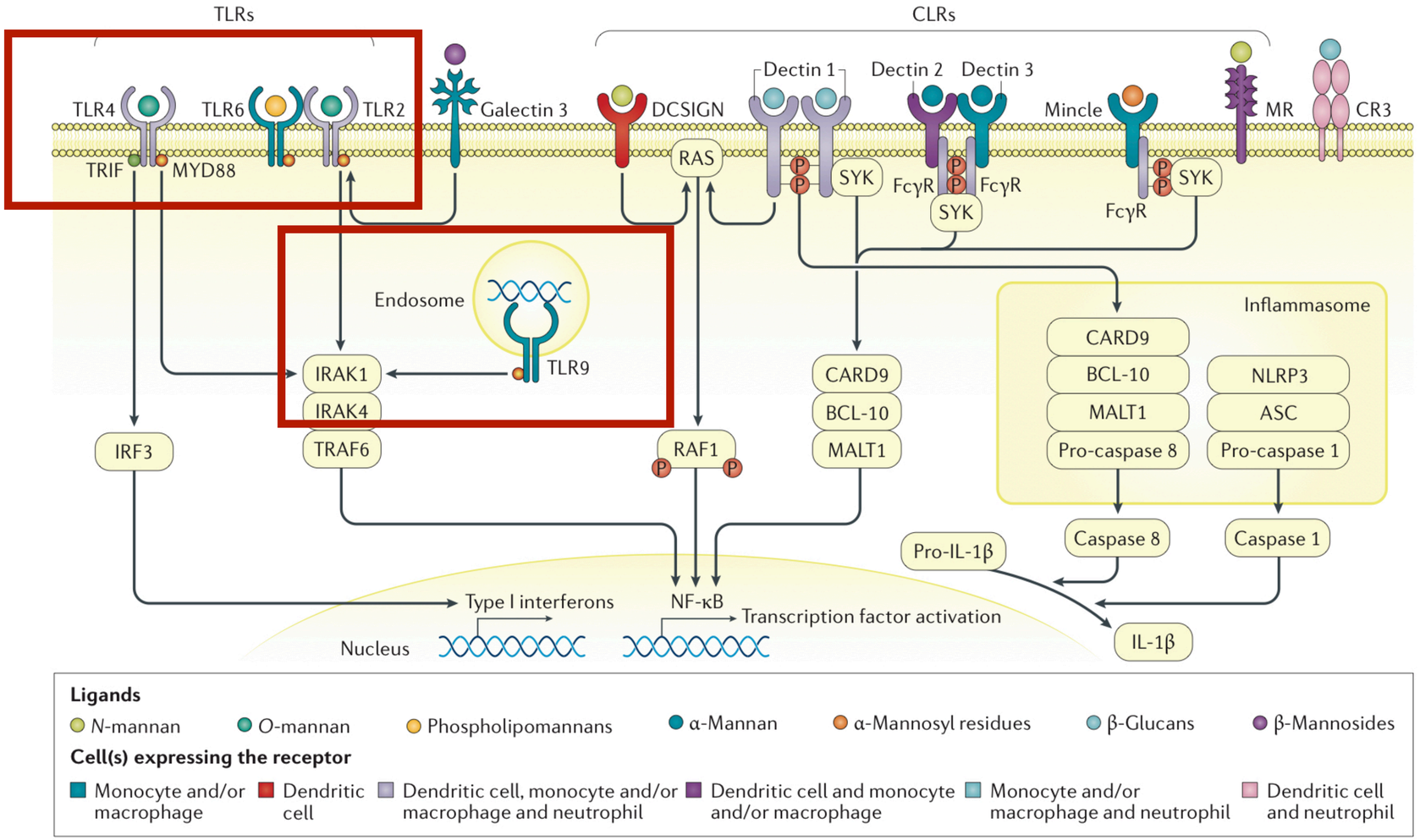

From Review literature , AR CARD9 deficiency, invasive candidiasis typically affects CNS, from case report CARD9 deficiency identified 60 patients with 24 mutations

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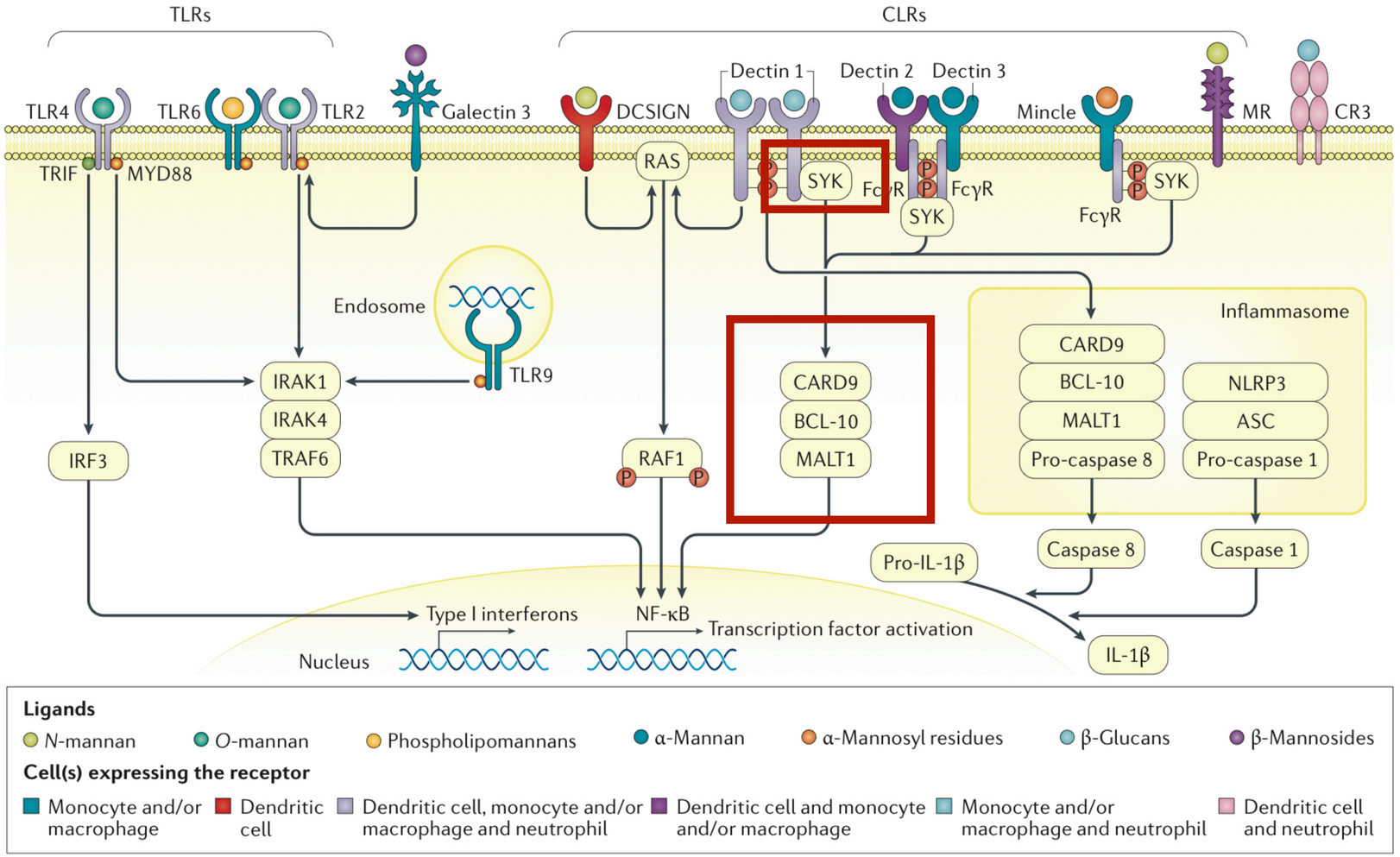

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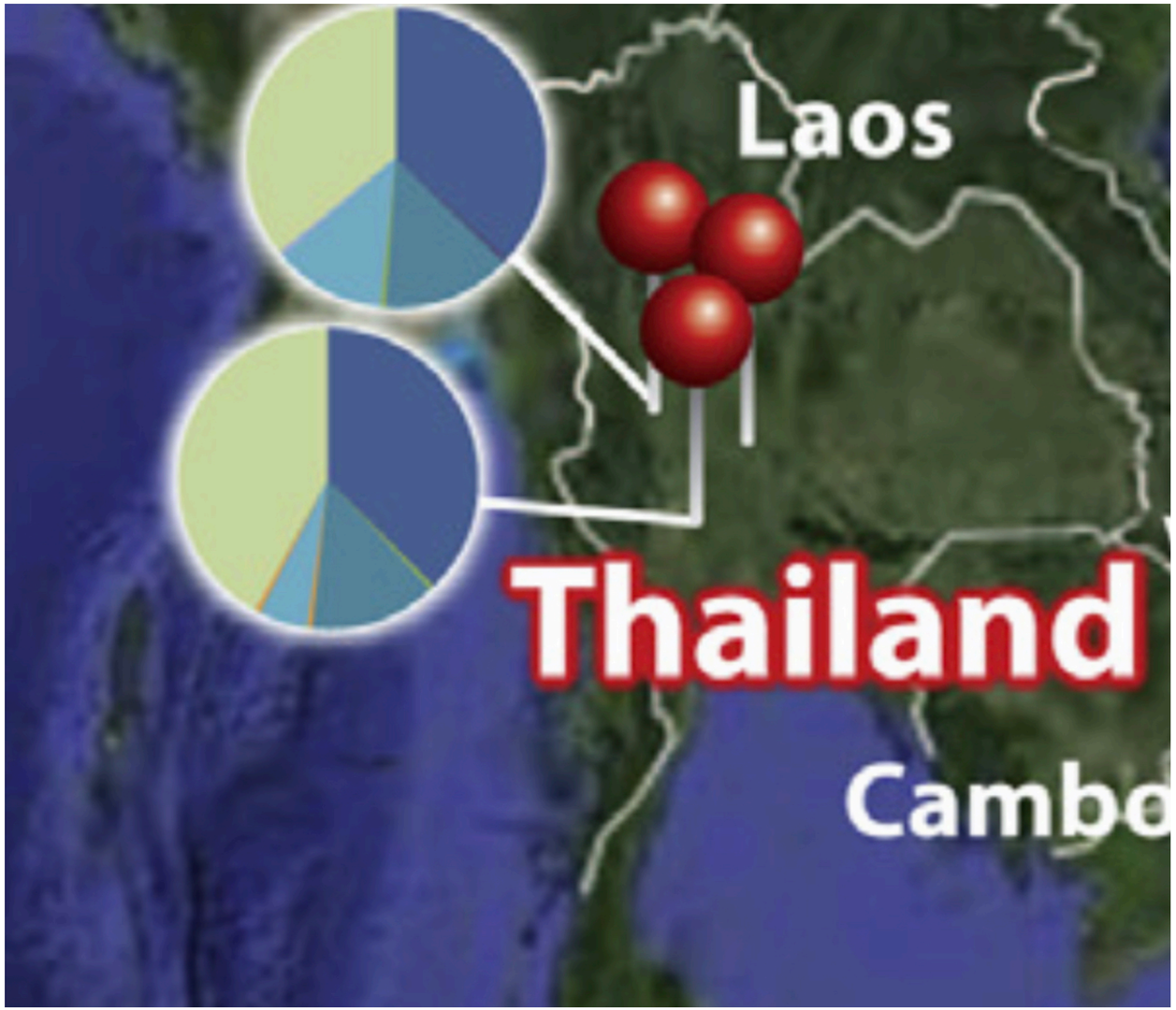
Species Distribution of Candida in Asia



- *Candida albicans*
- *Candida dubliniensis*
- *Candida glabrata*
- *Candida haemulonii*
- *Candida krusei*
- *Candida parapsilosis*
- *Candida pelliculosa*
- *Candida tropicalis*

Tan BH, Chakrabarti A, Li RY, Patel AK, Watcharananan SP, Liu Z, Chindamporn A, Tan AL, Sun PL, Wu UI, Chen YC; Asia Fungal Working Group (AFWG). Incidence and species distribution of candidaemia in Asia: a laboratory-based surveillance study. Clin Microbiol Infect. 2015 Oct;21(10):946-53.

Candida cerebral abscesses

Main Clinico-pathological disease groups

1. Cerebral microabscesses
2. Meningitis
3. Cerebral macroabscesses
4. Vascular complications

Hematogenous spread is likely a frequent source for the development of Candida cerebral abscess, but blood cultures revealed candidemia in only 55%

Lumbar puncture, Candida growth in only 23% of cases

J. Sa¬ nchez±Portocarrero et al. / Diagnostic Microbiology and Infectious Disease 37 (2000) 169 ±179

Andrea M. Fennelly, Amy K. Slenker, Lara C. Murphy, Michael Moussouttas, Joseph A. Desimone, Candida cerebral abscesses: a case report and review of the literature, Medical Mycology, Volume 51, Issue 7, October 2013, Pages 779–784,

Diagnostic Tests for Invasive Candidiasis

Table 2. Performance of Blood Cultures in Autopsy Studies of Invasive Candidiasis

Reference	Year	No. of Patients	Underlying Disease	Sensitivity
Louria (from [13])	1962	19	Hematologic malignancies, solid tumors, medical and surgical conditions	42%
Bodey (from [13])	1966	61	Acute leukemia	25%
Taschdjian (from [13])	1969	17	Malignancies and other medical conditions	47%
Hart (from [13])	1969	16	Hematologic malignancies, solid tumors, transplant, medical and surgical conditions	44%
Bernhardt (from [13])	1972	14	Transplant and surgical conditions	36%
Gaines (from [13])	1973	26	Hematologic malignancies, solid tumors, medical and surgical conditions	54%
Myerowitz (from [13])	1977	39	Hematologic malignancies, solid tumors, medical and surgical conditions	44%
Ness [9]	1989	7	Hematologic malignancies and bone marrow transplant recipients	71%
Singer [37]	1977	16	Hematologic malignancies	31%
Berenguer [13]	1993	37	Mostly hematologic malignancies and solid tumors	43%
Van Burik [38]	1998	62	Bone marrow transplant recipients	52%
Kami [39]	2002	91	Hematologic malignancies	21%
Thorn [40]	2010	10	Hematologic malignancies, gastrointestinal disease, transplant, prematurity	50%

Clancy CJ, Nguyen MH. Finding the "missing 50%" of invasive candidiasis: how nonculture diagnostics will improve understanding of disease spectrum and transform patient care. Clin Infect Dis. 2013 May;56(9):1284-92.

