CNS infection in immunocompromised host

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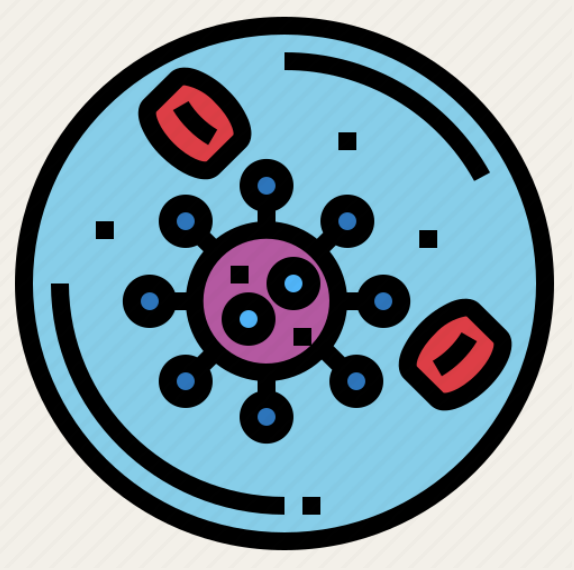
IMMUNOCOMPROMISED HOST



HIV related

Cancer associated

Immunosuppressive and immunomodulator therapies

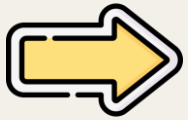
Posttransplantation

Non-HIV related

NON-HIV RELATED

Cancer associated

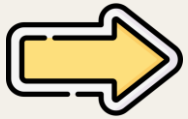
Immunosuppressive and immunomodulator therapies



Neoplastic

Non-neoplastic

Post transplantation



Haematopoietic cell

Solid organ

NON-HIV RELATED

Predisposing Condition	Infectious Risks	Relevant Drugs/ Therapies	Special Features/Syndromes
Barrier disruption, neurosurgery (particularly shunts, drains), radiation therapy, central lines/ports, urinary catheters, gastrointestinal surgery, skin injury (radiation, surgery, decubitus)	Bacteria: skin and gut-derived organisms: *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Propionibacterium acnes*, Enterobacteriaceae, *Acinetobacter*, *Streptococcus bovis* Parasites: *Strongyloides stercoralis* Viruses: herpes simplex virus, varicella-zoster virus, cytomegalovirus Fungi: *Aspergillus*, *Candida* species	Corticosteroids, vascular endothelial growth factor inhibitors	Meningitis may lack classic signs DRESS syndrome: drug reaction (or rash) with eosinophilia and systemic symptoms can sometimes be accompanied by herpes simplex virus reactivation
Neutropenia (absolute deficit or impaired function), hematopoietic cell transplantation, solid organ transplantation, intensive chemotherapy (without transplantation), bone marrow failure	Bacteria: *Klebsiella*, *Escherichia coli*, *Pseudomonas*, *S. aureus* Fungi: *Aspergillus*, *Mucor*, *Candida* Viruses: cytomegalovirus, herpes simplex virus, adenovirus, human herpesvirus 6, human herpesvirus 7, West Nile virus, travel-related viruses	Indwelling catheters, intensive chemotherapy	Posttransplant acute limbic encephalitis (human herpesvirus 6) Sinuses or lungs may be portal of entry for infection by bacteria or fungi
B-lymphocyte/ immunoglobulin deficit: chronic lymphocytic leukemia, multiple myeloma, splenectomy, lymphoplasmacytic lymphoma	Bacteria: *Streptococcus pneumoniae*, *Neisseria meningitidis*, *Haemophilus influenzae* Viruses: measles, West Nile virus, enteroviruses	Rituximab, ocrelizumab, brentuximab, mycophenolate mofetil, etanercept, cytotoxic chemotherapy	

Continuum (Minneap Minn). 2018 Oct;24(5, Neuroinfectious Disease):1370-1396

NON-HIV RELATED

Predisposing Condition	Infectious Risks	Relevant Drugs/ Therapies	Special Features/Syndromes
T-lymphocyte or macrophage dysfunction	Viruses: herpes simplex virus, varicella-zoster virus, Epstein-Barr virus (posttransplantation lymphoproliferative disorder), JC virus (progressive multifocal leukoencephalopathy), human herpesvirus 6, human herpesvirus 7 Fungi: *Cryptococcus*, *Blastomyces dermatitidis*, *Histoplasma capsulatum*, *Pseudallescheria boydii* Parasites: *S. stercoralis*, *Toxoplasma gondii* Bacteria: *Listeria*, *Nocardia*, *Mycobacterium tuberculosis* All organisms listed above, plus: donor organ-acquired pathogens, rabies, Arenavirus, lymphocytic choriomeningitis virus, West Nile virus	Antithymocyte globulin, alemtuzumab, azathioprine, bortezomib, corticosteroids, fludarabine; mycophenolate mofetil, cyclosporine, tacrolimus, sirolimus	At risk for posttransplantation lymphoproliferative disorder; primary central nervous system lymphoma Immune reconstitution inflammatory syndrome (IRIS) may put the transplanted organ at risk for rejection

Continuum (Minneap Minn). 2018 Oct;24(5, Neuroinfectious Disease):1370-1396

POSTTRANS-PLANTATION

Time From Transplant	Infectious Conditions	Noninfectious Conditions
Conditioning and infusion (hematopoietic cell transplantation)		Drug-related encephalopathy (busulfan, etoposide, ifosfamide, methotrexate, cytarabine), dimethylsulfoxide (DMSO)-related stroke,[a] posterior reversible encephalopathy syndrome (PRES), seizures, low intracranial pressure after lumbar puncture
<1 Month neutropenic period	Cytomegalovirus, human herpesvirus 6,[a] *Aspergillus, Toxoplasma gondii* Donor organ–acquired pathogens: lymphocytic choriomeningitis virus, West Nile virus, rabies, adenovirus, coxsackievirus B4, human T-cell lymphotropic virus type 1 (HTLV-I) myelitis *Candida* (IV lines) Nosocomial bacterial sepsis	Engraftment syndrome[a]; metabolic delirium (organ failure); seizures; PRES (tacrolimus[b] and cyclosporine more than sirolimus); other calcineurin inhibitor complications; parkinsonism (amphotericin B); subdural hematoma, intracranial hemorrhage, or subarachnoid hemorrhage due to coagulopathy
1–6 Months	*Aspergillus*, human herpesvirus 6,[a] herpes simplex virus, progressive multifocal leukoencephalopathy, Epstein-Barr virus (posttransplantation lymphoproliferative disorder), *T. gondii*, varicella-zoster virus	Acute disseminated encephalomyelitis (ADEM), osmotic demyelination syndrome, immune reconstitution inflammatory syndrome (IRIS), graft versus host disease (GVHD)
6 Months	Varicella-zoster virus, cytomegalovirus, progressive multifocal leukoencephalopathy, Epstein-Barr virus (posttransplantation lymphoproliferative disorder), *Aspergillus*, Mucoraceae	Secondary malignancy, disease relapse, Graves disease, sarcoidosis, demyelination, IRIS, GVHD (polymyositis, myasthenia, chronic inflammatory demyelinating polyradiculoneuropathy [CIDP])

Continuum (Minneap Minn). 2018 Oct;24(5, Neuroinfectious Disease):1370-1396

WHAT's THE DIFFERENCES?

- **Absence of classic signs of infections** such as fever and meningismus, particularly in patients receiving corticosteroids
- **Frequent presence of multiple concurrent infections**
- **Unusual virulence of potential pathogens** of low risk in hosts who are immunocompetent, such as Enterovirus, West Nile virus, or varicella-zoster virus (VZV)
- **Limited of vaccine use and inefficient of vaccination**

Continuum (Minneap Minn). 2018 Oct;24(5, Neuroinfectious Disease):1370-1396

WHAT's THE DIFFERENCES?

- **Mimicry of infection by numerous noninfectious conditions**, including drug toxicity; stroke; vasculitis; and, in transplant recipients, engraftment syndrome, graft versus host disease (GVHD), posttransplantation lymphoproliferative disorder (PTLD), immune reconstitution inflammatory syndrome (IRIS), and organ rejection
- **Lack of specificity of laboratory and imaging studies** as impaired hosts cannot mount effective inflammatory responses and neuroimaging may mimic disease recurrence or stroke or treatment-related abnormalities such as posterior reversible encephalopathy syndrome (PRES), radiation necrosis, or drug-induced leukoencephalopathy

Continuum (Minneap Minn). 2018 Oct;24(5, Neuroinfectious Disease):1370-1396

LABORATORY AND IMAGING

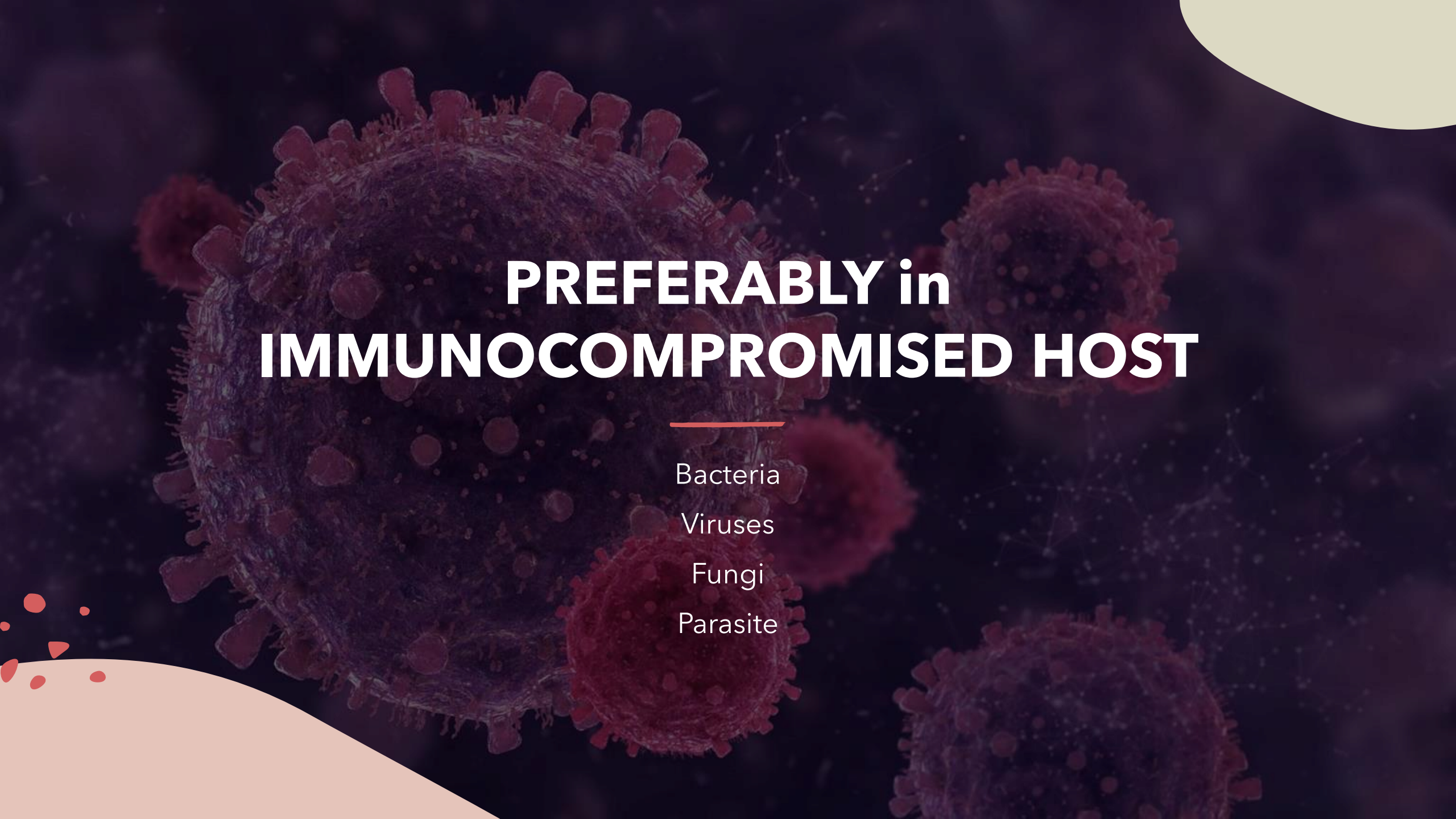
- **Corticosteroids** reduce contrast enhancement
- **Renal insufficiency** (glomerular filtration rate less than 30 mL/min) may preclude contrast use
- **Diffuse meningeal enhancement** mimicking carcinomatous meningitis or localized fluid-attenuated inversion recovery (FLAIR) abnormality can occur after multiple seizures
- **Diffuse dural enhancement** can mimic metastatic or granulomatous disease but most commonly indicates low intracranial pressure after lumbar puncture