Diagnostic test	Specimen(s)	Advantages	Disadvantages
Fungal culture	Blood	• Enables species identification and subsequent susceptibility testing	• Slow (median detection time 2–3 days) • Sensitivity suboptimal, particularly if high volume (≥60 ml) and a fungal blood culture bottle are not employed
	Tissue and sterile body fluids	• Enables species identification and subsequent susceptibility testing	• Selective media, proper spreading of the sample and 3 days of incubation required for optimal performance
Microscopy	Cerebrospinal fluid, tissue and sterile body fluids	• Highly sensitive, particularly if using fluorescent brightener staining	• No species identification • Lower sensitivity in absence of fluorescent brightener staining
Histopathology	Tissue and sterile body fluids	• Enables evaluation of tissue invasion and inflammation	• No species identification • Lower sensitivity in absence of fluorescent brightener staining
Mannan antigen and antimannan antibody detection	Serum or plasma (EDTA) or cerebrospinal fluid	• Increased diagnostic sensitivity when combined antigen and antibody testing is performed (although in neonates (in any sample) and in cerebrospinal fluid, antigen testing suffices)	• Heavy colonization (many non-sterile body sites culture positive for *Candida* spp. and/or with heavy growth in semi-quantitative culture) could cause positivity for blood testing
β-D-glucan detection	Serum or plasma (EDTA)	• Pan-fungal marker	• No separation between *Candida* spp. and other fungi • Many sources for false positivity
PCR	Blood (EDTA)	• Rapid tests • Some commercial tests are FDA approved	• Commercial tests are expensive • May not detect all species

Kullberg BJ, Arendrup MC. Invasive Candidiasis. N Engl J Med. 2015 Oct 8;373(15):1445-56. doi: 10.1056/NEJMra1315399. PMID: 26444731.

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Sensitivity 79-87% Specificity 82-90%

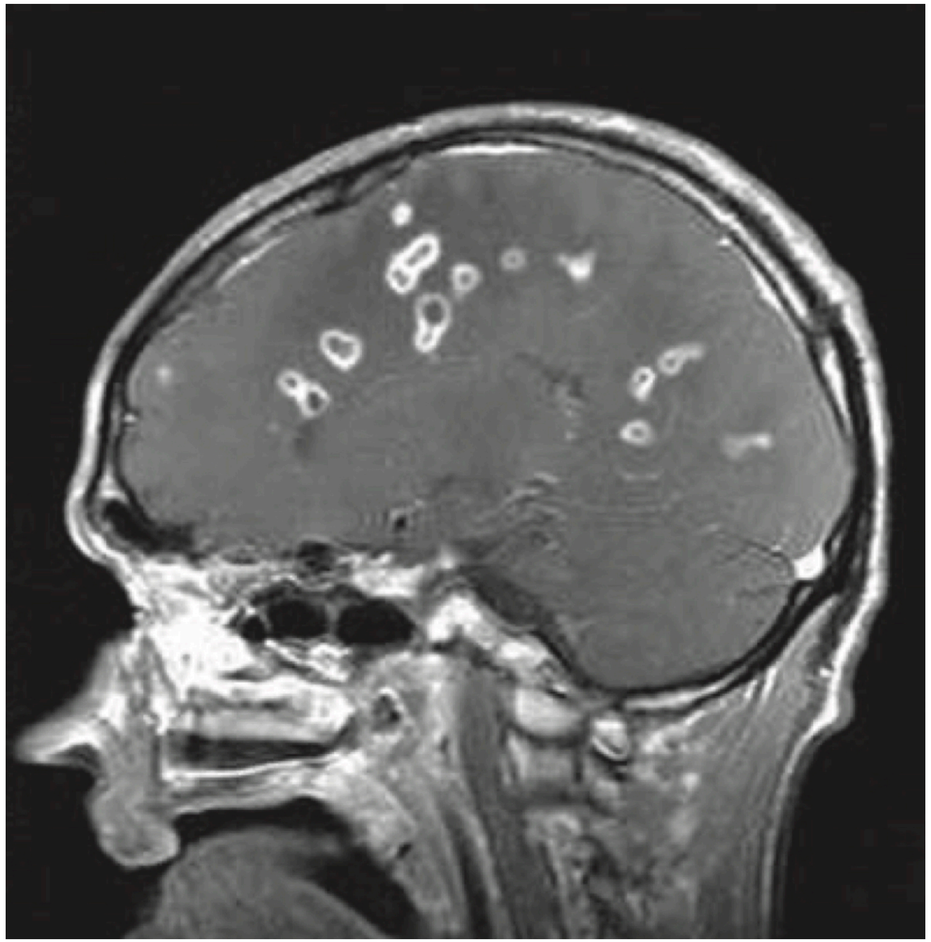
Sensitivity 65-100% Specificity 31-79%

Sensitivity 82-98% Specificity 87-98%

Kullberg BJ, Arendrup MC. Invasive Candidiasis. N Engl J Med. 2015 Oct 8;373(15):1445-56. doi: 10.1056/NEJMra1315399. PMID: 26444731.

Candida cerebral abscess

Features on Neuroimaging



Cerebral magnetic resonance imaging (MRI) revealed innumerable small (1 cm) ring-enhancing lesions within the supratentorial white matter with abundant surrounding vasogenic edema

A 57-year-old homeless man with a history of uncontrolled diabetes mellitus type 2 and prior intravenous drug abuse was admitted to our hospital after being found unresponsive

PE : the patient was afebrile with a heart rate of 68 BPM BP 128/77 mmHg
The patient was cachectic with **diffuse folliculitis and skin excoriations**
No heart murmur or evidence of oropharyngeal candidiasis was found on physical exam
Neurological examination revealed lethargy and disorientation

Stereotactic biopsy of a lesion in the right frontal lobe to obtain an accurate diagnosis

GMS stain of the aspirated material revealed fungal elements, and Candida albicans was obtained in culture

Andrea M. Fennelly, Amy K. Slenker, Lara C. Murphy, Michael Moussouttas, Joseph A. Desimone, Candida cerebral abscesses: a case report and review of the literature, Medical Mycology, Volume 51, Issue 7, October 2013, Pages 779–784,

Treatment for CNS Candidiasis

IDSA guidelines recommened treatment of CNS Candidiasis

Liposomal AmB 5 mg/kg daily with or without oral flucytosine 25 mg/kg 4 times daily

For step-down therapy after the patient has responded to initial treatment :
Fluconazole 400 –800 mg (6–12 mg/kg) daily

Therapy should continue until all signs and symptoms and CSF and radiological abnormalities have resolved

Infected CNS devices, including ventriculostomy drains,shunts, stimulators, prosthetic reconstructive devices, and biopolymer wafers that deliver chemotherapy **should be removed** if possible

For patients in whom a ventricular device **cannot** be removed, **AmB deoxycholate** could be administered through the device **into the ventricle** at a dosage ranging from 0.01mg to 0.5 mg in 2 mL 5% dextrose in water

uez, Thomas J. Walsh, Theoklis E. Zaoutis, Jack D. Sobel, Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America, Clinical Infectious Diseases, Volume 62, Issue 4, 15 February 2016, Pages e1–e50

Micafungin

Micafungin sodium	sterile pwdr (เฉพาะ 50mg)	จ(2)	5.2 Antifungal drugs	เงื่อนไข : ใช้รักษา Invasive candidiasis ที่ดื้อต่อยา fluconazole หรือไม่สามารถใช้ conventional amphotericin B ได้ โดยมีแนวทางกำกับการใช้ยาเป็นไปตามรายละเอียดในภาคผนวก 3

[illegible] Fluconazole [illegible] candida [illegible] Fluconazole [illegible] non-albicans Candida [illegible]

[illegible] Triazole [illegible] 7 [illegible] 3 [illegible]

[illegible] Fluconazole [illegible] 5 [illegible] candida

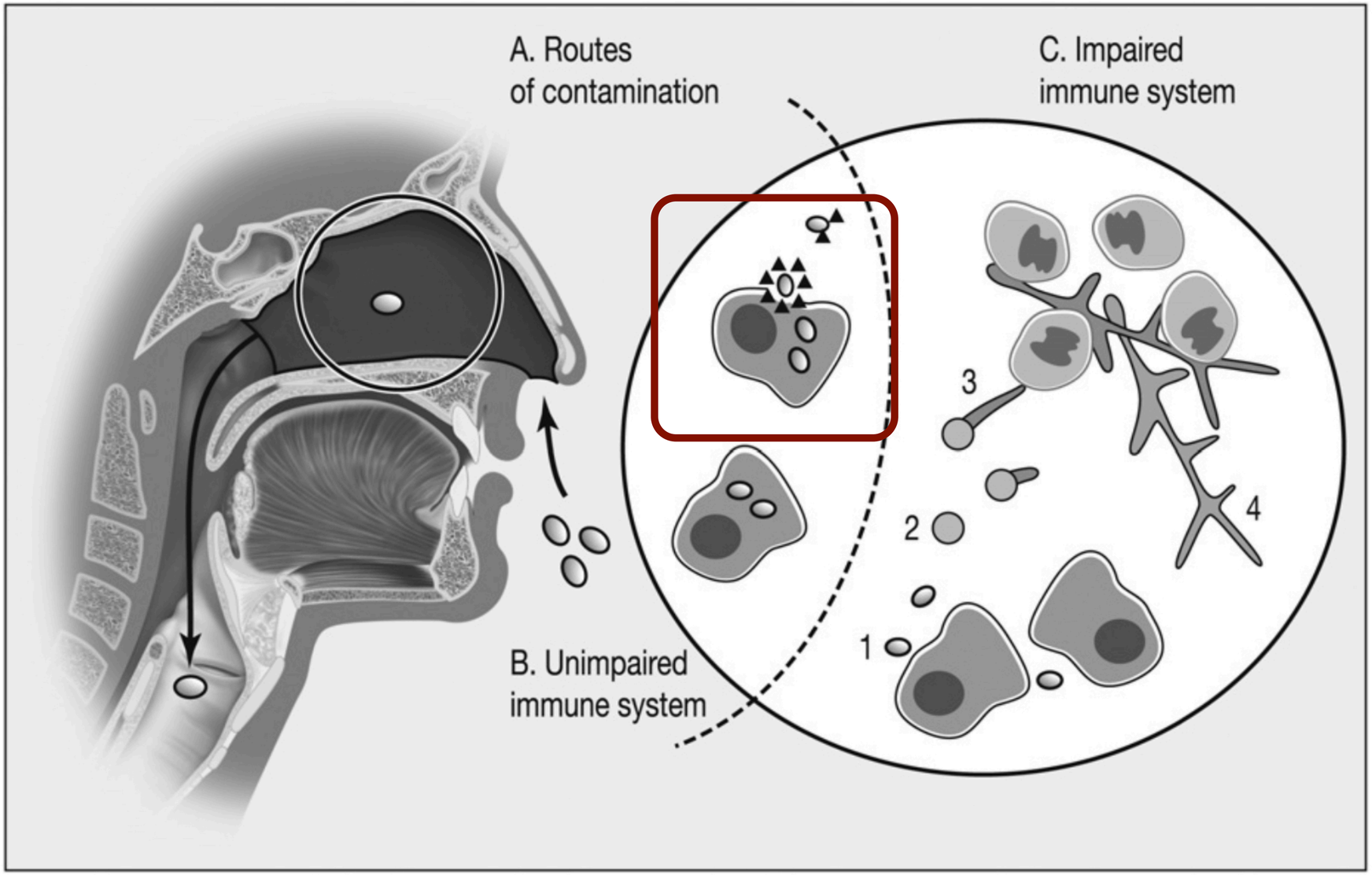
[illegible] Amphotericin B [illegible] 3 [illegible]

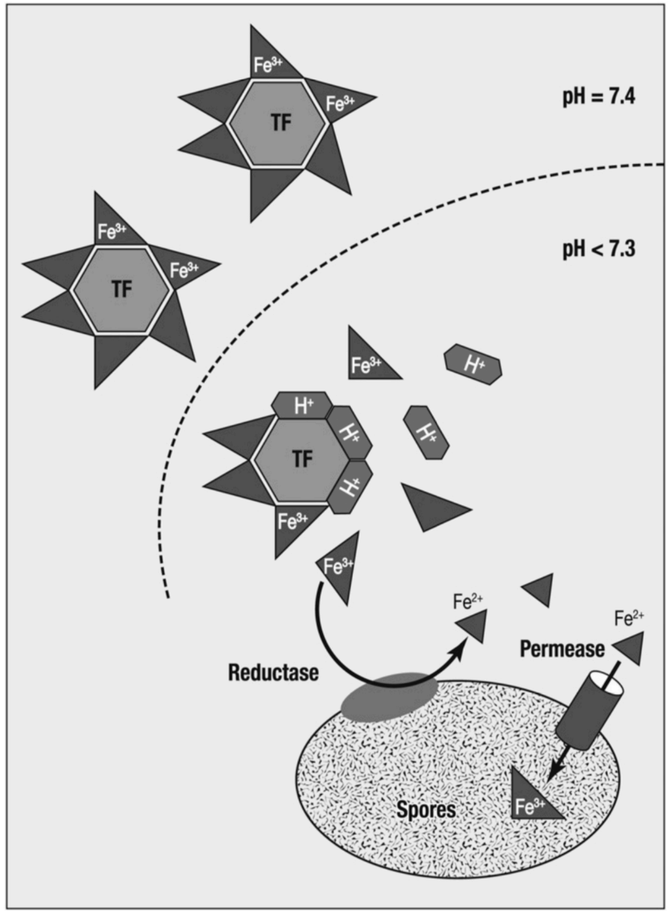
GFR< 60 ml/min [illegible] CKD / on long term RRT

[illegible]

Rhinocerebral Mucormycosis

Rhinocerebral Mucormycosis





Changes in iron metabolism in diabetes related to mucormycosis pathogenesis

B. Rammaert et al. / Diabetes & Metabolism 38 (2012) 193–204

Clinical Features of Mucormycosis

- Nasal obstruction or congestion with noisy breathing
- Headache, odontalgia, sinusitis with low-grade fever and unilateral facial swelling, maxillary pain and hyposmia or anosmia

CNS invasion presenting as : seizures, coma , CN palsy, Hemiplegia, Brain Abscess

Atypical clinical presentations with facial nerve palsy caused by extension of the disease into the infratemporal fossa

2nd Most common invasion in patient with DM : Pulmonary involvement , 13%

3rd Most common invasion in patient with DM : Skin involvement , 10%

B. Rammaert et al. / Diabetes & Metabolism 38 (2012) 193–204

Mucormycosis

Diagnosis

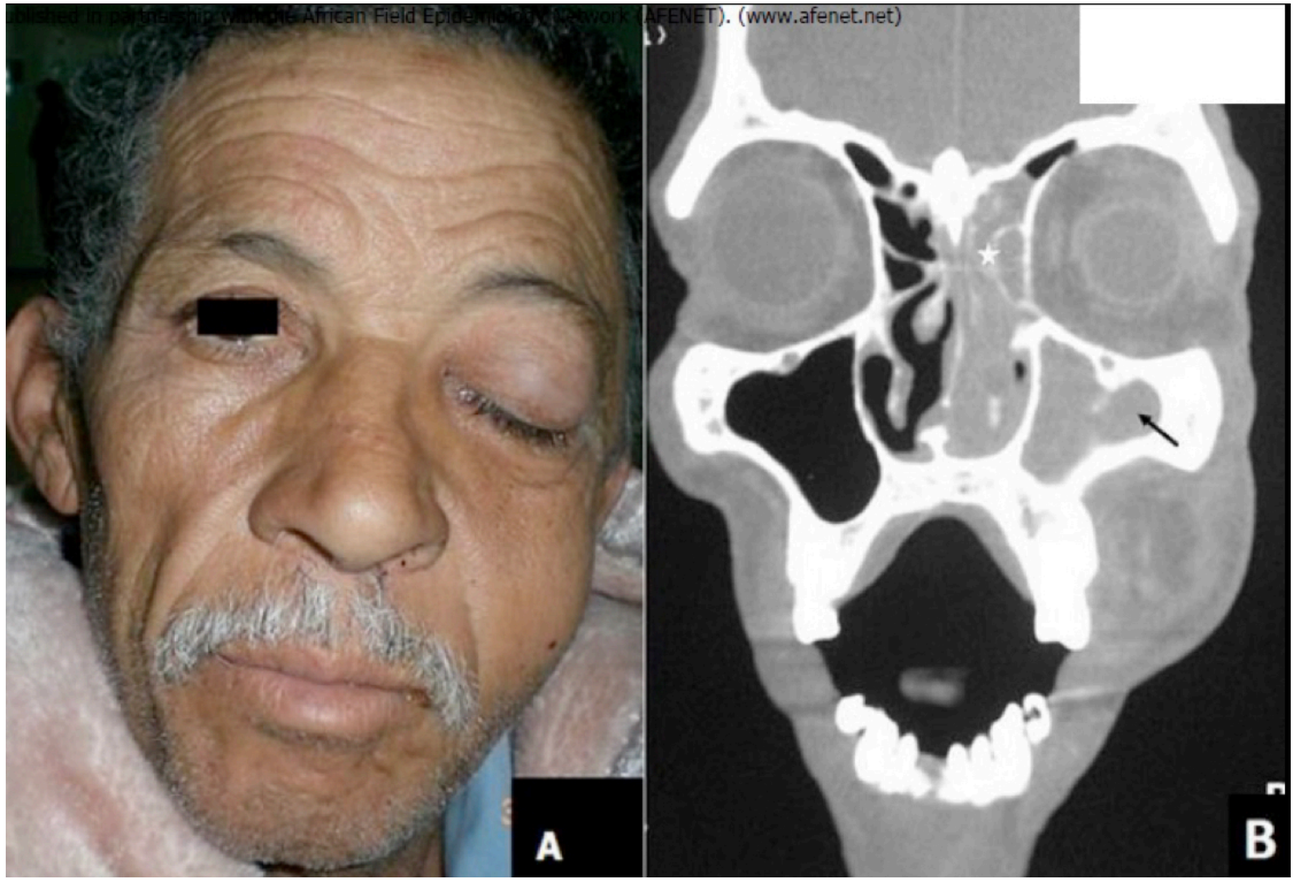
- Proven mucormycosis in the context of a compatible infectious process, tissue biopsies and/or positive cultures obtained from sterile sites

- Probable mucormycosis diagnosis requires the association of host factors : DM with clinical and/or radiological signs compatible with mucormycosis, and direct examination or a positive culture isolated from a sample obtained from a pathological site

B. Rammaert et al. / Diabetes & Metabolism 38 (2012) 193–204

Rhinocerebral mucormycosis

Spreading via direct extension with angioinvasion



J Fungi 2018; 4(90): 1-17.

Left eye ptosis and left cheek edema
CT: soft tissue opacification of left maxillary and ethmoid sinuses

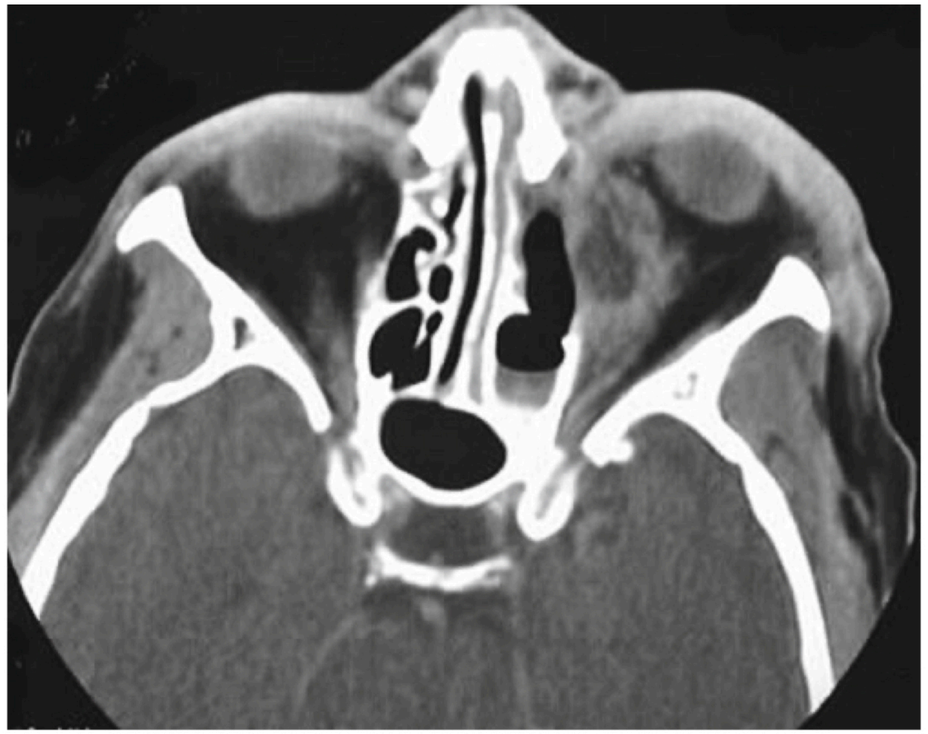
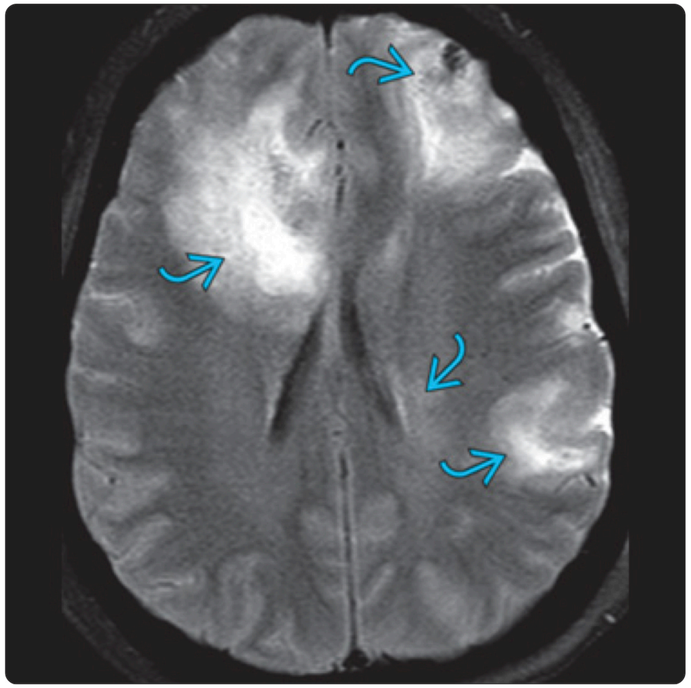
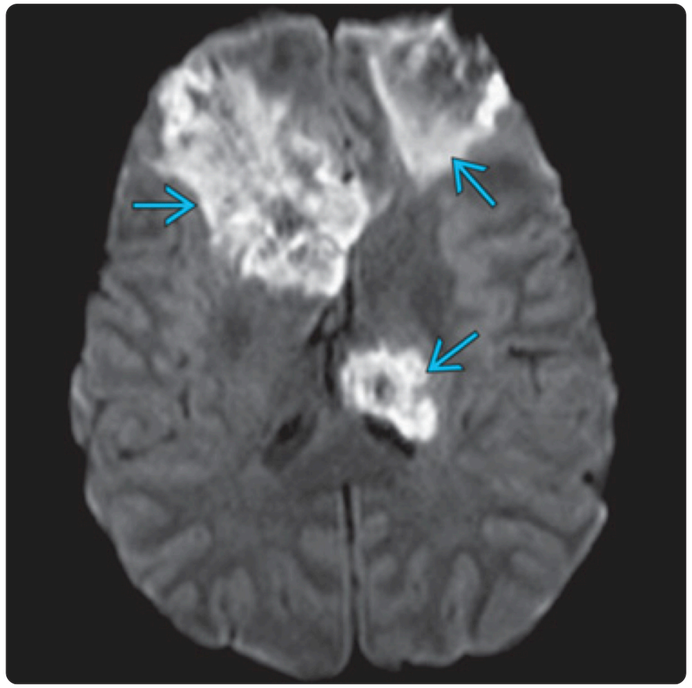


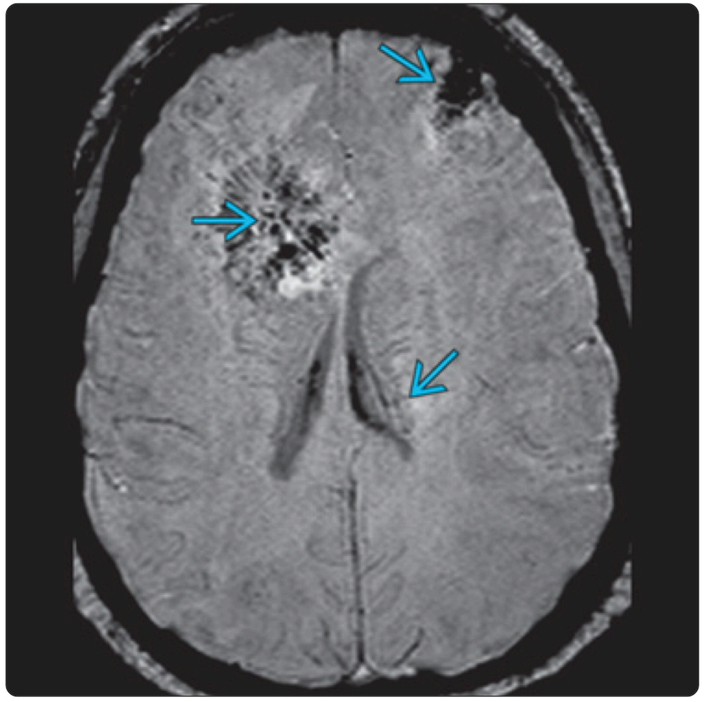
Fig. 22.25 Orbital mucormycosis. Image is a post-contrast axial CT section through the ethmoidal bridge. This case illustrates changes of a left subperiosteal, mesial, orbital abscess. There is little evidence of ethmoid sinusitis. However, it is not uncommon, as in this case, that invasive fungal infections arising either from sinusitis or rhinitis may have only subtle mucosal thickening on imaging, yet still can permeate bone creating soft tissue abscesses in the skull base

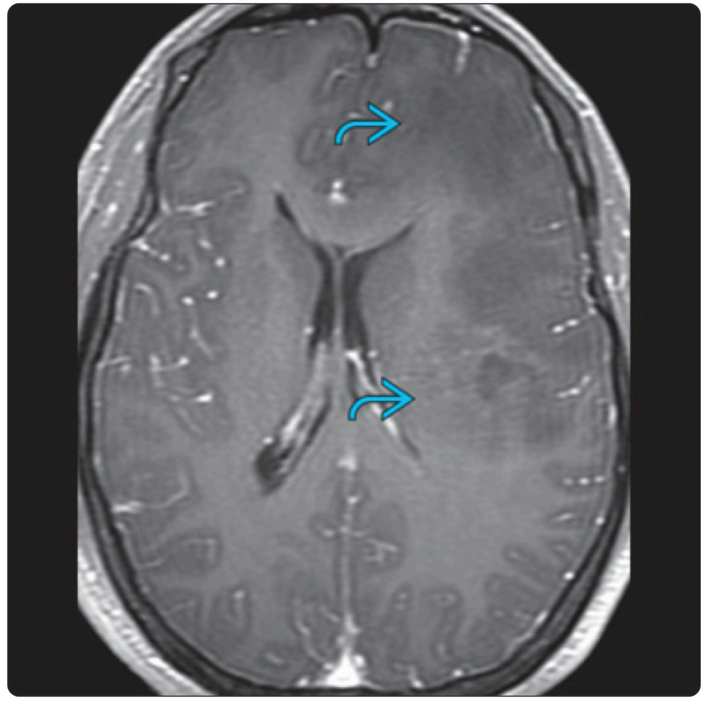
A.J. Layon et al. (eds.), Central Nervous System Infection Textbook of Neurointensive Care
DOI 10.1007/978-1-4471-5226-2_22,





(Left) Axial FLAIR MR in a patient with ALL status post stem cell transplant demonstrates large hyperintense areas involving the cortex, subcortical white matter, and basal ganglia. There is mass effect on the lateral ventricles greater on the right.
(Right) Axial DWI in the same patient shows corresponding large areas of restricted diffusion due to infarction.