Continuum (Minneap Minn). 2018 Oct;24(5, Neuroinfectious Disease):1370-1396

LABORATORY AND IMAGING

- **Hyperintensity in the subarachnoid space** can reflect blood, infection, or tumor involvement or may be seen in patients ventilated at high inspiratory oxygen concentrations
- **Ring-enhancing lesions** have a broad differential that includes tumor recurrence, infection, and pseudoprogression
- **White matter lesions with minimal enhancement** suggest JC virus–associated PML, but varying degrees of enhancement can occur depending on the host's immunocompetence
- **CSF pleocytosis** may be minimal or absent in the presence of cytopenias

Continuum (Minneap Minn). 2018 Oct;24(5, Neuroinfectious Disease):1370-1396



PREFERABLY in IMMUNOCOMPROMISED HOST

Bacteria

Viruses

Fungi

Parasite

BACTERIA

Listeria monocytogenes

Nocardia spp.

LISTERIA MONOCYTOGENES

REQUIRED NEUTROPHILS !! for phagocytosis, production of NOS and cytokine

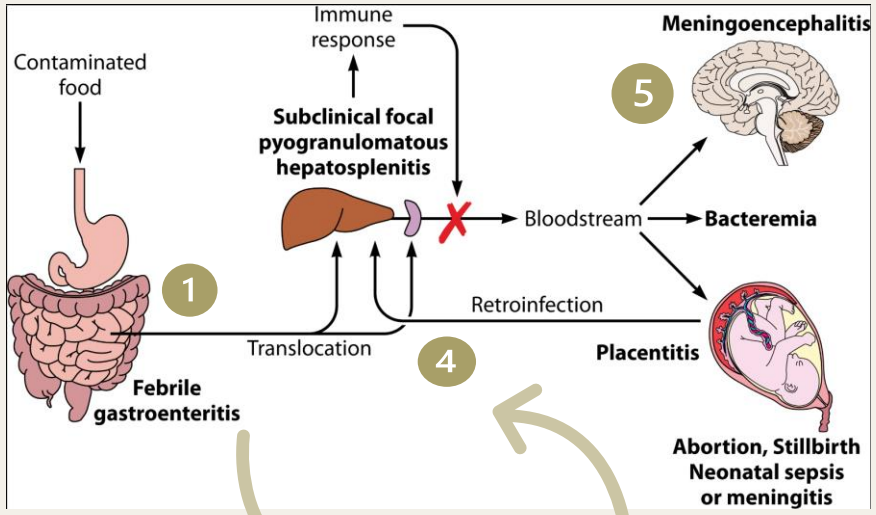
Gram positive intracellular pathogen
Able to live in extreme environment eg. Refrigerator
Food borne infection; raw meat, processed food

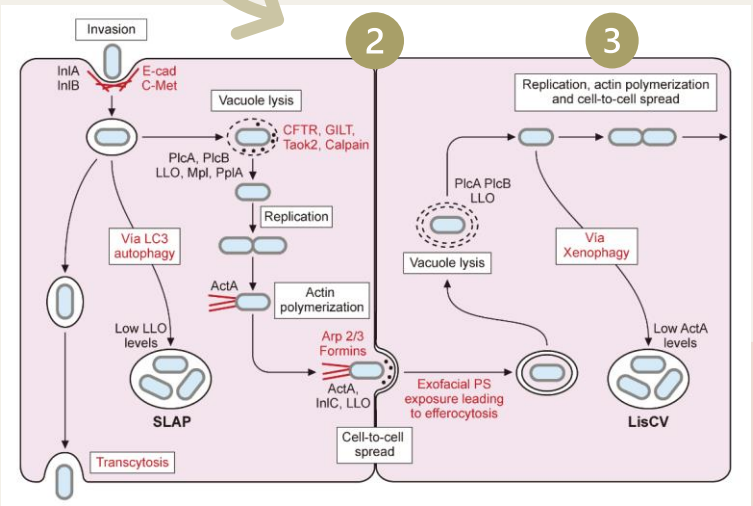
Pathophysiology:

1) Crossing intestinal barrier
2) Entry and proliferation inside eukaryotic cells
3) Cell-to-cell spread
4) Disseminated in blood
5) Invade CNS

Retrograde axonal transport:
1. Oropharyngeal -> cranial nerve (esp. CN V) -> rhombencephalitis
2. Olfactory epithelium -> contact in newborn case

Crossing blood brain barrier
- extra/intracellular -> cross BBB through infected leukocyte -> meningitis/meningoencephalitis





Virulence. 2021 Dec;12(1):2509-2545

LISTERIA MONOCYTOGENES

Risk factor: Extreme age (< 1 month and > 65 yrs), immunocompromised, pregnancy

Clinical manifestation:

Neurolisteriosis: encephalitic symptoms (87%), nuchal rigidity (65%) aphasia (19%), seizures (18%), brainstem abnormalities (17%)

Bacteremia (fever, flu-like symptoms, diarrhea)

Maternal-neonatal

Investigation:

CSF profile: pleocytosis, polymorphonuclear or mononuclear, low glucose, elevated protein

Blood culture, CSF culture

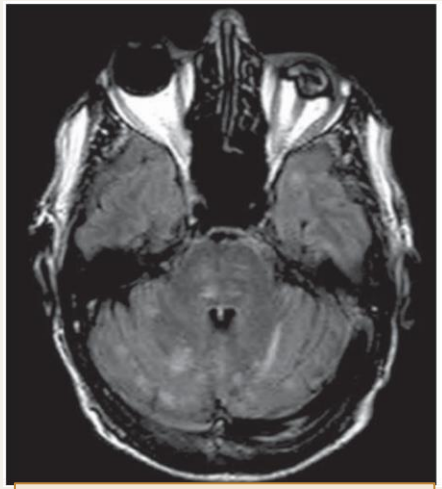
CT/MRI: non-specific

Treatment:

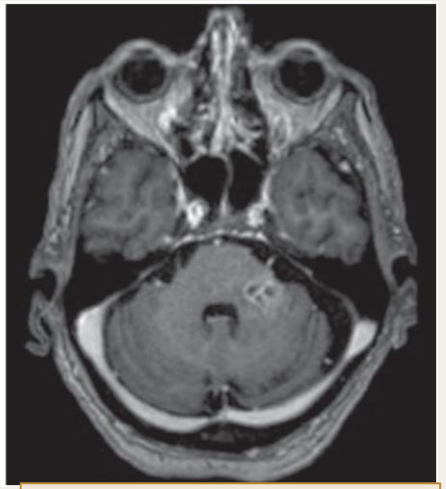
Ampicillin 2gm IV q4-6h (or penicillin G 4 MU IV q4h) + gentamicin 1.7mg/kg IV q8h x ≥ 3wks.

prolonged at least 6wk for brain abscess, rhombencephalitis

Corticosteroid should be AVOIDED



Rhombencephalitis

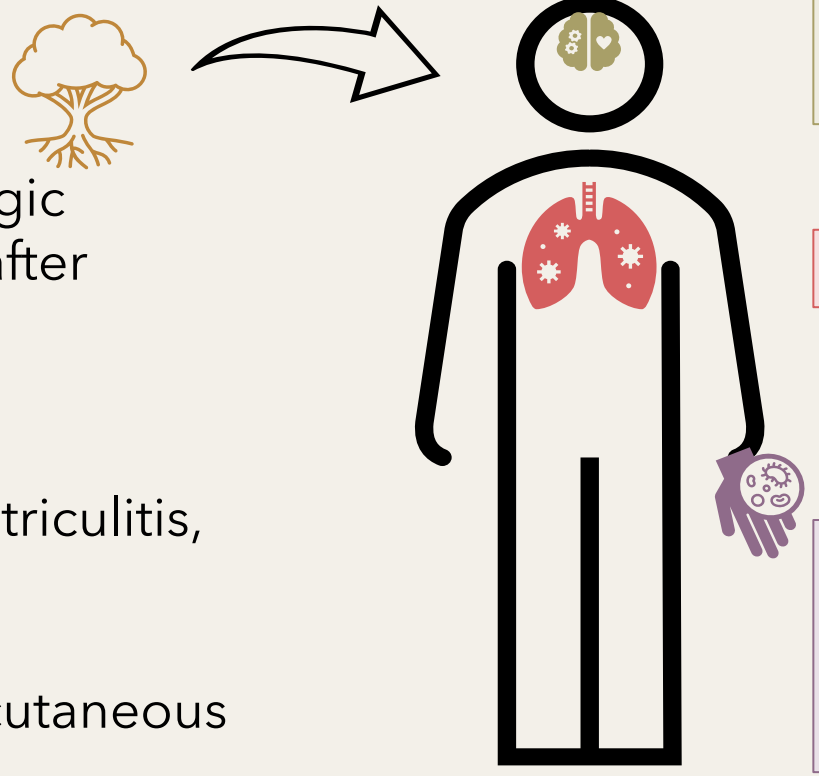


Lt.pontine abscess

Radiol Bras. 2016 Sep-Oct;49(5):329-336.
Lancet Infect Dis. 2017 May;17(5):510-519.
Clin Microbiol Rev. 2023 Mar 23;36(1):e0006019.
Clin Microbiol Infect. 2016 May;22 Suppl 3:S37-62.

NOCARDIA SPP.

Soil-dwelling, aerobic, gram positive bacteria



CNS
Abscess,
Ventriculitis,
Meningitis

PULMONARY

CUTANEOUS
Primary cutaneous
Lymphocutaneous
Mycetoma

Risk factor:

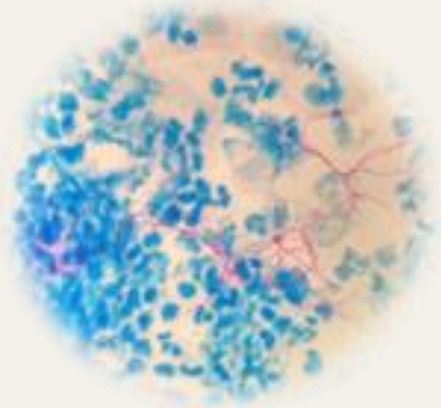
HIV (CD4<200) , Cancer (mostly hematologic malignancy), Posttransplantation (1-6mth after transplant), Corticosteroid

Clinical manifestation:

- CNS: **Brain abscess***, Leptomeningitis, Ventriculitis, Vasculitis, Intramedullary abscess
- Pulmonary
- Cutaneous eg. Primary cutaneous, lymphocutaneous tissues, mycetoma
- Other: ocular, osteomyelitis, septic arthritis

Med Princ Pract. 2022;31(4):333-341.
Clin Microbiol Rev. 2022 Dec 21;35(4):e0002721.
J Community Hosp Intern Med Perspect. 2021 Mar 23;11(2):258-262.