(Left) Axial SWI MR in the same patient shows multiple punctate "blooming" foci within the areas of FLAIR signal abnormality consistent with petechial hemorrhages.
(Right) Axial T1+C MR in the same patient does not show any significant enhancement

Angioinvasive mucormycosis was found at surgery.

Angioinvasive fungi (Mucor, Aspergillus) produce enzyme elastase which compromises blood vessel wall leading to inflammatory reaction, vasculitis, thrombosis, and infarction

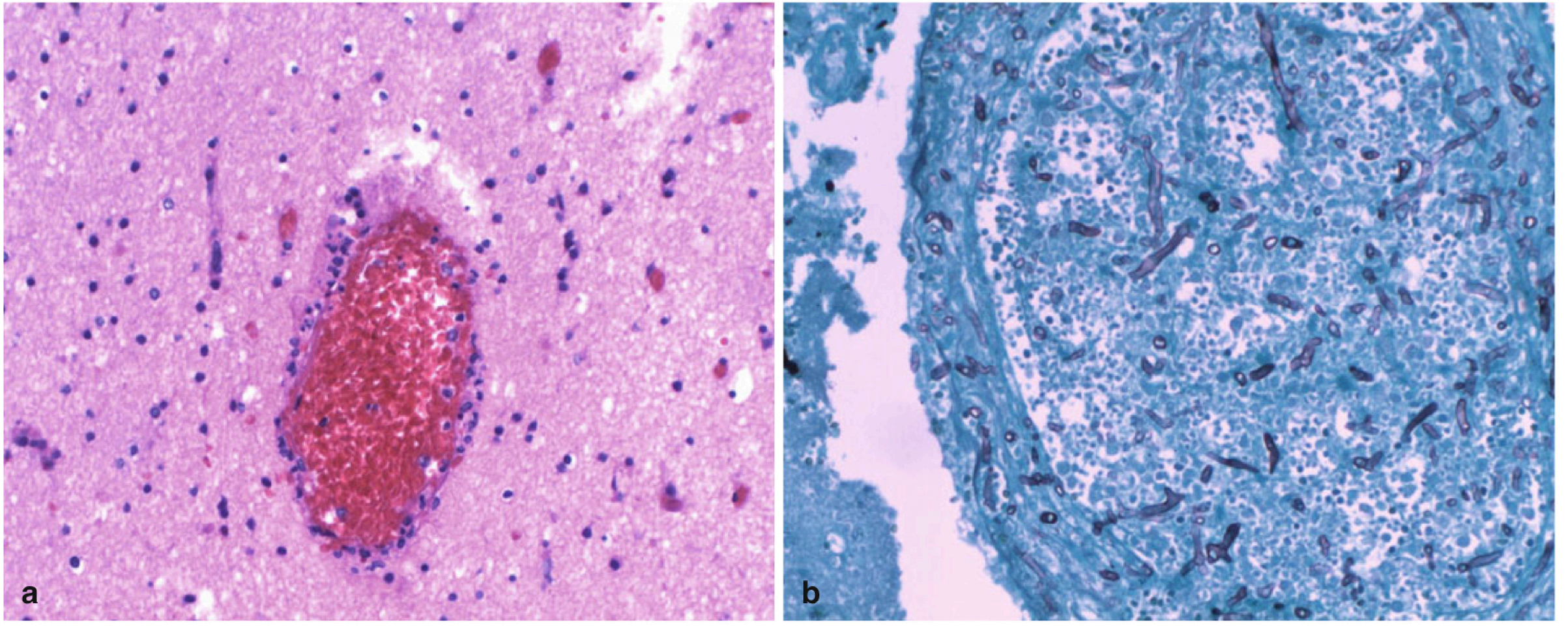


Fig. 22.24 (**a**) A 63-year-old male with disseminated mucor infection. Shows CNS vasculitis with neutrophils invading CNS parenchymal vessels with early vessel wall destruction (H&E, 20×). (**b**) Same patient. Features a Gomori methenamine silver (GMS)-stained specimen demonstrating angioinvasion by fungi with broad aseptate hyphae and right-angle branching (GMS, 20×) (Both courtesy of Anthony Yachnis, MD, and Kelly Devers, MD, University of Florida College of Medicine)

A.J. Layon et al. (eds.), Central Nervous System Infection Textbook of Neurointensive Care, DOI 10.1007/978-1-4471-5226-2_22,

Rhinocerebral Mucormycosis

Treatment

- Treatment of the condition is based on three main principles
  - **Rapid reversal of underlying predisposing factors**
  - Antifungal therapy with **L-amphotericin B 1 mg/kg/day**
  - Surgical intervention : Extensive surgical debridement of necrotic tissue

B. Rammaert et al. / Diabetes & Metabolism 38 (2012) 193–204

Parasitic disease of the Nervous system in Thailand

Parasitic disease of the Nervous system in Thailand

Angiostrongylus costaricensis

Gnathostoma spinigerum

Cysticercus cellulosae

Vejjajiva A. **Parasitic diseases of the nervous system in Thailand**. Clin Exp Neurol. 1978;15:92-7. PMID: 756025.

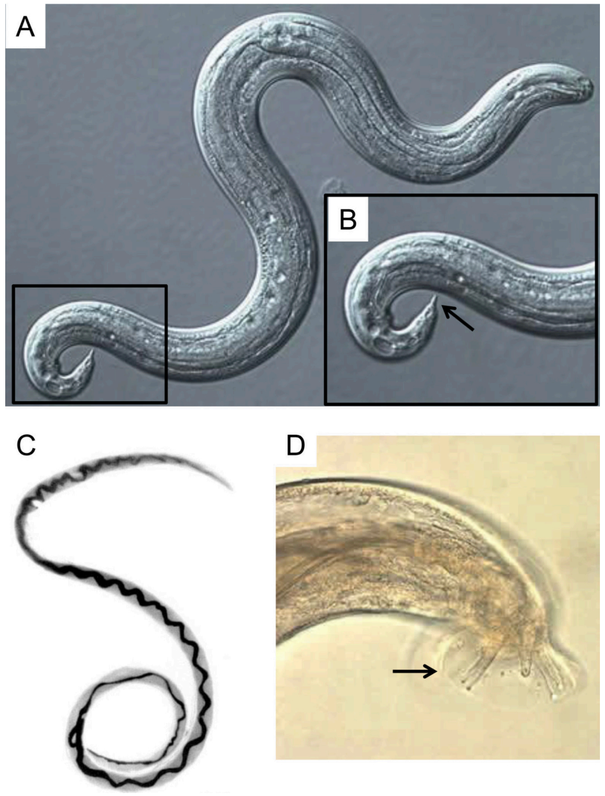
TABLE 11-1

Selected Helminthic Infections of the Central Nervous System

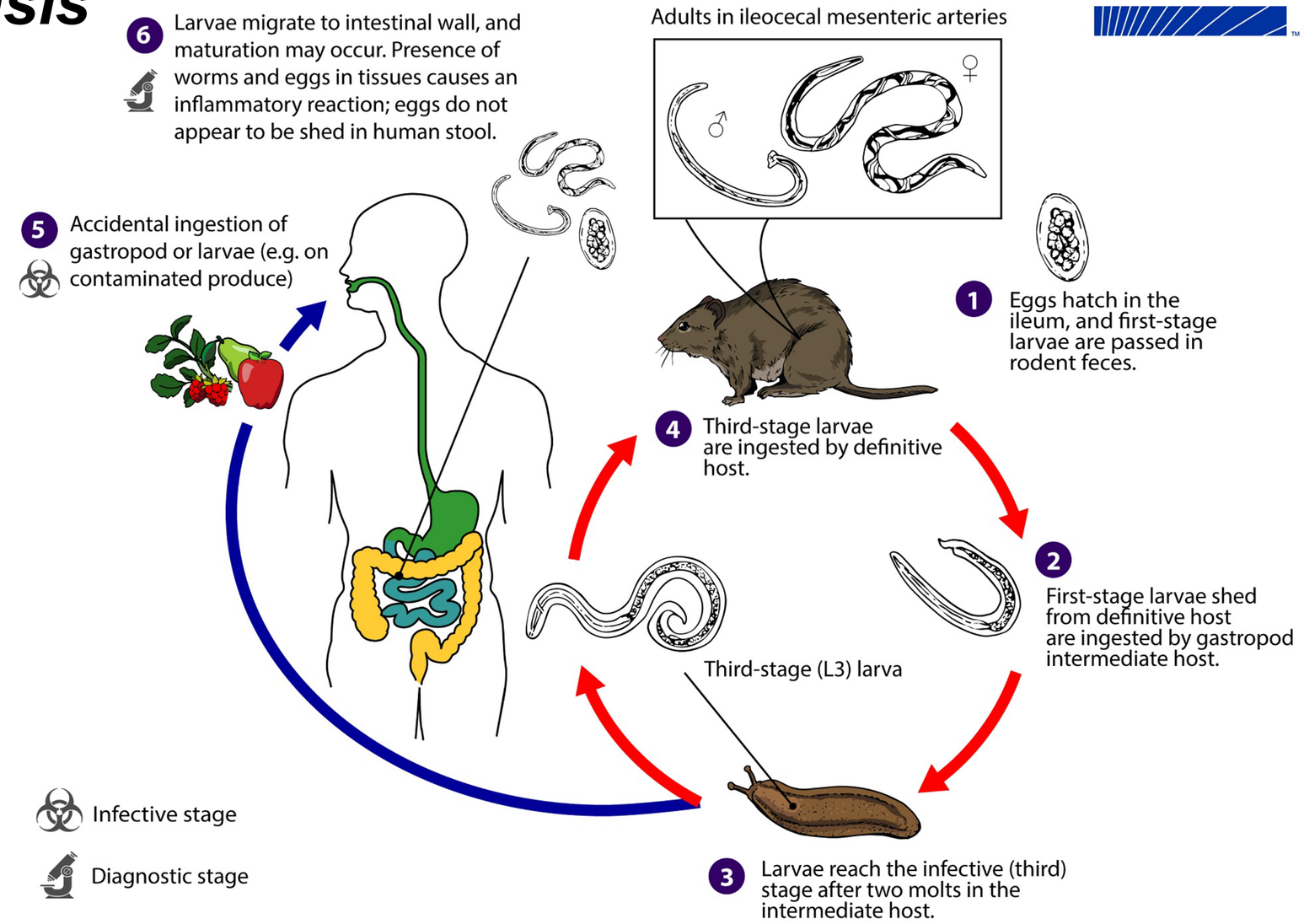
Organism	Disease	Neurologic Localization/Syndrome	Geographic Distribution
Taenia solium	Cysticercosis	Parenchymal and extraparenchymal cysts, headache, epilepsy, hydrocephalus, stroke	Central America, South America, sub-Saharan Africa, Asia
Echinococcus granulosus	Hydatid disease	Cystic brain disease, headache, epilepsy	Mediterranean, Middle East, East Africa, Russia, South America
Angiostrongylus cantonensis	Angiostrongyliasis	Eosinophilic meningitis	Southeast Asia, Pacific Islands, Caribbean
***Gnathostoma* species**	Gnathostomiasis	Eosinophilic meningitis, cranial neuropathies, sudden severe headache or radicular pain	Southeast Asia, Japan, Central America, South America
Schistosoma mansoni*, *Schistosoma haematobium	Schistosomiasis	Myeloradiculopathy, encephalitis	South America, Caribbean, sub-Saharan Africa, Southwest Asia, Middle East
Schistosoma japonicum	Schistosomiasis	Encephalitis	Southeast Asia, Japan, China, Philippines
***Paragonimus* species**	Paragonimiasis	Parenchymal granuloma, arachnoiditis, epilepsy, meningitis	Southeast Asia, East Asia

Angiostrongylus cantonensis Infection of CNS

Angiostrongylus cantonensis



A) Differential interference contrast microscopy image of third-stage (L3) infective larvae recovered from a slug. L3 larvae are about 0.45 by 0.02 mm and present cuticle with faint transverse striations
B) Higher magnification of demarcated region in A showing terminal projection on the tip of the tail (arrow) which is characteristic of A. cantonensis
C) Adult female and tail of adult male
D) worms recovered from rat lungs



Angiostrongylus cantonensis Infection of CNS

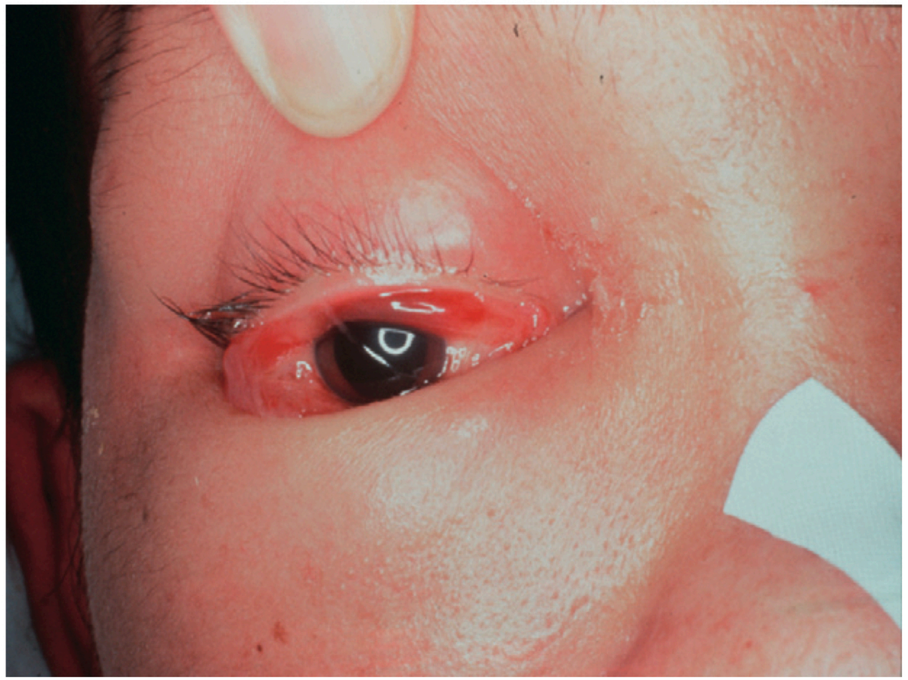
Clinical Manifestation

Eosinophilic meningitis

Encephalitis/encephalomyelitis

Radiculitis

Cranial nerve abnormalities and ataxia



A patient with ocular angiostrongyliasis. Blurred vision with chemosis is presenting symptom

K. SAWANYAWISUTH AND V. CHOTMONGKOL, Eosinophilic Meningitis. Handbook of Clinical Neurology, Vol. 114 (3rd series) Neuroparasitology and Tropical Neurology

Martins YC, Tanowitz HB, Kazacos KR. Central nervous system manifestations of Angiostrongylus cantonensis infection. Acta Trop. 2015;141(Pt A):46-53. doi:10.1016/j.actatropica.2014.10.002

Angiostrongylus cantonensis Infection of CNS

Clinical Manifestation

Observation/Finding*	Present, No.	Absent, No.	Proportion with symptom/sign present (%)†
Symptom/Sign			
Subjective fever	8	2	8/10 (80)
Generalized weakness	7	2	7/9 (78)
Headache	6	2	6/8 (75)
Numbness/Tingling	3	3	3/6 (50)
Photophobia	4	5	4/9 (44)
Visual changes	3	4	3/7 (43)
Vomiting	3	6	3/9 (33)
Stiff neck	2	7	2/9 (22)
Rash	2	7	2/9 (22)
Nausea	1	5	1/6 (17)
Phonophobia	1	6	1/7 (14)
Abdominal pain	1	7	1/8 (13)
Itching	1	8	1/9 (11)
Diarrhea	3	NA	NA
Hyperesthesias/diffuse allodynia	2	NA	NA

Observation/Finding*	Present, No.	Absent, No.	Proportion with symptom/sign present (%)†
Physical exam			
Vital signs			
Fever (temperature ≥100.4°F [≥38.0°C])	3	8	3/11 (27)
Tachycardia (>100 bpm in adults aged ≥16 yrs, age-dependent in persons aged <16 yrs)	1	10	1/11 (9)
Hypoxia (O_2 saturation <90%)	0	10	0/10 (0)
Neurologic exam findings			
Cranial nerve deficits	5	6	5/11 (45)
Nuchal rigidity	4	8	4/12 (33)
Focal weakness	3	7	3/10 (30)
Paresthesias	1	7	1/8 (12)
Loss of consciousness	0	10	0/10 (0)
Irritability	3	NA	NA
Ataxia	2	1§	NA

Symptoms, physical exam findings, and laboratory results for 12 patients with angiostrongyliasis with detectable A. cantonensis DNA on polymerase chain reaction testing

CDC Weekly / August 3, 2018 / 67(30);825–828

Angiostrongylus cantonensis Infection of CNS

Clinical Manifestation

- **Prodromal syndromes** due to the passage of L3 larvae through different organs
  - Enteritis can be associated with invasion of the gastrointestinal tract
  - Cough, rhinorrhea, and sore throat can develop when worms pass through the lungs and trachea
  - Fever and malaise are nonspecific symptoms of infection and can also occur before the development of CNS disease

The **incubation period** for the development of eosinophilic meningitis is typically about **2 weeks**, which coincides with the time it takes for the L3 larvae to migrate into CNS tissue and incite a reaction, it can range from one day to several months

Symptoms, physical exam findings, and laboratory results for 12 patients with angiostrongyliasis with detectable A. cantonensis DNA on polymerase chain reaction testing

CDC Weekly / August 3, 2018 / 67(30);825–828

Angiostrongylus cantonensis Infection of CNS

Diagnosis

An important factor suggesting A. cantonensis infection is a **history** of **eating uncooked fresh water snails, crustaceans, or monitor lizard's liver during the 2–3 months** before the neurological symptoms appear.

Laboratory tests supporting diagnosis include complete blood count, CSF fluid analysis, immunological examination, and radiological examination.

Martins YC, Tanowitz HB, Kazacos KR. Central nervous system manifestations of Angiostrongylus cantonensis infection. Acta Trop. 2015;141(Pt A):46-53. doi:10.1016/j.actatropica.2014.10.002

Angiostrongylus cantonensis Infection of CNS

Diagnosis

Definitive diagnosis is made by detection of **A. cantonensis larvae** in the CSF

Detection rate is frequently low which makes the diagnosis primarily based on clinical history, CSF eosinophilia, and immunological tests

CSF analysis

CSF leukocyte count is often between 150 and 2,000 cells/μL

Eosinophilic pleocytosis exceeds 10% in more than 95% of patients

The CSF protein concentration is elevated

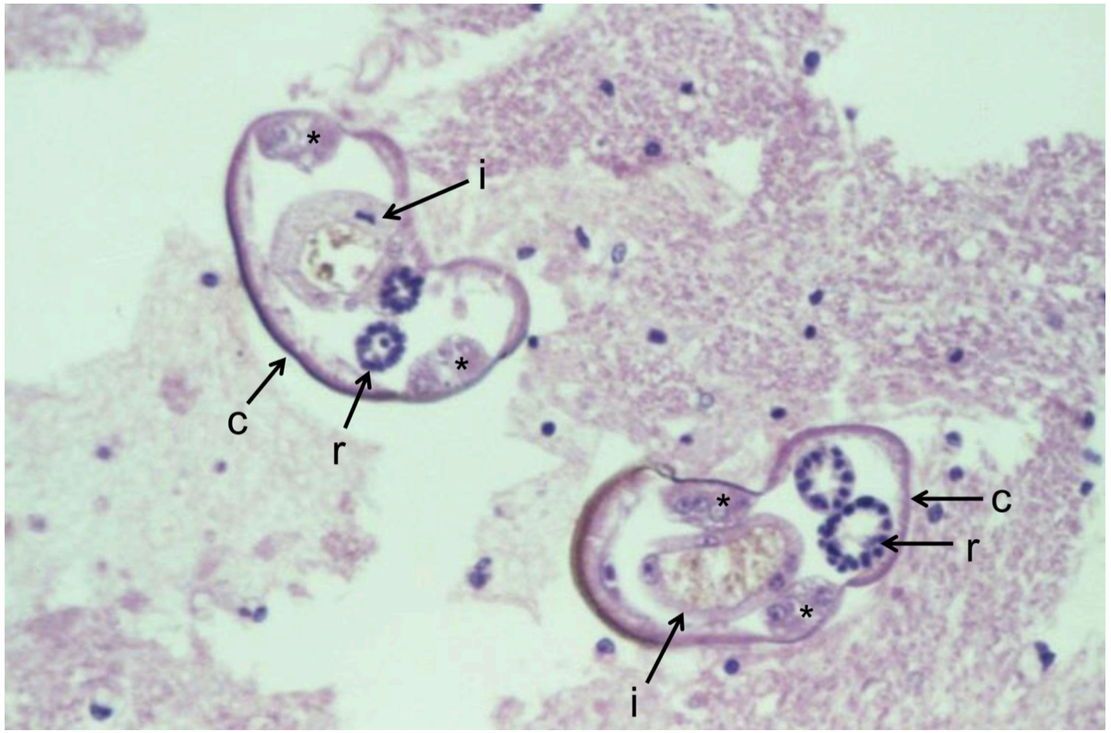
Glucose level is normal or slightly reduced

Opening CSF pressures are elevated in nearly 40% of cases

Immunological examinations ELISA or the immunoblotting test ,Antigen with a molecular weight of 29 or 31 kDa is highly specific for A. cantonensis

The specificity of was 100% in patients with eosinophilic meningitis

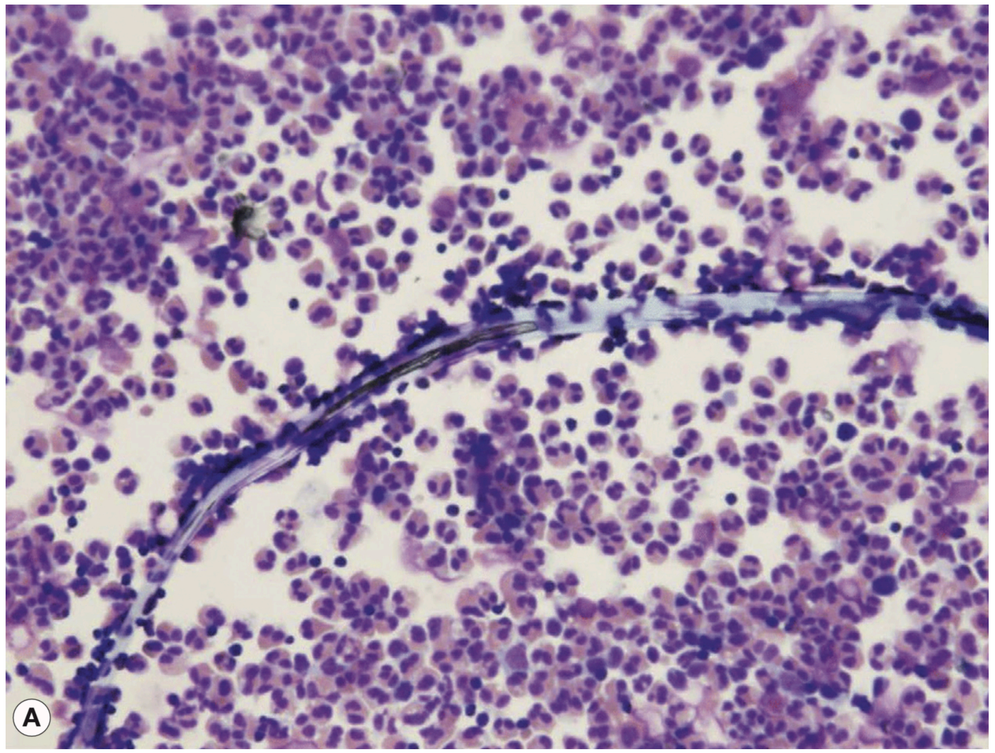
Martins YC, Tanowitz HB, Kazacos KR. Central nervous system manifestations of Angiostrongylus cantonensis infection. Acta Trop. 2015;141(Pt A):46-53. doi:10.1016/j.actatropica.2014.10.002



a) Meningeal infiltration by eosinophils, macrophages, and lymphocytes

b) Distinct tracks within the brain parenchyma associated with cell debris, micro thrombi and inflammatory cells

c) Presence of eosinophilic granulomas and sometimes Charcot-Leyden crystals surrounding dead worms



Cross-section of two Angiostrongylus cantonensis larvae in the spinal cord

Symptoms, physical exam findings, and laboratory results for 12 patients with angiostrongyliasis with detectable A. cantonensis DNA on polymerase chain reaction testing

Angiostrongylus cantonensis Infection of CNS

Laboratory : CSF

Patient with alteration of consciousness should always receive CT brain before LP

Observation/Finding*	Present, No.	Absent, No.	Proportion with symptom/sign present (%)†
Laboratory results on initial evaluation			
Cerebrospinal fluid			
Pleocytosis of CSF (≥6 WBC/mm^3)	12	0	12/12 (100)
CSF eosinophilia (eosinophils ≥10% of all leukocytes in CSF or ≥10 eosinophils/mm^3)	10	2¶	10/12 (83)
Hypoglycorrhachia (CSF glucose <40 mg/dL)	6	5	6/11 (54)
Complete blood count			
Peripheral eosinophilia (>600 eosinophils/mm^3)	8	2	8/10 (80)
Leukocytosis (>11x10^3 WBC/mm^3 in persons aged >21 yrs, age-dependent in persons aged ≤21 yrs)	3	9	3/12 (25)

Symptoms, physical exam findings, and laboratory results for 12 patients with angiostrongyliasis with detectable A. cantonensis DNA on polymerase chain reaction testing

CDC Weekly / August 3, 2018 / 67(30);825–828

Angiostrongylus cantonensis Infection of CNS

Laboratory : CSF

An eosinophil count of more than 798 cells , for the diagnosis of meningitic angiostrongyliasis