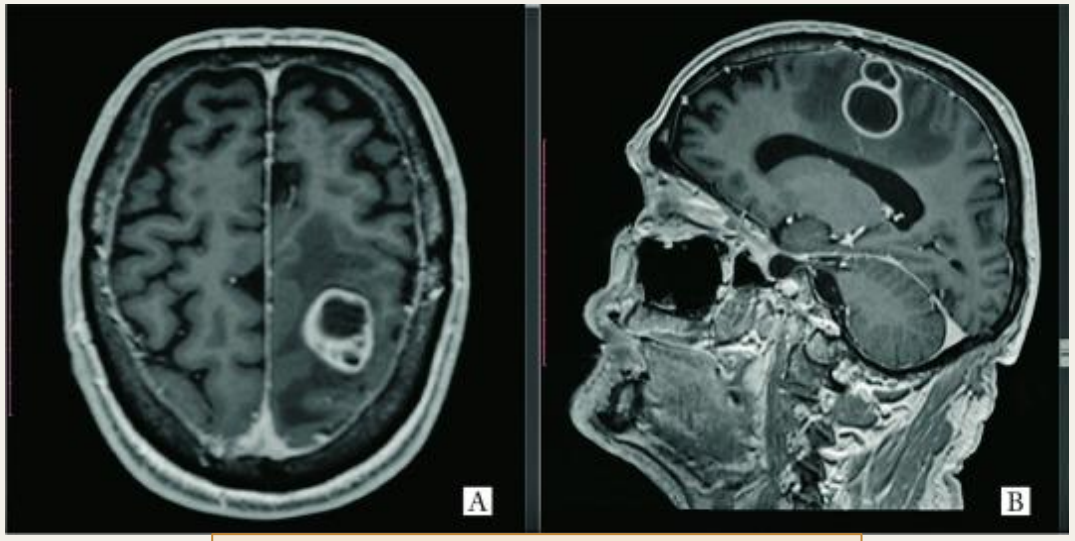
NOCARDIA SPP.



Investigation:

CSF profile: neutrophilic pleocytosis, elevated protein, and decreased glucose levels
CSF mAFB: branching filamentous bacilli
CSF cultures (sensitivity 60%)
MRI Brain: single or multifocal brain abscess
Brain biopsy

Should be differential diagnoses with **BRAIN METASTASIS !!!**



Brain abscess: single / multiple

Treatment: No standard guideline

Monotherapy: **TMP/SMX** (5mg/kg/d of TMP)
-May up to 15mg/kg/d; CNS infection, Severe extensive infection, AIDS
Combination therapy **(TMP/SMX+Imipenem or amikacin)**
Duration: intravenous therapy for 3-6 weeks then oral therapy for at least 1 year

Med Princ Pract. 2022;31(4):333-341.
Clin Microbiol Rev. 2022 Dec 21;35(4):e0002721.
J Community Hosp Intern Med Perspect. 2021 Mar 23;11(2):258-262.

VIRUSES

Epstein-Barr virus (EBV)

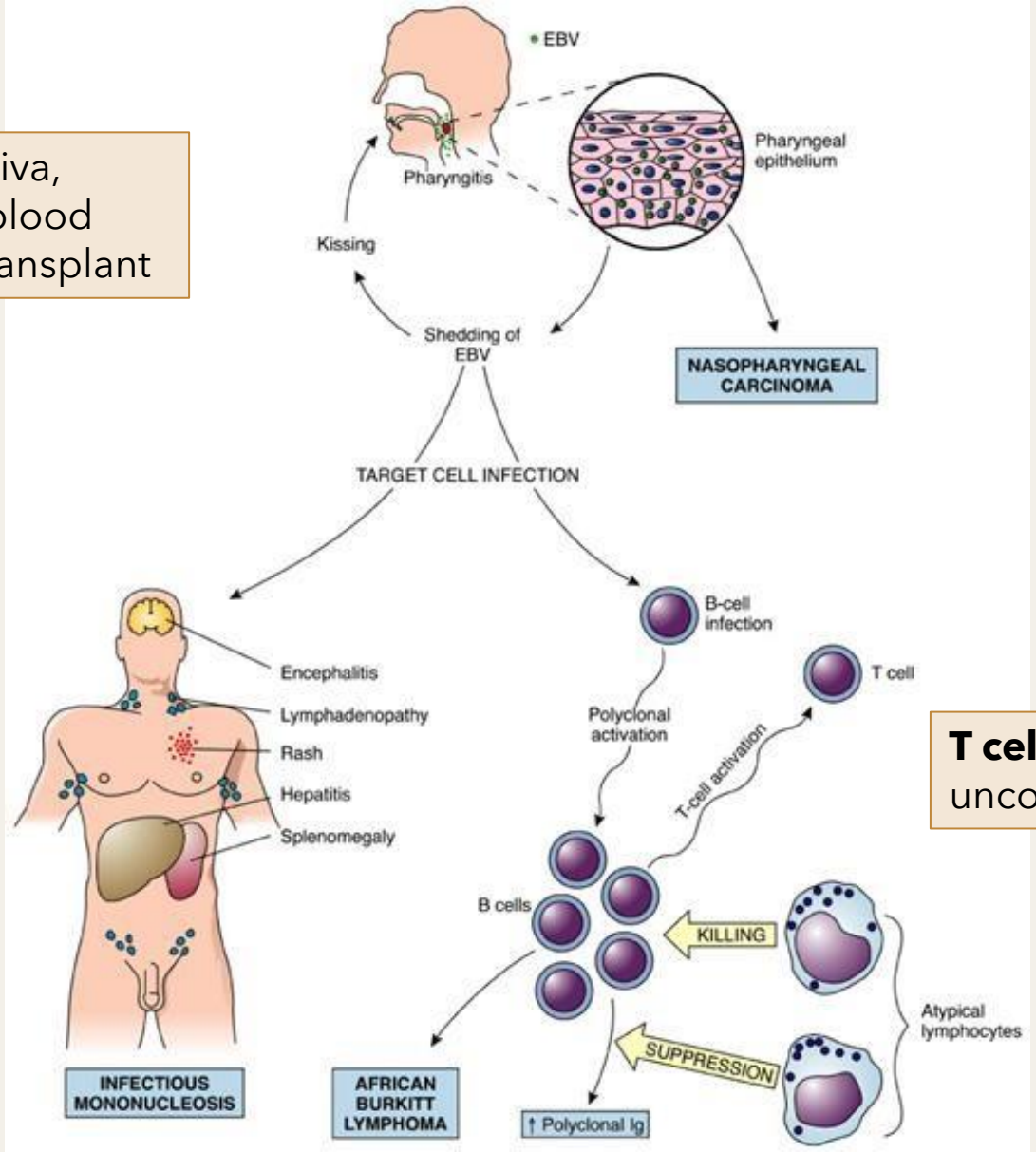
Cytomegalovirus (CMV)

Human Herpes Virus-6 (HHV-6)

JC virus (JCV)

EPSTEIN-BARR VIRUS (EBV)

Transmission via saliva, sexual transmitted, blood transfusion, organ transplant



T cell dysfunction led to uncontrolled infection

Epstein-Barr virus (EBV). Intergenetics. (2020, January 20). https://intergenetics.eu/en/exam/epstein-barr-virus-ebv/

EPSTEIN-BARR VIRUS (EBV)

Risk factor:

HIV (initially tolerate EBV infection, but later higher risk for EBV-driven malignancies)
Solid organ transplant, HSCT (1st –2nd year posttransplant)

Clinical manifestation:

Primary infection = Infectious mononucleiosis

Classic Triad:
Fever, pharyngitis, lymphadenopathy

Other process related to EBV

HEENT: Oral hairy leukoplakia (HIV), Nasopharyngeal carcinoma
Hemato: Burkitt's lymphoma, Primary CNS lymphoma and other lymphomas (esp.HIV),
Posttransplant lymphoproliferative disorder (PTLD)
Chronic active EBV: pancytopenia, chronic LN, pneumonitis, abnormal LFTs
Hemophagocytic lymphohistiocytosis (HLH)
CNS: Meningitis, encephalitis, myelitis, and vasculitis
Postinfectious complications: GBS, ADEM, transverse myelitis, and polyradiculomyelitis

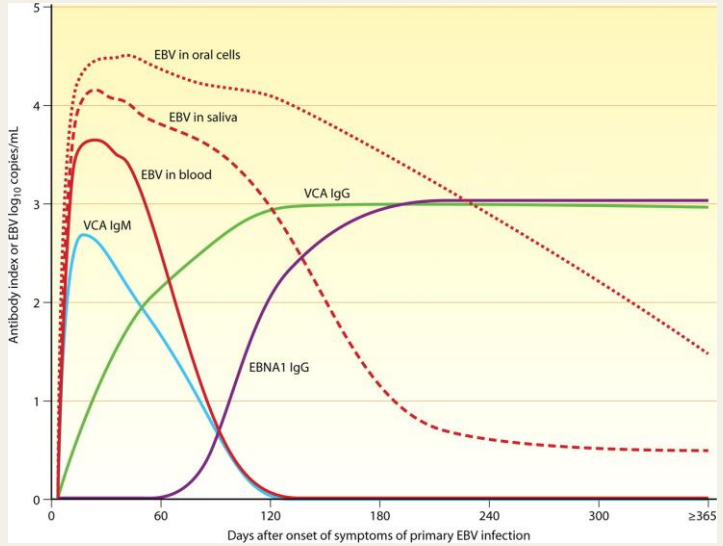
Front Mol Biosci. 2022 Jan 10;8:816098.
Biomed Pharmacother. 2022 Jan;145:112392.

EPSTEIN-BARR VIRUS (EBV)

Investigation:
For infectious mononucleiosis
- Serologic testing:
  - Viral capsid antigen (VCA),
  - Early antigen (EA),
  - EBV nuclear antigen (EBNA)

For CNS lymphoma (in HIV)
- **CSF PCR for EBV (sens 97%, spec 98%)**
- MRI Brain: non-specific

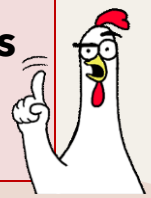
Treatment: No standard guideline
Report of antiviral (**Ganciclovir**, Acyclovir) and immunosuppressant were reduced
Ganciclovir is more potent 10x to acyclovir



VCA IgM	VCA IgG + EA IgG	EBNA IgG	Interpretation
-	-	-	Negative EBV status
+	-	-	Early primary infection [2]
+	+	-	Acute primary infection
-	+	+ [1]	Past infection
-	-	+	Isolated EBNA IgG [2]
-	+	-	Isolated VCA/EA IgG [2]
+	+	+	Indeterminate [2]

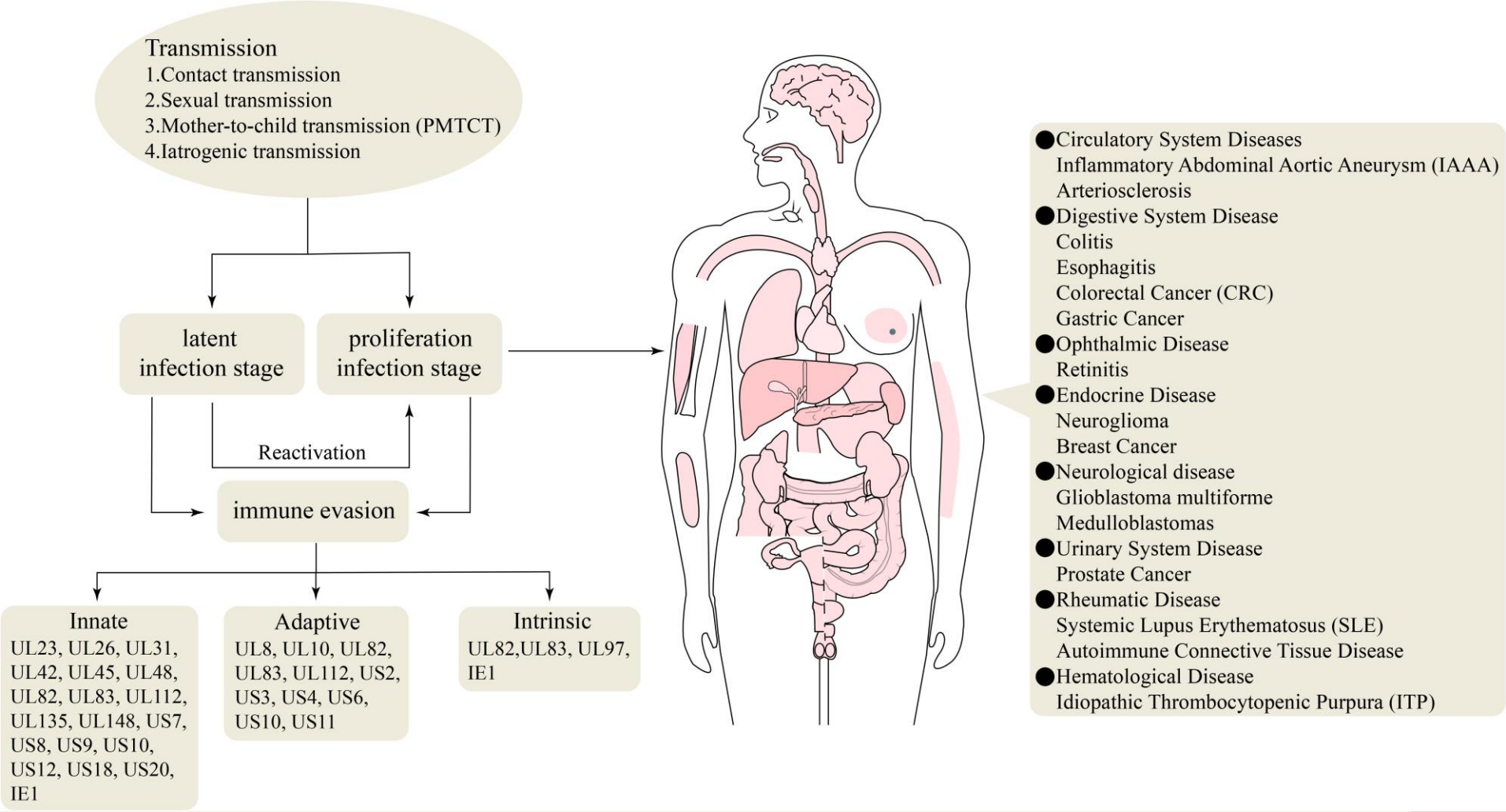
[1] In rare cases, anti-EBNA antibodies are not detected in patients with past infection status.
[2] To be confirmed on a new sample 1 to 2 weeks later or with another technique.

= **infectious mononucleiosis** (if symptoms **<4-6wk**)



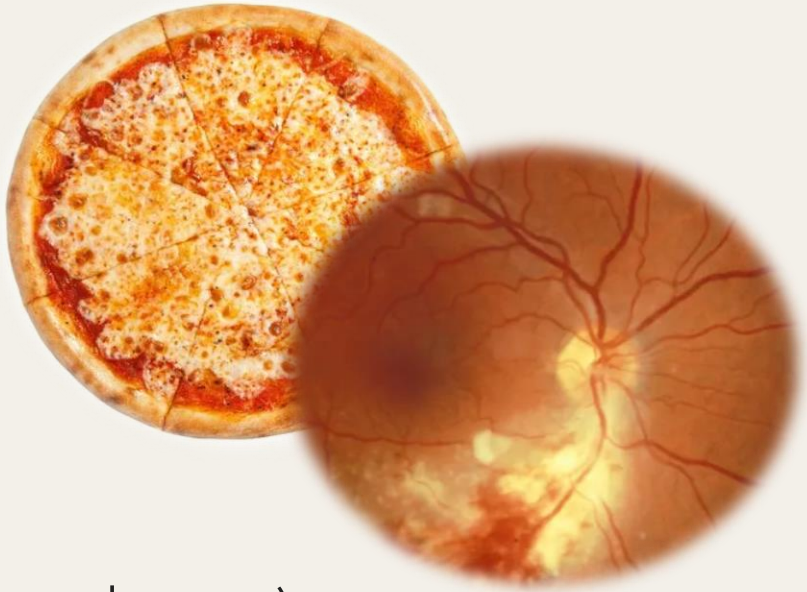
Front Mol Biosci. 2022 Jan 10;8:816098.
Biomed Pharmacother. 2022 Jan;145:112392.

CYTOMEGALOVIRUS (CMV)



Lele Ye et al. Front Microbiol. 2020.

CYTOMEGALOVIRUS (CMV)



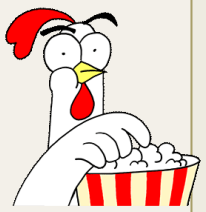
Most likely due to reactivation of latent infection or reinfection

Risk factor: cell-mediated immunosuppression

HIV (CD4 <100),
Cancer (decline in lymphocyte counts during CMT, RT or immunotherapy),
Solid organ transplant, HSCT

Clinical manifestation:

CNS: **Ventriculoencephalitis,**
Glial nodular encephalitis,
Polyradiculitis*,
polyneuropathy, vasculopathy with stroke
Retinitis
Gastrointestinal: esophagitis, colitis
Pulmonary



Ventriculoencephalitis:
-Rapidly fatal course, esp. with necrotizing periventricular encephalitis
-Infection of choroid plexus and ependyma resulted in periventricular necrosis

Handb Clin Neurol. 2018;152:151-166.
Rev Esp Quimioter. 2022 Oct;35 Suppl 3(Suppl 3):74-79.

CYTOMEGALOVIRUS (CMV)

Glial nodular encephalitis	*Polyradiculomyelitis*
Subacute to chronic progressive encephalopathy or dementia (6-12mth) Presented with confusion, disorientation, seizures, and focal neurological signs	initially involves the lower limbs, with ascending areflexia, hypotonic paresis, paraesthesias, hypaesthesia and early urinary retention

Should be distinguish with **HIV-associated dementia**
Onset >1yr
(more RAPID in CMV!)

Clinical characteristics of *C jejuni*-associated GBS and CMV-asociated GBS

	***C jejuni*-associated GBS**	**CMV-associated GBS**
Sex	Predominantly male	Predominantly female
Age	Not specific	Younger
Antecedent episode	Diarrhoea	Upper respiratory infections
Cranial nerve involvement	Less frequent	Frequent facial palsy
Sensory impairment	Less common	Frequent and severe
Electrodiagnosis	AMAN	AIDP
Autoantibody	IgG antibodies to GM1, GM1b, GD1a, or GalNAc-GD1a	IgM antibody to GM2

CNS Drugs. 2002;16(5):303-15.
Lancet Infect Dis. 2001 Aug;1(1):29-37

CYTOMEGALOVIRUS (CMV)

Investigation:

CSF profile: lymphocytic pleocytosis, low to normal glucose, and normal to slightly elevated protein (in ventriculoencephalitis)
CSF CMV PCR
MRI Brain: diffuse cerebral atrophy, progressive ventriculomegaly, and a variable degree of **periventricular or subependymal contrast enhancement**

Treatment:

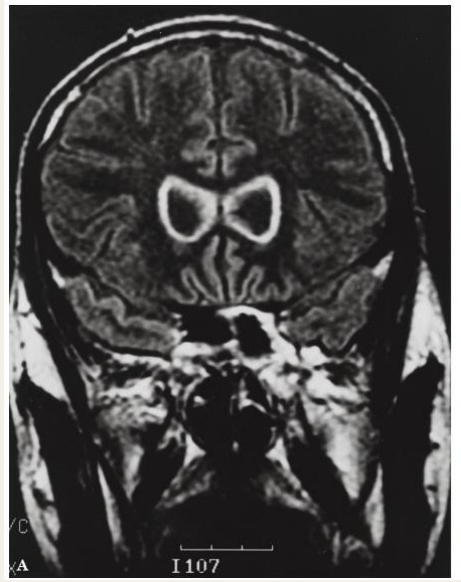
Induction therapy for 2wk or until resolution of neurologic symptoms

Ganciclovir 5mg/kg IV q12hr PLUS
Foscarnet 90mg/kg IV q12hr

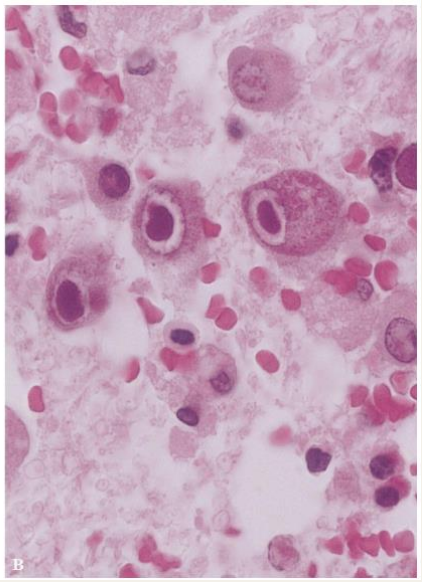
Followed by maintenance (until CD4>200)

Valganciclovir 900mg po bid

OWL'S EYE



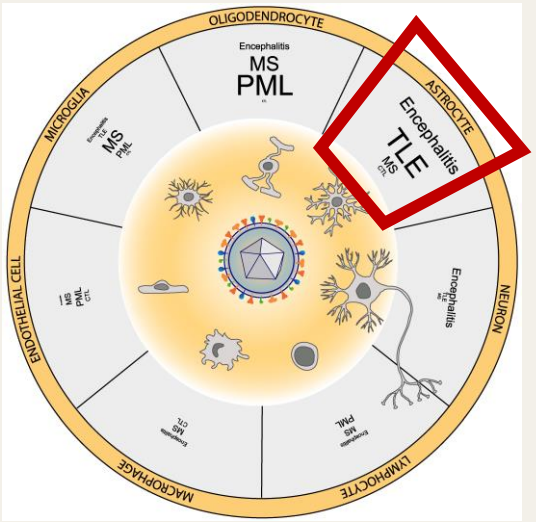
Periventricular enhancement in ventriculoencephalitis



Intranuclear inclusion bodies

Neurology 2000;54;2217
Handb Clin Neurol. 2018;152:151-166.