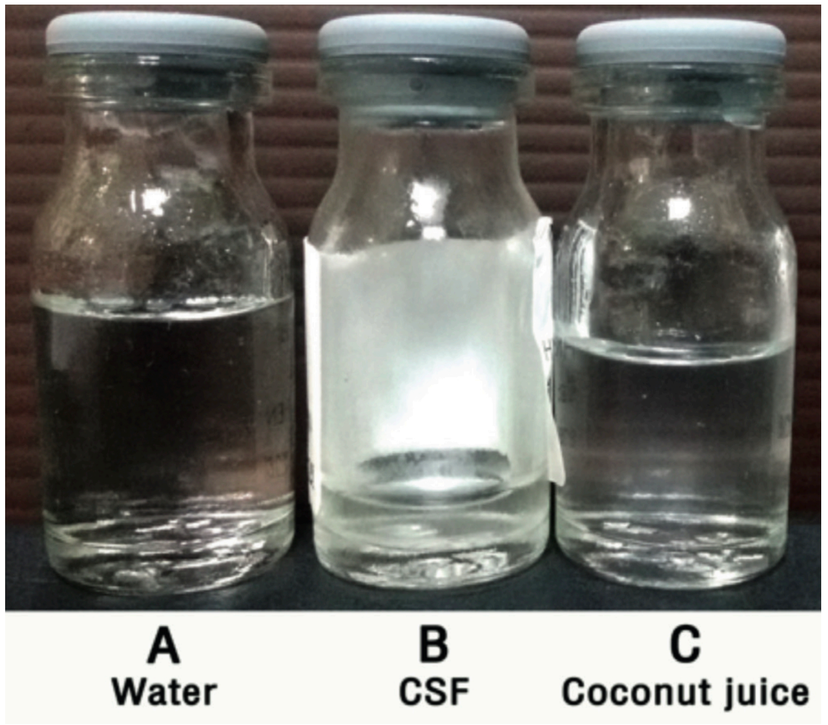
: sensitivity 76.6% , specificity 80.2%, PPV 58.1%, and NPV 90.5%

The average leukocyte count in CSF fluid is 700 cells/mm3 and can be as high as 5000 cells/mm3

Protein levels usually do **not** exceed 500 mg/dL

Sugar levels in CSF fluid can be as **low** as 17% when compared to plasma glucose

Abnormalities in CSF fluid from meningitis and encephalitis patients are similar in terms of **turbidity like coconut juice** and opening pressure was high in 38%



Prakaykaew Charunwatthana and Yupaporn Wattanagoon Hunter's Tropical Medicine and Emerging Infectious Diseases, 122, 891-894

Martins YC, Tanowitz HB, Kazacos KR. Central nervous system manifestations of Angiostrongylus cantonensis infection. Acta Trop 2015;141(Pt A):46–53.

Angiostrongylus cantonensis Infection of CNS

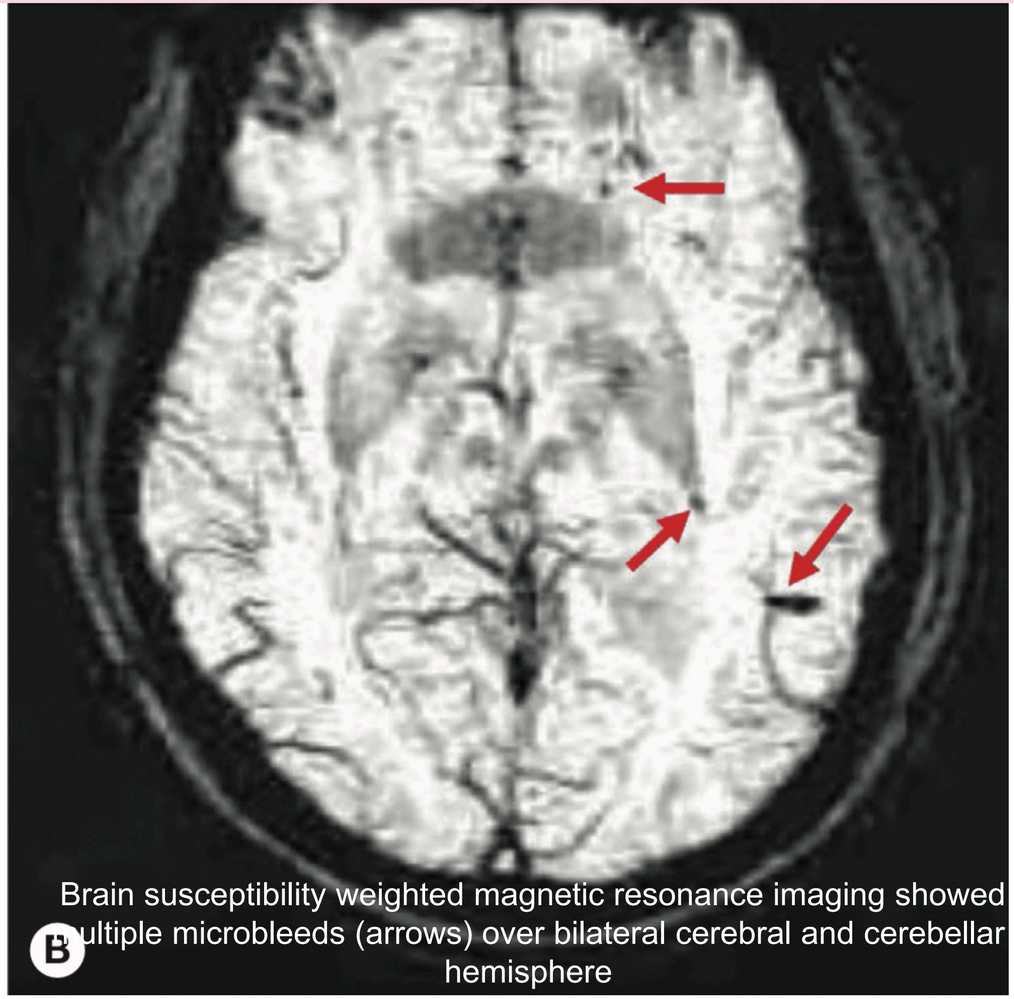
Imaging

The absence of focal lesions on CT or MRI scans of the brain distinguishes A. cantonensis meningitis from other helminthic infections of the CNS (gnathostomiasis or neurocysticercosis)

Nonspecific abnormalities MRI in patients with the encephalitic form

- tract-like lesion
- white matter involvement
- nodular enhancement
- myelitis

Radiological examination is not specific



Brain susceptibility weighted magnetic resonance imaging showed multiple microbleeds (arrows) over bilateral cerebral and cerebellar hemisphere

Shen HC, Chao CM, Hsieh CF: Brain worms with cerebrospinal fluid eosinophilia. Am J Trop Med Hyg 2017;97:1633–1634.

Angiostrongylus cantonensis Infection of CNS

Treatment

There is **no specific treatment** for A. cantonensis infection

The best treatment for meningitic angiostrongyliasis is **prednisolone 60 mg/day for 2 weeks**

2-week course of albendazole tends to decrease the duration of headaches when compared to placebo

Studies of the **combination** of prednisolone with antihelminthics found it to be as **effective** as prednisolone alone

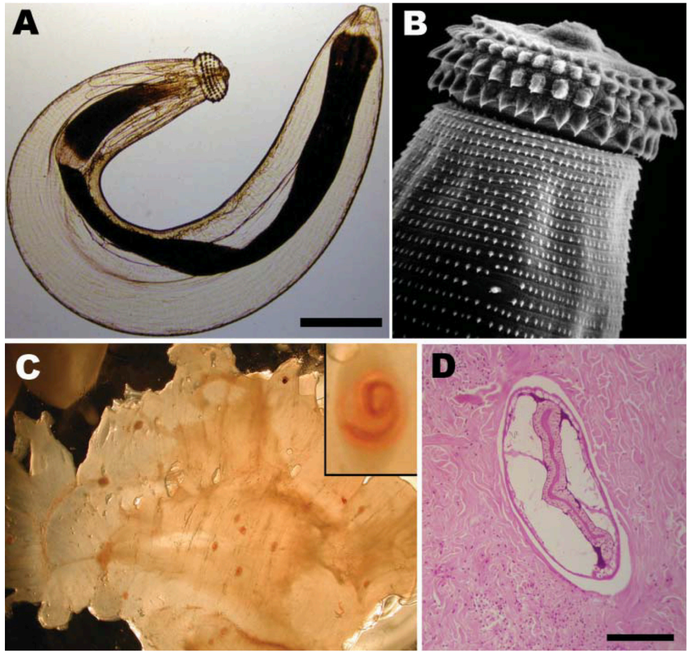
Defo AL, Lachaume N, Cuadro-Alvarez E, et al. Angiostrongylus cantonensis Infection of Central Nervous System, Guiana Shield. *Emerging Infectious Diseases*. 2018;24(6):1153-1155.

Neurognathostomiasis

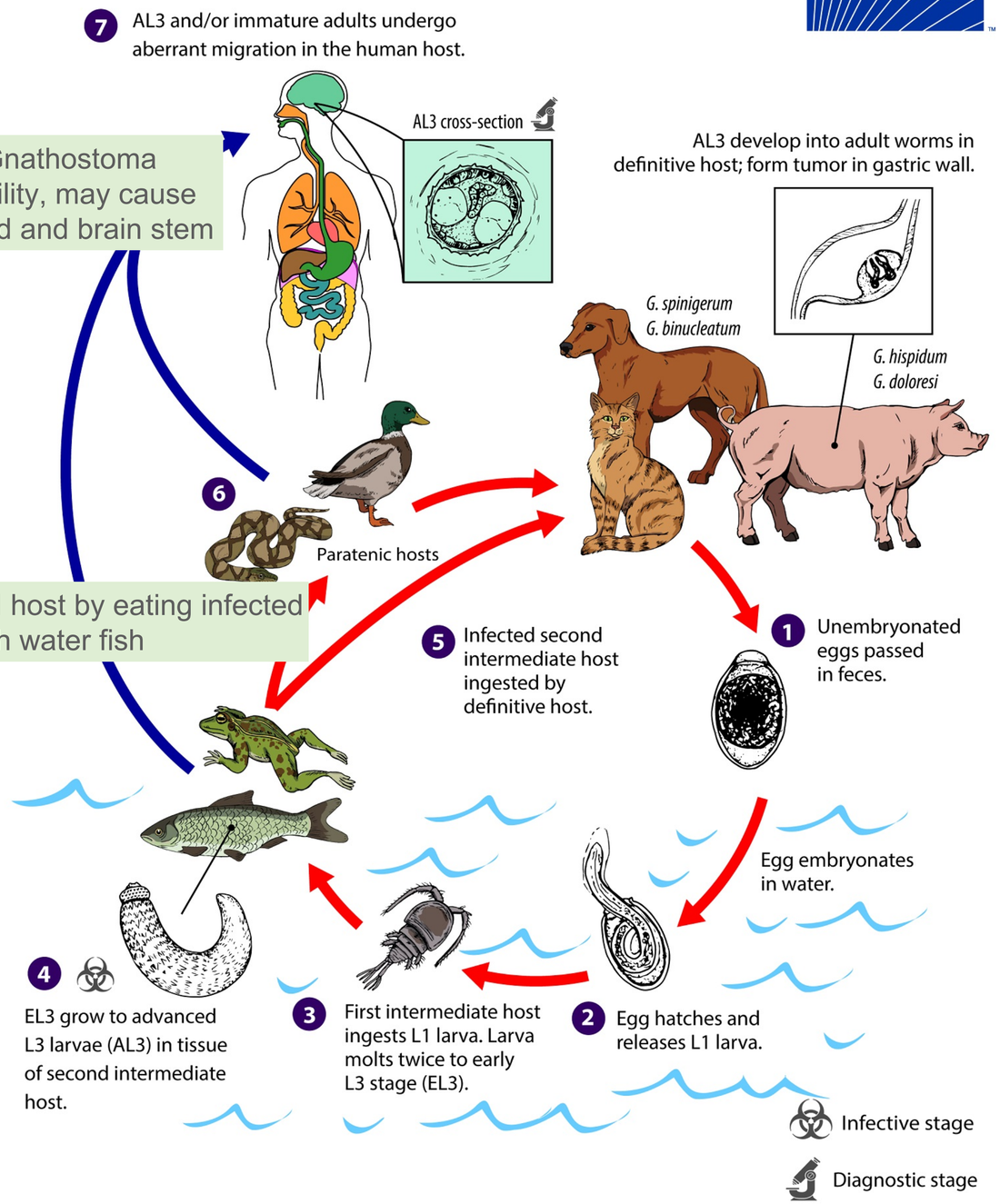
Gnathostoma spinigerum

The tissue nematode involved, Gnathostoma spinigerum, because of its high motility, may cause widespread damage in the spinal cord and brain stem

Human becomes an accidental host by eating infected under-cooked fresh water fish



A) Third-stage larva of the nematode Gnathostoma sp.
B) Scanning electronic microscopy image depicting head bulb with 4 cephalic hooklet rows
C) Gnathostoma sp. larvae in the flesh Eleotris picta fish
D) Cross- section of a Gnathostoma sp. larva in human skin biopsy sample (hematoxylin and eosin stain)



Neurognathostomiasis

Clinical Signs of Neurologic Involvement

- Pain — Radicular pain is characteristically intermittent, severe, and localized to an arm, leg, or one side of the body
- Myelitis — Paraplegia and quadriplegia, paraparesthesia, and urinary retention
  Some patients may develop Brown–Sequard or cauda equina syndrome
- Intracranial hemorrhage
- Subarachnoid hemorrhage
- Combination of these

Katchanov, J., Sawanyawisuth, K., Chotmongkoi, V., & Nawa, Y. (2011). Neurognathostomiasis, a neglected parasitosis of the central nervous system. *Emerging infectious diseases*, *17*(7), 1174–1180.