HUMAN HERPES VIRUS-6 (HHV-6)



HHV-6 infected multiple neural cell types
Dysregulate astrocyte glutamate uptake in tissue culture
Reactivation of HHV-6
HHV-6A (more neurotropism), HHV-6B

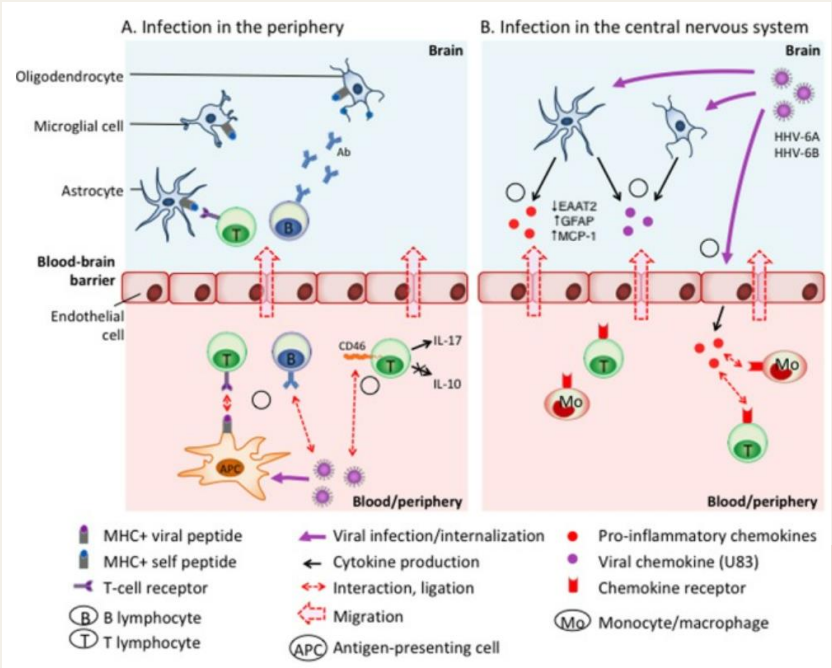
Risk factor:

HSCT (within 2mth posttransplantation)

Clinical manifestation:

Post-transplant acute limbic encephalitis (PALE)

- Acute mental status alterations; dense anterograde amnesia, with variable retrograde memory loss, temporal lobe seizure, and/or visual hallucination
- Following HSCT, solid organ transplant



Epilepsy Res. 2019 Jul;153:34-39.
Biomolecules. 2020 Nov 6;10(11):1520.
Curr Infect Dis Rep. 2008 Jul;10(4):292-9

HUMAN HERPES VIRUS-6 (HHV-6)

Investigation:

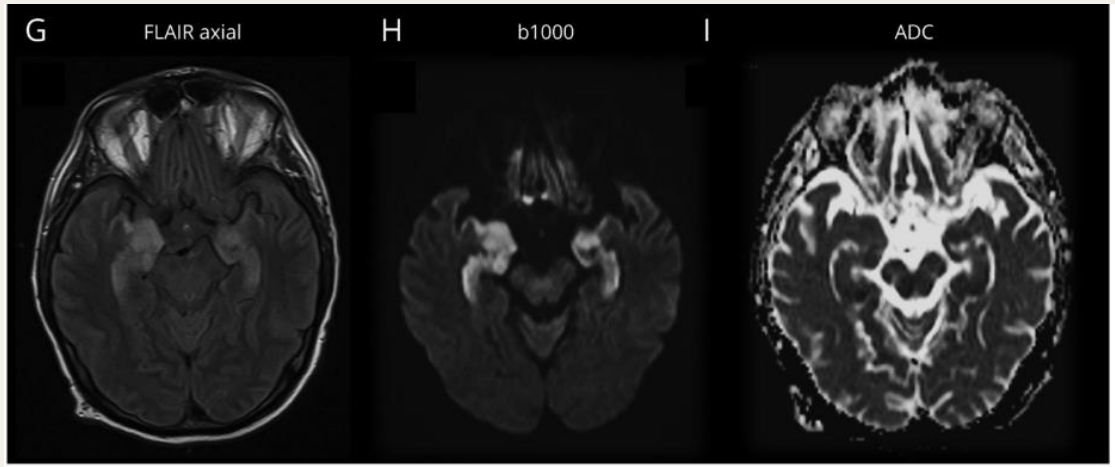
CSF profile
- Mild pleocytosis, monocyte predominance,
- elevated protein

PCR for HHV-6 DNA
- CSF often positive
- Peripheral

if >= 10,000 copies/ml (sens 100%, spec 64.6%)
if >= 100,000 copies/ml (sens 57.1-70%, spec 90.6-94%)

MRI Brain:
- **Focal medial temporal lobe MRI signal hyperintensities (DWI, FLAIR, T2)**
- Frequently bilateral but may be unilateral

Hyponatremia (SIADH)



Lesion may become **more pronounce in follow-up studies** shortly after symptom onset

Curr Infect Dis Rep. 2008 Jul;10(4):292-9
Neurol Neuroimmunol Neuroinflamm. 2021 Jan 12;8(2):e942.

HUMAN HERPES VIRUS-6 (HHV-6)

Treatment:

FOSCARNET

- 60 mg/kg every 8 hours for 21 to 28 days

Ganciclovir

- reduced efficacy for some HHV-6A isolates

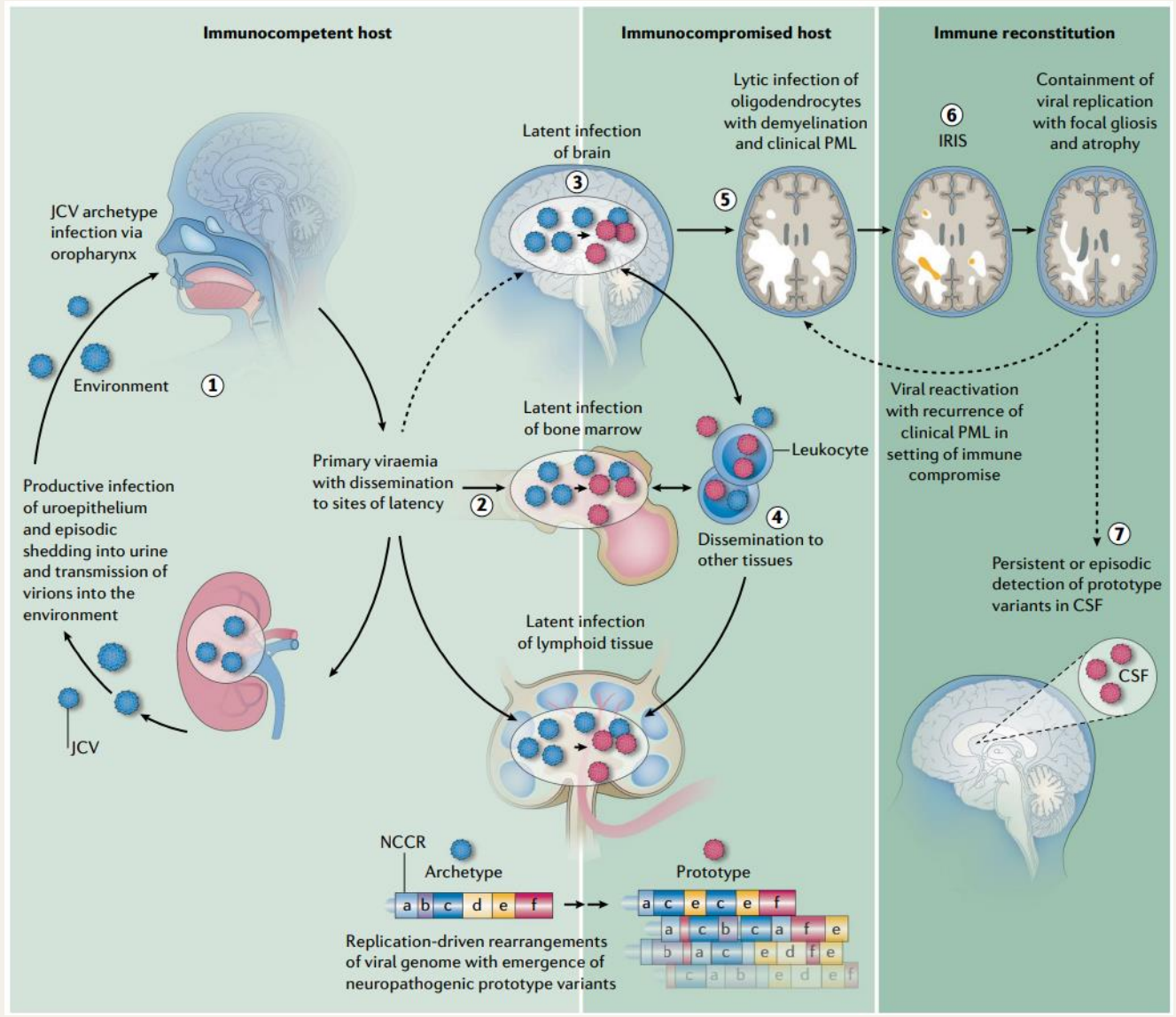
Cidofovir

- Less commonly used

Still need to be caution for ADR: myelosuppression, nephrotoxicity, and electrolyte abnormalities

Curr Infect Dis Rep. 2008 Jul;10(4):292-9

JC VIRUS

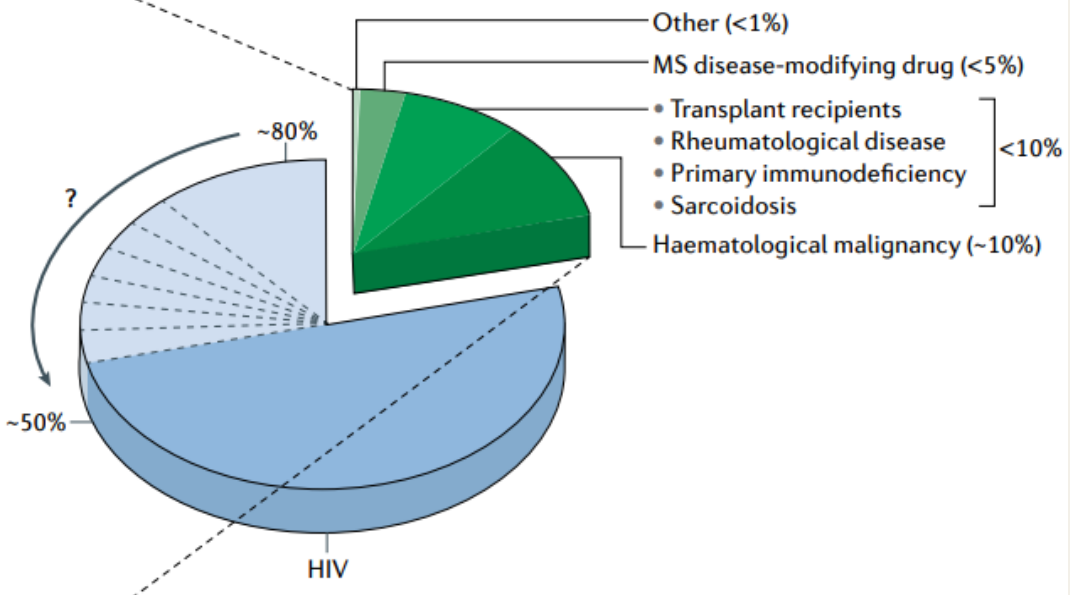


Nat Rev Neurol. 2021 Jan;17(1):37-51.

JC VIRUS

Risk factor:

Drug	Indications
Belatacept	Kidney transplantation
Belimumab	SLE
Brentuximab vedotin	Hodgkin lymphoma
Cyclosporine	Transplantation
Dimethyl fumarate	RRMS
Efalizumab	Psoriasis
Fingolimod	RRMS
Ibrutinib	CLL, mantle cell lymphoma, marginal zone lymphoma, WM, cGVHD
Mycophenolate mofetil	Transplantation
Natalizumab	RRMS
Obinutuzumab	CLL
Ocrelizumab	RRMS, PPMS
Ofatumumab	CLL
Rituximab	CLL, non-Hodgkin lymphoma, RA, WG, MPA
Ruxolitinib	Myelofibrosis
Sirolimus	Transplantation
Tacrolimus	Transplantation
Vedolizumab	UC, Crohn's disease



Nat Rev Neurol. 2021 Jan;17(1):37-51.

JC VIRUS

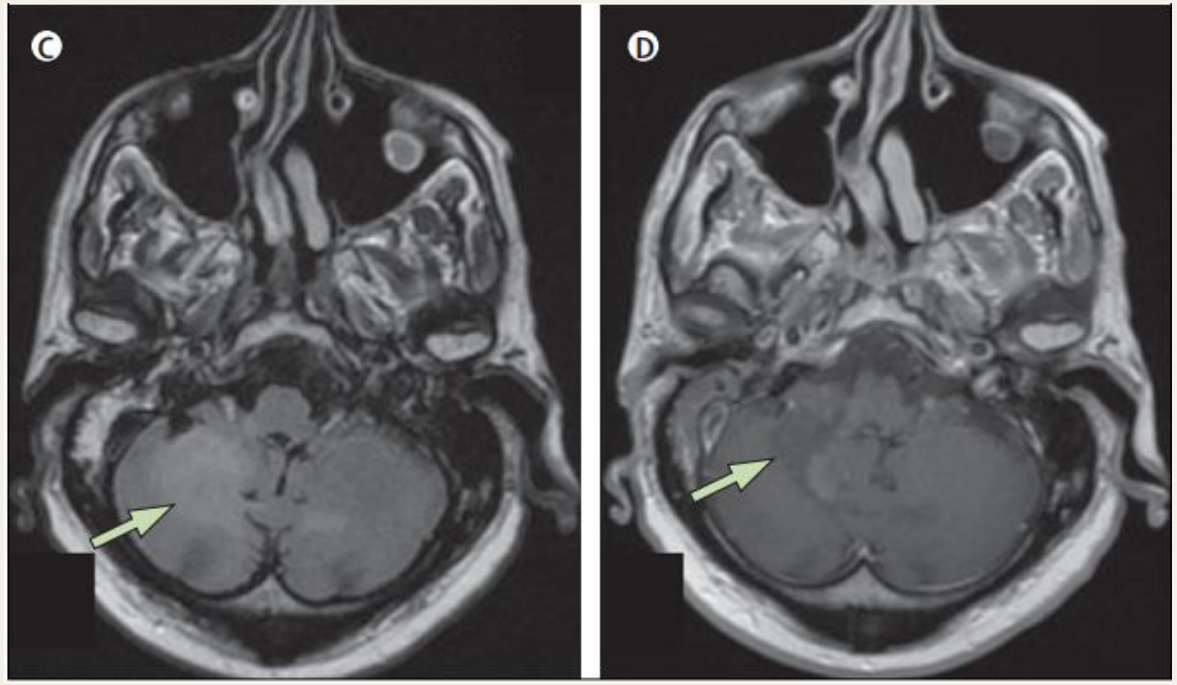
	Classic PML	PML-IRIS	JC virus granule cell neuronopathy	JC virus encephalopathy	JC virus meningitis
Onset	Subacute	Immune recovery	Chronic	Subacute	Acute
Radiological findings (MRI)	Asymmetric, well demarcated, non-enhancing subcortical white matter lesions, hyperintense in T2 and FLAIR, hypointense in T1	Contrast enhancement and mass effect	Cerebellar atrophy	Cortical lesions	No defined brain lesions, ventricular dilatation
Neurological symptoms	Based on location	Based on location and inflammation	Cerebellar syndrome	Encephalopathy	Headache, stiff neck, fever
Diagnosis	JC virus detection in the CSF, brain biopsy, radiographical findings and symptoms	JC virus in the CSF, brain biopsy, radiographical findings and symptoms	Cerebellar biopsy, JC virus in the CSF, radiographical findings and symptoms	Brain biopsy, JC virus PCR in the CSF, radiographical findings and symptoms	JC virus in the CSF and exclusion of other viruses
Histology	Demyelinating lesions often at grey/white junction, JC virus detected in enlarged oligodendrocytes, bizarre astrocytes	Demyelination similar to classic PML, with addition of inflammatory infiltrates	Lytic infection of granule cell neurons in the cerebellum by JC virus	Lytic infection of cortical pyramidal neurons and cortical astrocytes by JC virus	
Treatment	cART for HIV-positive patients, discontinue or decrease immunosuppression for HIV-negative patients, plasma exchange for natalizumab-treated patients	Similar to PML, consider steroids in cases with notable neurological worsening or signs of impending brain herniation	Similar to classic PML	Similar to classic PML	Similar to classic PML

cART=combined antiretroviral therapy. FLAIR=fluid-attenuated inversion recovery. IRIS=immune reconstitution inflammatory syndrome. PML=progressive multifocal leukoencephalopathy.

Table: **Clinical presentations of JC virus neurological infection**

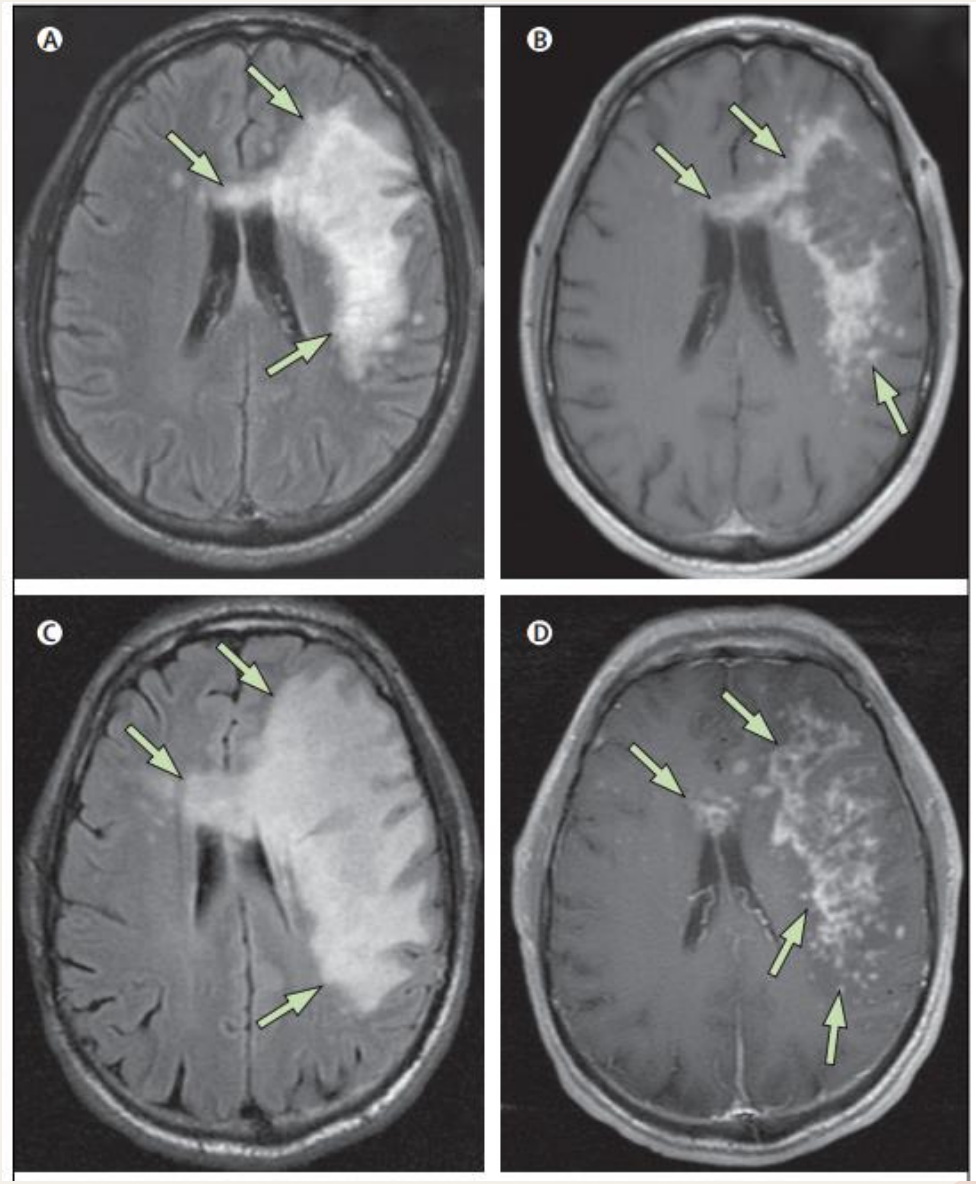
Lancet Neurol. 2010 Apr;9(4):425-37.

JC VIRUS



Classic PML

Asymmetric, well demarcated, non-enhancing subcortical white matter lesions, hyperintense in T2 and FLAIR, hypointense in T1



PML-IRIS

Contrast enhancement and mass effect

Lancet Neurol. 2010 Apr;9(4):425-37.

PML and RELAPSED MS

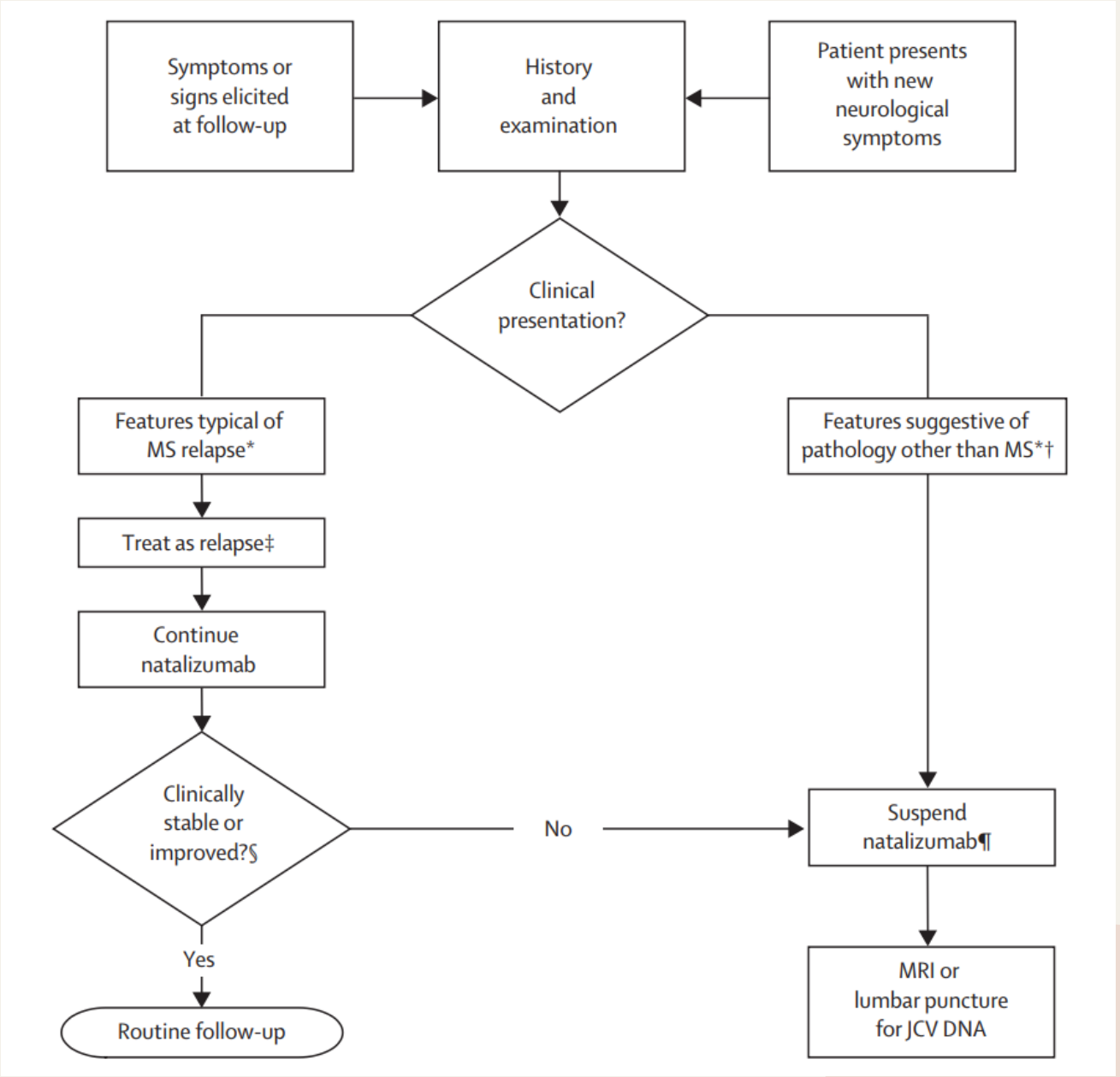
***Panel:* Clinical features indicative of MS relapse and PML**