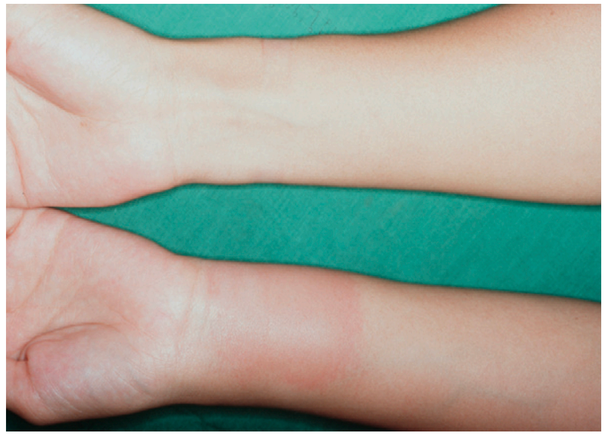
Clinical Signs

History of larva exposure : Regularly eating raw or undercooked meat

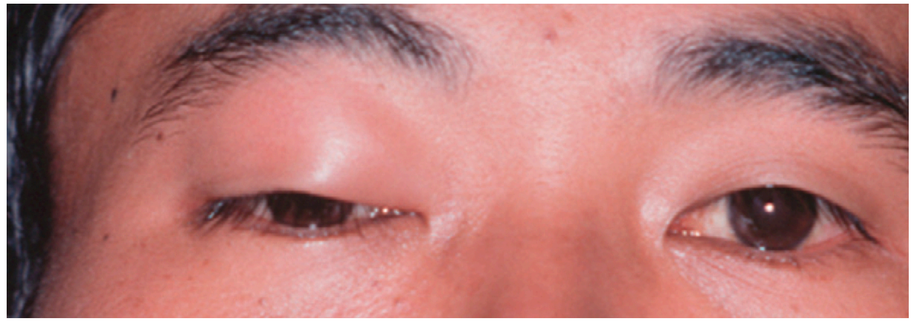
A history of The true incuba-tion period is always uncertain

Skin manifestations are the common suggestive signs for gnathostomiasis

two forms including intermittent migratory swelling and creeping eruption



Migratory swelling on left forearm caused by G. spinigerum



A patient with ocular gnathostomiasis. Ocula swelling is presenting symptom

Katchanov, J., Sawanyawisuth, K., Chotmongkoi, V., & Nawa, Y. (2011). Neurognathostomiasis, a neglected parasitosis of the central nervous system. *Emerging infectious diseases*, *17*(7), 1174–1180.

Clinical Signs of Neurologic Involvement

Table 1. Clinical presentation of 248 patients with neurognathostomiasis*

Syndrome	Probable entry portal entry	Clinical signs and symptoms	No. (%) cases
Radiculomyelitis/myelitis/ myeloencephalitis	Intervertebral foramina along the spinal nerves and vessels	Sharp radicular pain and a spinal syndrome (paraplegia, monoplegia, quadriplegia, bladder dysfunction, sensory disturbances), can progress to cerebral involvement (myeloencephalitis)	140 (55)
Meningitis/ meningoencephalitis	Neural foramina of the skull base along the cranial nerves and vessels	Severe headache, stiffness of the neck, cranial nerve palsies, disturbance of consciousness, focal neurologic signs	77 (30)
Intracerebral hemorrhage	Intervertebral or neural foramina	Headache, sudden-onset focal neurologic signs	21 (8)
Subarachnoid hemorrhage	Intervertebral or neural foramina	Thunderclap headache, meningeal signs	16 (7)

*Because the larvae migrate, patients can have sequential signs and symptoms; thus, the total number of clinical syndromes shown exceeds the number of reported patients.

Katchanov, J., Sawanyawisuth, K., Chotmongkoi, V., & Nawa, Y. (2011). Neurognathostomiasis, a neglected parasitosis of the central nervous system. *Emerging infectious diseases*, *17*(7), 1174–1180.

Neurognathostomiasis

Diagnosis : CSF Studies

Normal or high normal opening pressure

Number of white blood cells in the CSF ranges from 20 to 1430 cells/mm3

CSF Eosinophilia in patients is usually prominent , ranges from 20 - 1430 cells/mm3

Median values were 40%-54%

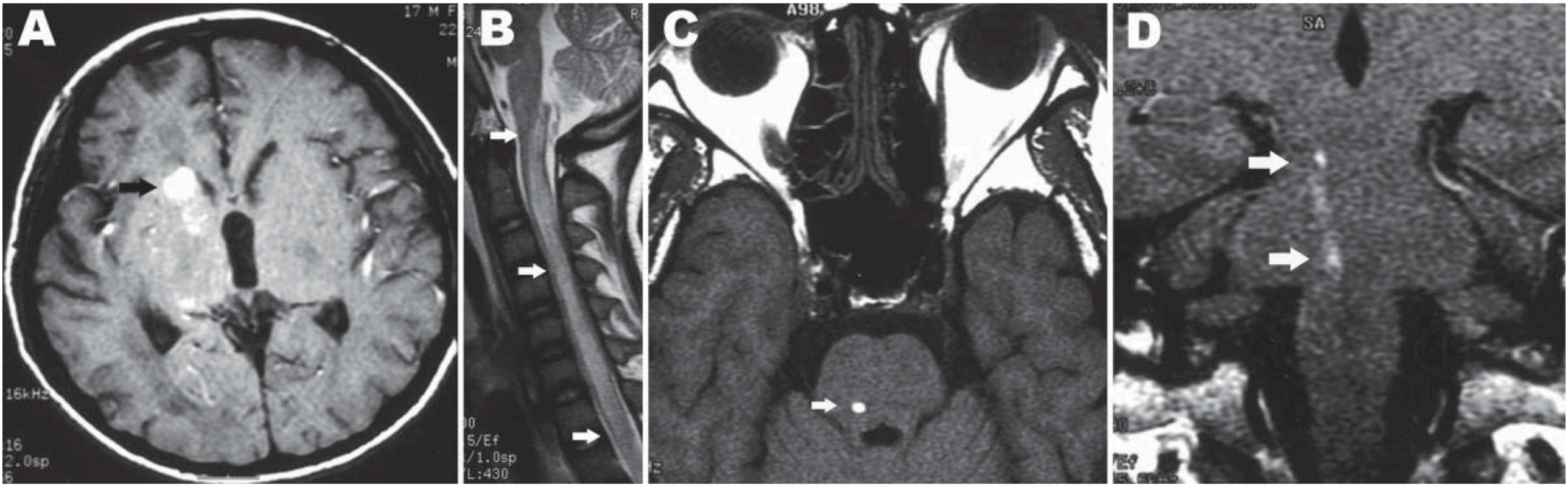
CSF has been reported as xanthochromic or bloody (64%)

CSF glucose is usually normal or only mildly reduced

Mild elevation of protein

Katchanov, J., Sawanyawisuth, K., Chotmongkoi, V., & Nawa, Y. (2011). Neurognathostomiasis, a neglected parasitosis of the central nervous system. *Emerging infectious diseases*, *17*(7), 1174–1180.

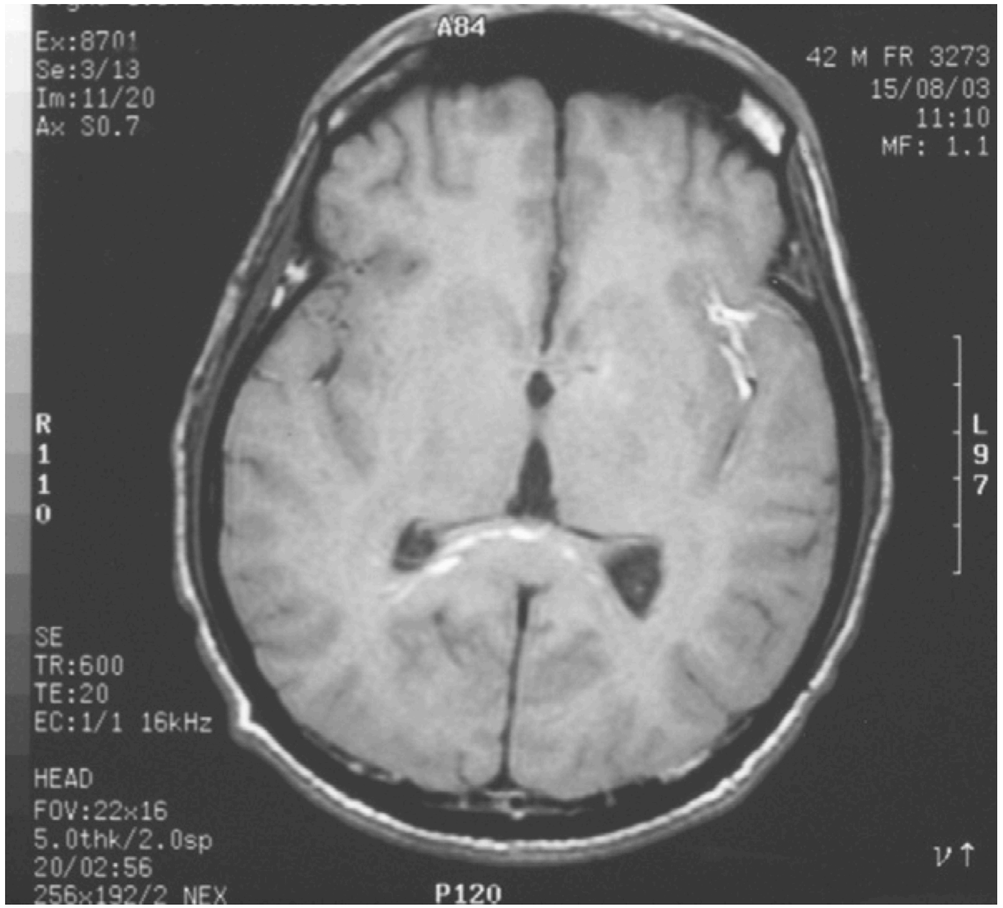
Diagnosis : Neuroradiologic Features



A) Axial T1-weighted image showing small hemorrhage in the right basal ganglia
B) Sagittal T2-weighted images showing diffuse cord enlargement with longitudinal T2 hyperintensity
C) Axial T1-weighted image showing a hemorrhagic track in the tegmentum of the pons
D) Coronal T1-weighted postgadolinium image, showing the longitudinal extension of the same hemorrhagic track as in panel C
Images from K. Sawanyawisuth et al.

Katchanov, J., Sawanyawisuth, K., Chotmongkoi, V., & Nawa, Y. (2011). Neurognathostomiasis, a neglected parasitosis of the central nervous system. *Emerging infectious diseases*, *17*(7), 1174–1180.

Diagnosis : Neuroradiologic Features



MRI of the brain showed hemorrhagic tract at corpus collasum and subarachnoid hemorrhage at left sylvian fissure

Katchanov, J., Sawanyawisuth, K., Chotmongkoi, V., & Nawa, Y. (2011). Neurognathostomiasis, a neglected parasitosis of the central nervous system. *Emerging infectious diseases*, *17*(7), 1174–1180.

Neurognathostomiasis

Diagnosis : Immunodiagnosis

Two methods have been established for clinical routine : ELISA and Western blot

by using crude Gnathostoma spp. antigens from larval extract

The 24-kD band on Western blot was shown to have **nearly 100% specificity** for gnathostomiasis

The current practice for serologic diagnosis is to use the ELISA (e.g., multiple-dot ELISA) as the first step and to confirm the results by Western blot

Katchanov, J., Sawanyawisuth, K., Chotmongkoi, V., & Nawa, Y. (2011). Neurognathostomiasis, a neglected parasitosis of the central nervous system. *Emerging infectious diseases*, *17*(7), 1174–1180.

Neurognathostomiasis

Treatment

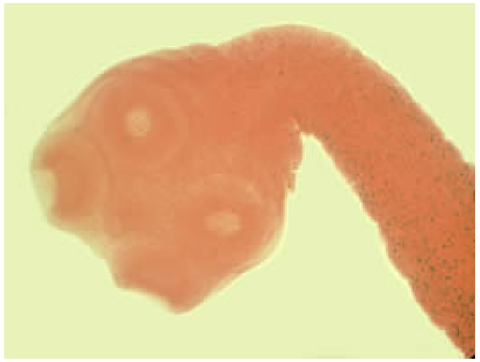
Albendazole (800 mg/d for for 3-4 weeks and 400 mg 2×/d for 4 weeks

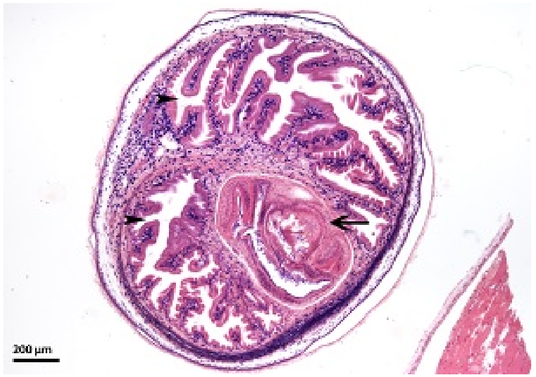
Corticosteroids have been used in neurognathostomiasis to treat cerebral and spinal edema, might prevent or alleviate paradoxical worsening after initiation of antihelminthic treatment

Katchanov, J., Sawanyawisuth, K., Chotmongkoi, V., & Nawa, Y. (2011). Neurognathostomiasis, a neglected parasitosis of the central nervous system. *Emerging infectious diseases*, *17*(7), 1174–1180.

Neurocysticercosis

Cysticercus cellulosae





Carried by blood stream, lodge in small blood vessels develop into viable cysts after 2-3 months

Oncosphere-larva of tapeworm through stomach wall

Neurocysticercosis

Clinical signs and symptoms

Taenia solium, commonly results in epilepsy, and sometimes increased intracranial pressure from intraventricular obstruction or from basal arachnoiditis

Spinal cord and cauda equina involvement occurs much less frequently

Cysticercus complement fixation tests on the CSF and computerised axial tomography have been found to be of great diagnostic value

Depend on number, location, growth, stage of degeneration of cysts, host factors, parasitic genotype

Most of the pathophysiology of cysticercosis results from acute or chronic **inflammatory responses** against the membranes and residual antigens of degenerating cysts

Mass effects & mechanical obstruction of cerebrospinal fluid (CSF) flow

Carabin, H. et al. Clinical manifestations associated with neurocysticercosis: a systematic review. PLoS Negl. Trop. Dis. 5, e1152 (2011).

Neurocysticercosis

Clinical signs and symptoms

- 78.8% of patients presented with seizures-GTC
- 37.9% presented with headaches
- 16% had focal neurological deficits
- 11.7% showed signs of intracranial hypertension
- 7.9% had meningitis, 6% had gait abnormalities
- 5.6% reported visual changes
- 4.5% had an altered mental state
- 2.8% had cranial nerve palsies

Carabin, H. et al. Clinical manifestations associated with neurocysticercosis: a systematic review. PLoS Negl. Trop. Dis. 5, e1152 (2011).

Neurocysticercosis

Parenchymal disease

: Frequently locate at watershed area between white-grey matter

– Viable cyst

– Degenerating cyst

– Calcified cyst

Extra parenchymal disease

: Large basal subarachnoid lesion

Small cyst at choroid plexus
“Ventricular cyst”

> obstruction of 4th ventricle

– Ventricular neurocysticercosis

– Subarachnoid disease of brain tissue

– Basal subarachnoid neurocysticercosis

Carabin, H. et al. Clinical manifestations associated with neurocysticercosis: a systematic review. PLoS Negl. Trop. Dis. 5, e1152 (2011).

Table 1. Differences between parenchymal and extraparenchymal neurocysticercosis.

		Extraparenchymal		
		Subarachnoideal		Intraventricular
	Parenchymal	Cysts in basal cisterns	Arachnoiditis	
Main clinical manifestations	Seizures, focal deficits	Cranial hypertension	Cranial hypertension, symptoms of cranial neuropathy	Cranial hypertension, Bruns' syndrome
Pathology	Focal tissue inflammation and/or gliosis	Mass effect	Thickening of leptomeninges	Obstruction of CFS circulation
CSF analysis	Often inconclusive	Inflammatory pattern	Inflammatory pattern	Inflammatory pattern (less intense than in subaracnoidal parasites)
Immunological tests	Antibodies >50%, antigens <50%	–	Antibodies >90%, antigens >70%	Antibodies >90%, antigens >70%
Complications	Epilepsy, cognitive decline	Hydrocephalus, vasculitis, cerebral infarcts, chiasmatic syndrome	Hydrocephalus, vasculitis, cerebral infarcts, chiasmatic syndrome	Hydrocephalus, ependymitis, sudden death
Prognosis	Good, clinical manifestations usually self-limited	'Malignant,' clinical manifestations usually progressive	'Malignant,' usually permanent sequelae	Heterogeneous. Can be good after excision by endoscopic surgery

Arturo Carpio, Agnès Fleury, Matthew L. Romo & Ronaldo Abraham (2018) Neurocysticercosis: the good, the bad, and the missing, Expert Review of Neurotherapeutics, 18:4, 289-301, DOI: 10.1080/14737175.2018.1451328

1. Parenchymal neurocysticercosis

Definitive parenchymal neurocysticercosis[a], one of the following:

(1) Parenchymal cyst with pathological diagnosis

(2) Single or multiple active parenchymal cysts, with at least one cyst with scolex on CT or MRI

(3) Multiple parenchymal vesicles without scolex associated with at least one of the following:

(a) Seizures: focal or generalized tonic-clonic

(b) Positive serum or CSF immunological test (ELISA, EITB)

(4) Any combination of the parenchymal cysticercus in different evolutive stages: vesicular with or without scolex, degenerative (colloidal or nodular) and calcified

Probable parenchymal neurocysticercosis, one of the following:

(1) Single parenchymal calcification or vesicle (without scolex) or degenerating cyst(s), establishing differential diagnoses with other etiologies, associated with at least two of the following:

(a) Seizures: focal or generalized tonic-clonic

(b) Subcutaneous or muscle cysts location confirmed by biopsy

(c) Positive serum or CSF immunological test (ELISA, EITB)

(d) Plain X-ray films showing 'cigar-shaped' calcifications

(e) Individual who lives or has lived in or has traveled frequently to endemic countries

(2) Multiple parenchymal calcifications in an individual who lives or has lived in or has traveled frequently to endemic countries and in whom clinical state excludes other etiologies of calcifications

Neurocysticercosis most commonly manifests in the parenchyma of the brain and typically involves the cerebral hemispheres, Basal ganglia, brainstem, and cerebellum

The lesions are commonly found at the graye-white matter junction, presumably resulting from deposition of the larvae in terminal small vessels of these regions

Arturo Carpio, Agnès Fleury, Matthew L. Romo & Ronaldo Abraham (2018) Neurocysticercosis: the good, the bad, and the missing, Expert Review of Neurotherapeutics, 18:4, 289-301,

2. Extraparenchymal neurocysticercosis (intraventricular/basal subarachnoid)

Definitive extraparenchymal neurocysticercosis, one of the following:

(1) Extraparenchymal cyst with pathological diagnosis

(2) One or more extraparenchymal cysts on MRI special sequences with scolex in at least one of them

(3) One or more extraparenchymal cysts on MRI special sequences without scolex associated with at least two of the following:

(a) Hydrocephalus

(b) Inflammatory CSF

(c) Positive CSF immunological test (ELISA, EITB)

(d) Presence of single or multiple calcifications or parenchymal vesicular or degenerative cyst

3. Definitive parenchymal and extraparenchymal neurocysticercosis

Combination of the above definitive parenchymal and definitive extraparenchymal criteria

Arturo Carpio, Agnès Fleury, Matthew L. Romo & Ronaldo Abraham (2018) Neurocysticercosis: the good, the bad, and the missing, Expert Review of Neurotherapeutics, 18:4, 289-301,

Investigation : Serology

EITB (enzyme-linked immunoelectrotransfer blot) : detect antibodies in the serum that recognize a range of specific antigens, identified and cloned from T. solium cysts -very specific for identifying exposure to T. solium

> Lacks sensitivity in patients with low disease burden

Enzyme-linked immunosorbent assay (ELISA)-based antigen-detection

tests that use monoclonal antibodies

	ELISA		EITB	
Specimen	Serum	CSF	Serum	CSF
Sensitivity (%)	41.0	71	**86**	**86**
Specificity (%)	**95.7**	**95.7**	92.8	92.8

Diagnosis and Treatment of Neurocysticercosis: 2017 Infectious Diseases Society of America (IDSA) and the American Society of Tropical Medicine and Hygiene (ASTMH). Clinical Infectious Diseases 2018; 66: e49-75.

Investigation : Serology

Serial measurements of Ag levels

– to establish the efficacy of treatment,

– indicate clearance of parasites from the patient,

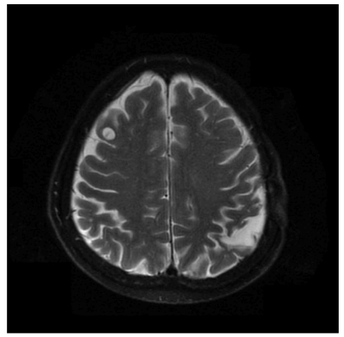
– suggest when antihelminthic treatment can be stopped

Monitoring drug efficacy for follow-up of treated individuals

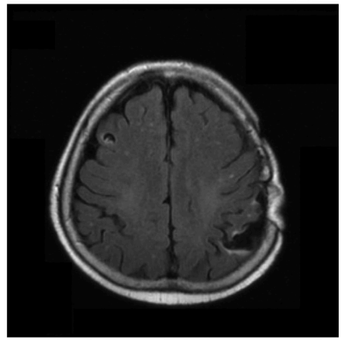
Diagnosis and Treatment of Neurocysticercosis: 2017 Infectious Diseases Society of America (IDSA) and the American Society of Tropical Medicine and Hygiene (ASTMH). Clinical Infectious Diseases 2018; 66: e49-75.

Imaging spectrum of Neurocysticercosis

Vesicular stage (active)



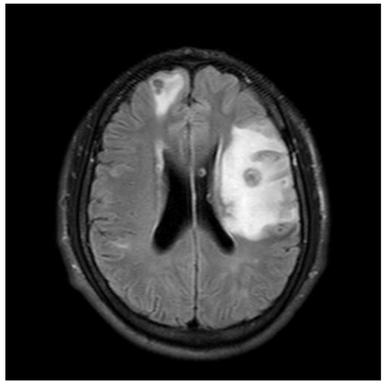
A



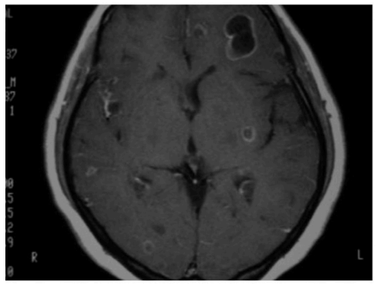
B

Small CSF-like cyst with thin wall and an eccentrically located scolex, no contrast enhancement of the cyst's wall, no surrounding tissue edema.

Colloidal Vesicular stage (active)



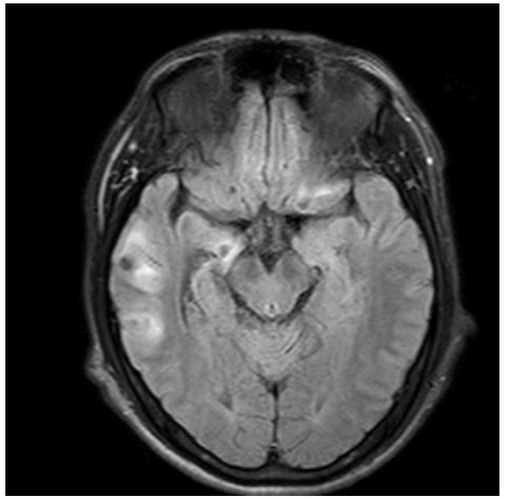
A



B

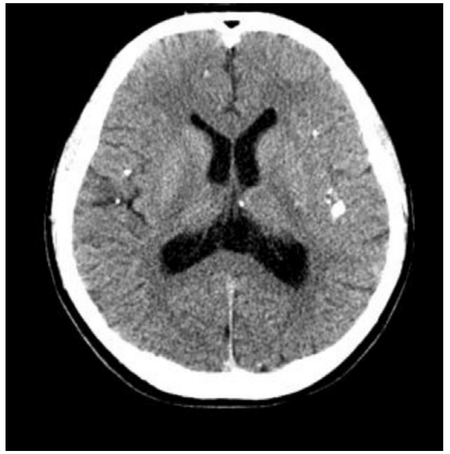
The density and signal intensity of the cystic fluid change from that of CSF. The cystic wall is thicker. The scolex becomes ill defined and finally shrinks in its size. Ring-like enhancement is seen. The surrounding tissue edema is obvious.

Granular Nodular stage (active)



Small enhancing cyst or nodule, with mild surrounding edema and little mass effect.

Nodular Calcified stage (non active)



Small calcified nodule, no surrounding edema, better seen on CT.

Jing-Long Zhao, Imaging spectrum of neurocysticercosis Radiology of Infectious Disease, Volume 1, Issue 2, March 2015, Pages 94-102

Neurocysticercosis

Treatment

	Parenchymal[f]	Subarachnoideal		Intraventricular
		Cysts in basal cisterns	**Arachnoiditis**	
Symptomatic therapy	Antiseizures, analgesics, and steroids drugs according to clinical manifestations[a]	Ventriculo peritoneal shunt for clinical intracranial hypertension management and steroids[a]	Analgesics and steroids drugs according to clinical manifestations[a]; ventriculo peritoneal shunt for hydrocephalus[a]	Ventriculo peritoneal shunt for hydrocephalus[a] and steroids[a]
Antihelminthic drugs	Albendazole or praziquantel[d] for vesicular cysts[b] or single enhancing cyst[c]	Albendazole or praziquantel[a,e]	No indication[a]	Albendazole or praziquantel [a,e]
Surgical treatment	Excision of 'giant' cyst with mass effect[a]	No indication[a]	No indication[a]	Neuroendoscopic excision[a]

[a]There is no controlled clinical trial; [b]based on controlled clinical trials (30–40% of disappearance of cysts); [c]controversial results of clinical trials; [d]albendazole 15 mg/kg/day for 1 week, praziquantel 50 mg/kg/day for 2 weeks (usual doses recommended by consensus); [e]doses of albendazole or praziquantel have not been systematically standardized although 30 mg/kg of albendazole was reported more efficient than the classical doses of 15 mg/kg/day in one randomized study (Gongora-Rivera et al.); [f]includes cysts in sulcus of the convexity.

Eosinophilic Meningitis

presence of at least 10% eosinophils in the total CSF leukocyte count

TABLE 122.1 Differential Diagnosis of Eosinophilic Meningitis

Parasitic Infections	Non-Parasitic Infections	Non-Infectious Causes
• Angiostrongyliasis • Gnathostomiasis • Baylisascariasis • Toxocariasis • Cysticercosis • Paragonimiasis • Schistosomiasis • Fascioliasis • Trichinellosis	• Coccidioidomycosis • Cryptococcosis • Myiasis	• Idiopathic hypereosinophilic syndromes • Sarcoidosis • Leukemia or lymphoma with CNS involvement • Ventricular shunts • Post-vaccination Drug induced: • NSAIDs: ibuprofen • Antibiotics: ciprofloxacin, trimethoprim–sulfamethoxazole, vancomycin, gentamicin • Myelography contrast agents

CNS, Central nervous system; *NSAIDs,* nonsteroidal anti-inflammatory drugs.

Prakaykaew Charunwatthana and Yupaporn Wattanagoon Hunter's Tropical Medicine and Emerging Infectious Diseases, 122, 891-894

Thank you