MS relapse

- Acute onset
- Occurs over several hours to days, reaches usually stable phase, and resolves spontaneously, even without treatment
- Clinical presentation includes diplopia, optic neuritis, and myelopathy (eg, paraparesis, discrete sensory level)

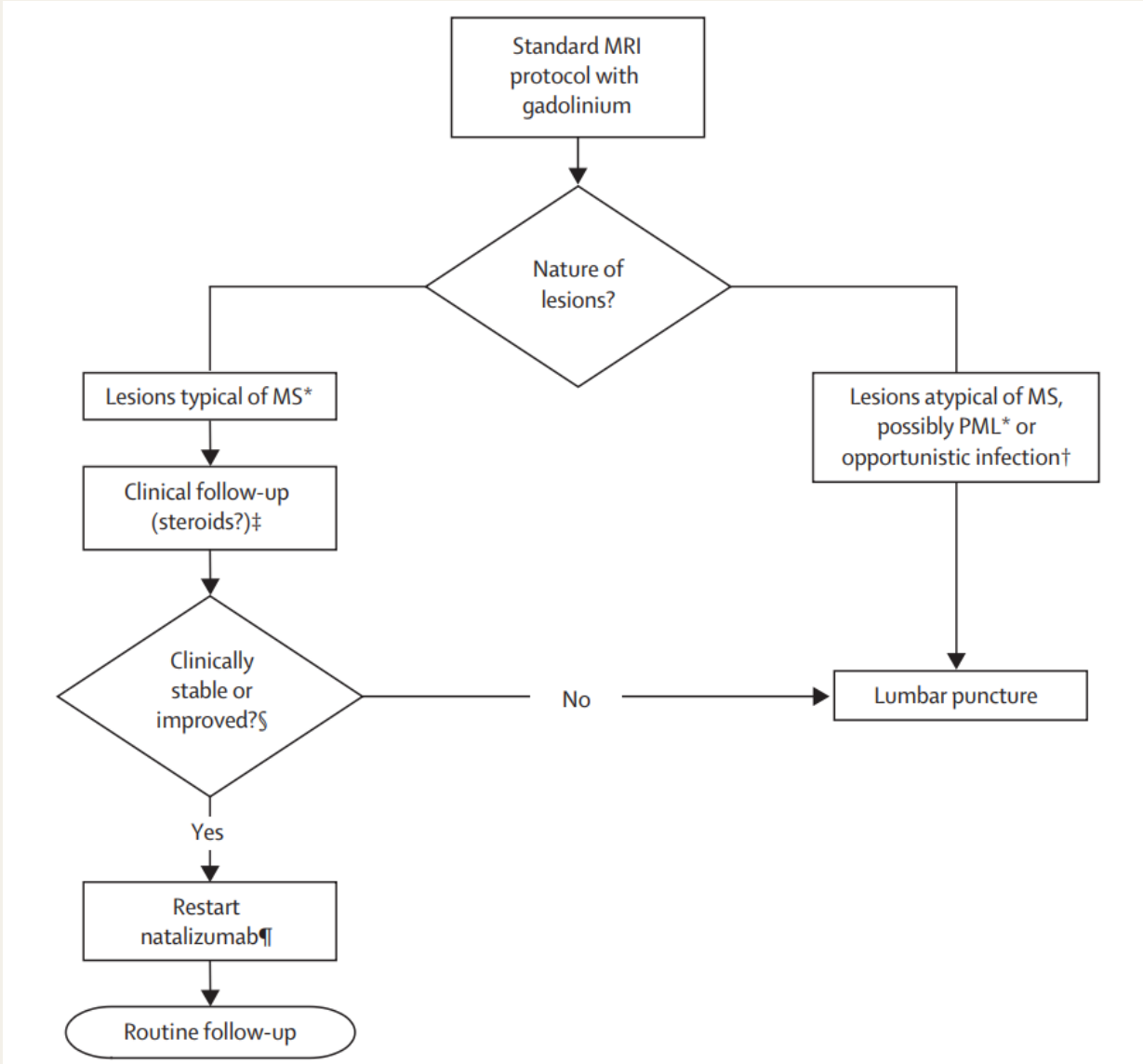
PML

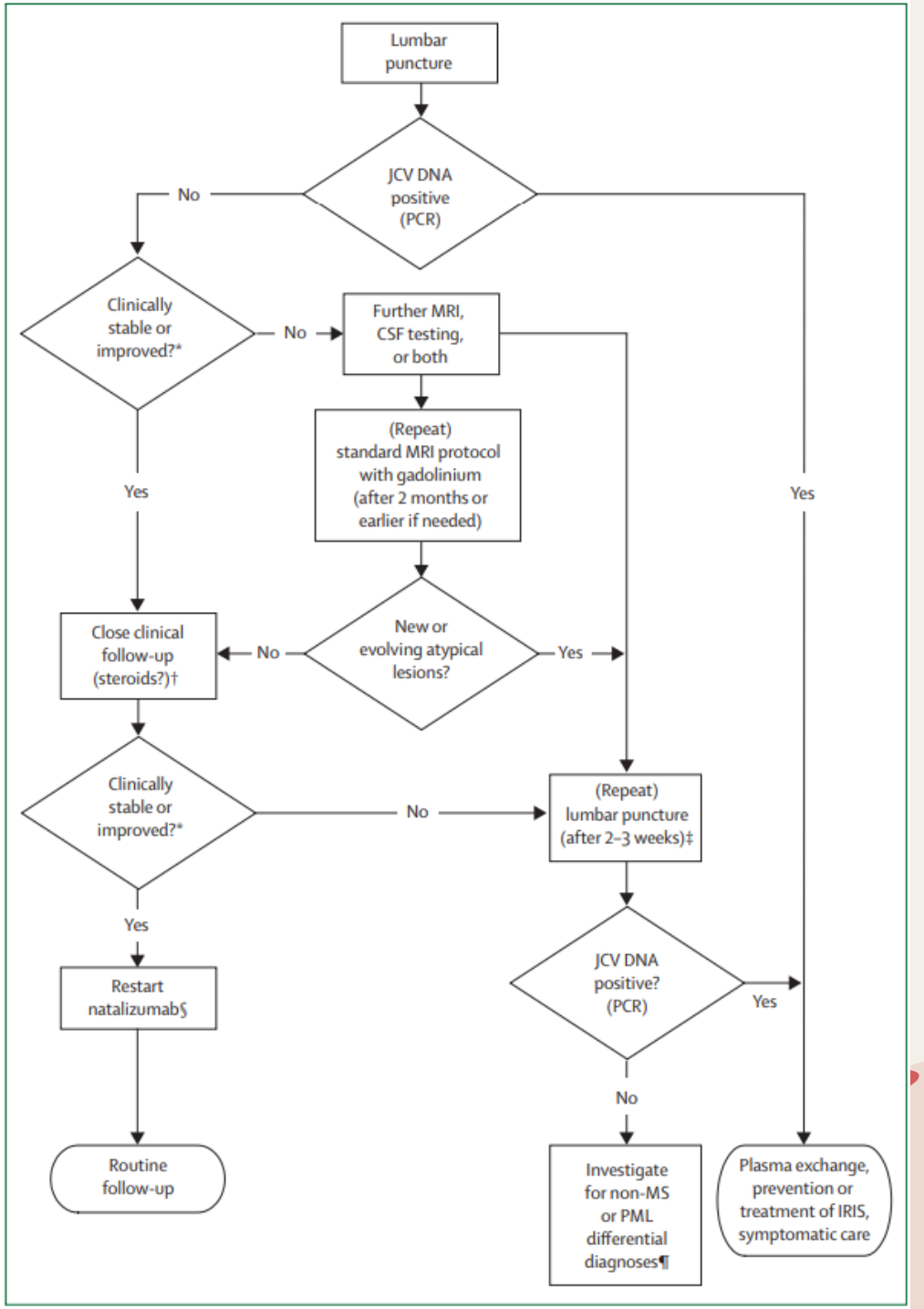
- Subacute onset
- Occurs over several weeks and is progressive
- Clinical presentation includes aphasia, behavioural and neuropsychological alteration, retrochiasmal visual deficits, hemiparesis, and seizures



Lancet Neurol. 2011 Aug;10(8):745-58.

PML and RELAPSED MS





Lancet Neurol. 2011 Aug;10(8):745-58.

PML and RELAPSED MS

	MS	PML
Aspect and location of new lesions	Mostly focal; might affect entire brain and spinal cord, in white and possibly grey matter	Diffuse and asymmetric lesions (initially sometimes unifocal but usually multifocal or widespread), mainly subcortical and rarely periventricular, located almost exclusively in white matter, with occasional extension to deep grey matter; posterior fossa frequently involved (cerebellum, brainstem), rarely in spinal cord
Borders	Sharp edges; mostly round or finger-like in shape (especially periventricular lesions), confluent with other lesions; U-fibres might be involved	Ill-defined edges; infiltrating; irregular in shape; confined to white matter, sparing grey matter; pushing against the cerebral cortex; U-fibres destroyed; typical spread along white-matter tracts
Mode of extension	Initially focal; lesions enlarge within days or weeks and decrease in size within months	Lesions extend homogeneously, continuously, and sometimes rapidly to contiguous (multifocal) and non-contiguous regions (widespread); confined to white-matter tracks, sparing the cortex
Mass effect	Acute lesions show some mass effect	No mass effect even in large lesions (but lesion slightly abuts cerebral cortex), apart from when inflammatory response is present
On T2-weighted sequence	Acute lesions have a hyperintense centre, isointense ring, and discrete hypointensity outside the ring structure; subacute and chronic lesions are hyperintense with no ring structure	Diffuse hyperintensity; slightly increased intensity of newly involved areas compared with old areas; little irregular signal intensity of lesions; sometimes granular appearance
On T1-weighted sequence	Acute lesions are densely hypointense (large lesions) or isointense (small lesions); increasing signal intensity over time in 80%; decreasing signal intensity (axonal loss) in about 20%	Slightly hypointense at onset, with signal intensity decreasing over time and along the affected area; no reversion of signal intensity
On FLAIR sequence	Hyperintense, sharply delineated	Preferred sequence for diagnosis because hyperintensity is most obvious; true extension of abnormality more clearly visible than on T2-weighted images, especially in coronal cuts
With gadolinium enhancement	Acute lesions have dense homogeneous enhancement and sharp edges, and contrast enhancement covers whole extension of the new lesion; subacute lesions have ring enhancement with eventual resolution over 1–2 months; chronic lesions show no enhancement	About half the cases to date have shown some enhancement, typically with a patchy aspect; some peripheral enhancement is possible; enhancement usually increases with inflammatory response or decreases with steroid administration
Atrophy	Focal atrophy is possible due to focal white-matter degeneration; no progression	Initially no focal atrophy; later in the course atrophy can arise

Findings suggest a typical target-like lesion pattern on diffusion-weighted images (DWI), with increased DWI contrast at margins and less in the centre where the apparent diffusion coefficient is raised. In some cases, PML lesions were wrongly thought to be infarcts on the basis of their DWI pattern. MS=multiple sclerosis. PML=progressive multifocal leukoencephalopathy. FLAIR=fluid-attenuated inversion recovery. *No MRI features are pathognomonic of MS or PML.

Table: **MRI features for differential diagnosis of MS and PML***

Lancet Neurol. 2011 Aug;10(8):745-58.

FUNGI

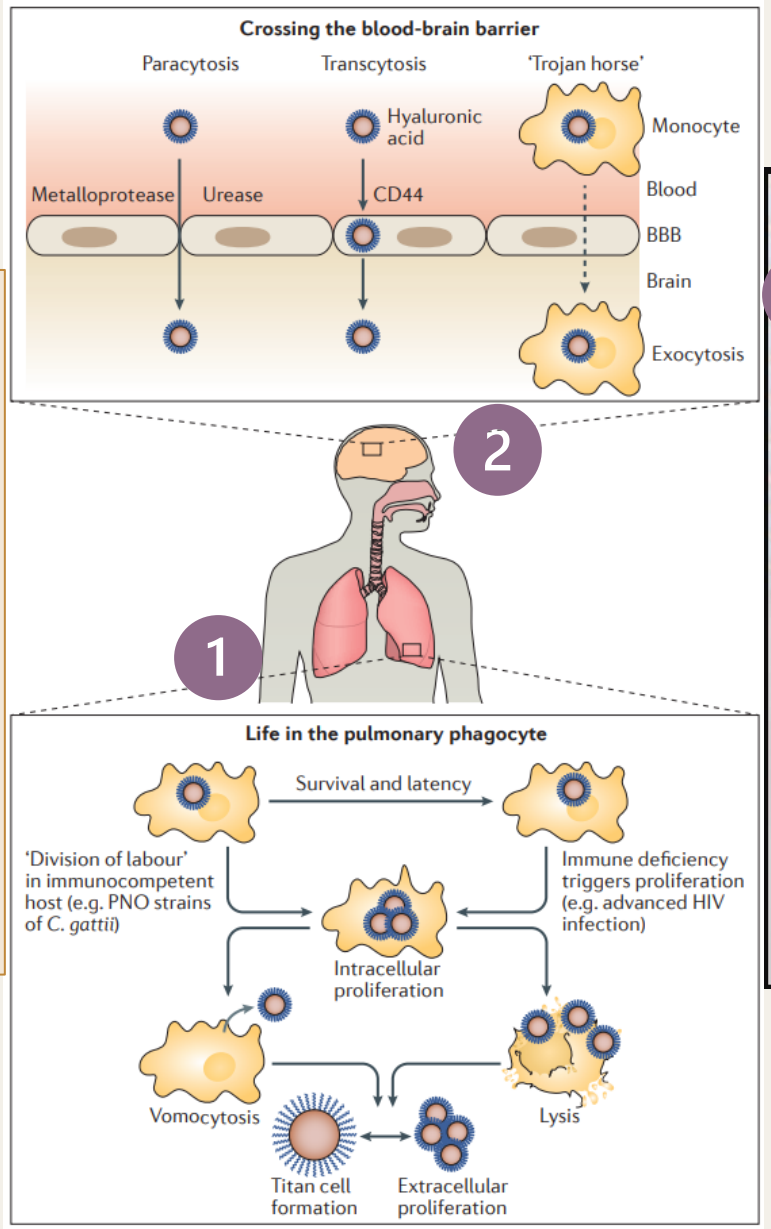
Cryptococcus
Candida
Aspergillus
Mucormycosis

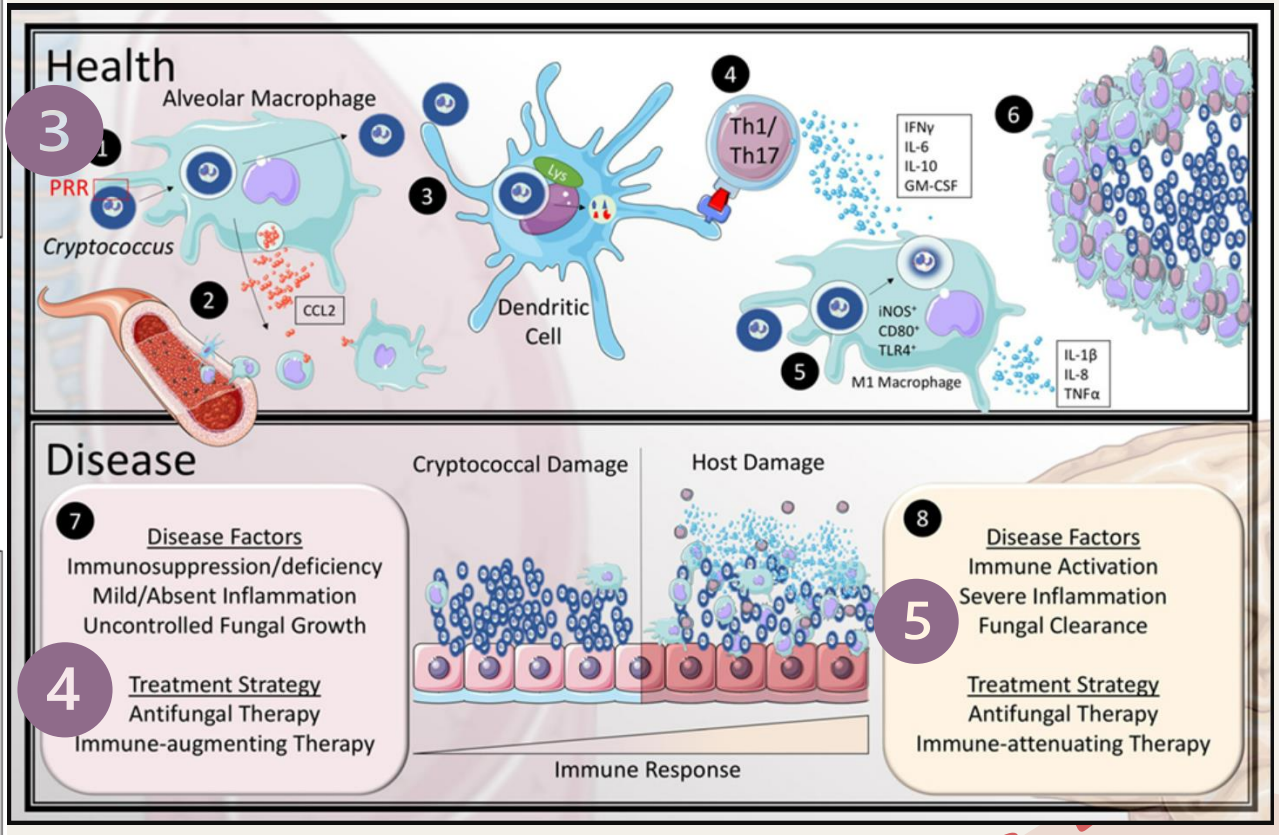
CRYPTOCOCCOSIS

Cryptococcus = an invasive fungus, transmitted through the inhalation of spores

Pathophysiology:

1.Inhalation of spores and lives in pulmonary phagocyte
2.Crossing the blood-brain barrier
3.Healthy host: normal immune response
4.Immunocompromised host: poorly control of infection
5.Hyperimmune response develop IRIS





Nat Rev Microbiol. 2016.
Front Immunol. 2018 Apr 4;9:651.

CRYPTOCOCCOSIS

Risk factor:

HIV (CD4<100), Chronic steroid used, Cancer, immunotherapy (esp. Fingolimod, S1P receptor modulator therapy), posttransplantation

Clinical manifestation:

- Cryptococcal meningitis
- Disseminated cryptococcosis
- Pulmonary cryptococcosis
- Primary cutaneous cryptococcosis
- Cryptococcus-IRIS

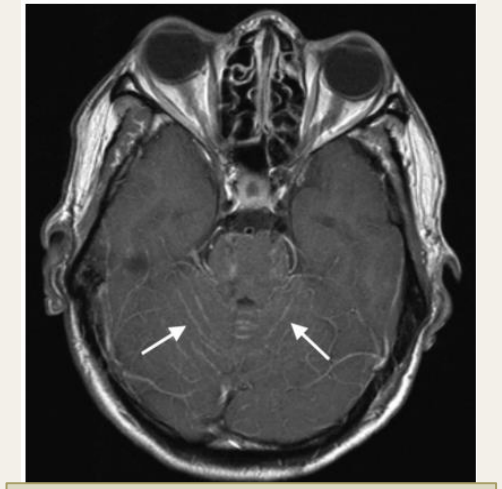
Investigation:

- CSF profile: elevated OP, lymphocytic pleocytosis, low glucose, elevated protein
- CSF india ink (sens 42-86%, spec 97.3%),
- CSF cryptococcal Ag (sens 99.3%, spec 99.1%)
- CSF culture (sens 44-80%, spec 100%)
- CT Brain: calcification

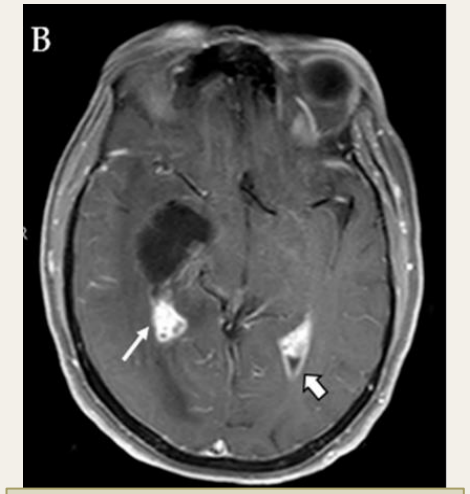
HIV: more Acute onset <2wk
Non-HIV: Subacute onset 6-12wk

Mycoses. 2020 Aug;63(8):840-853.
J Neurol Sci. 2021 Mar 15;422:117325.

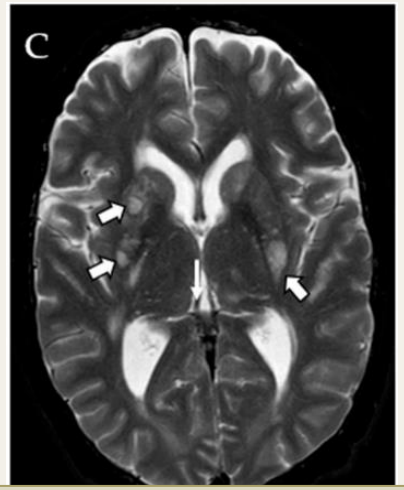
CRYPTOCOCCOSIS



Basal meningeal enhancement



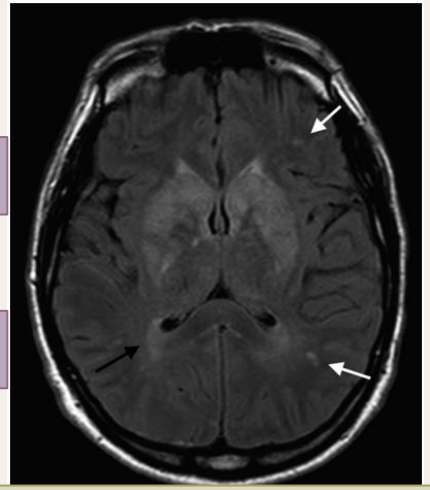
Choroid plexus involvement



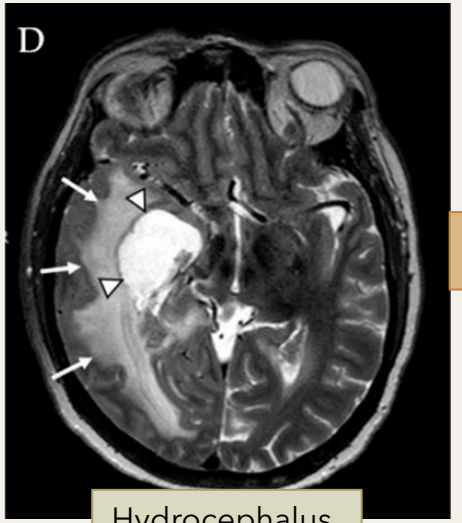
Enlarged Virchow-Robin spaces, so called; Pseudocysts

Hazy brain sign

More common in HIV



Parenchymal involvement, so called; Cryptococcoma



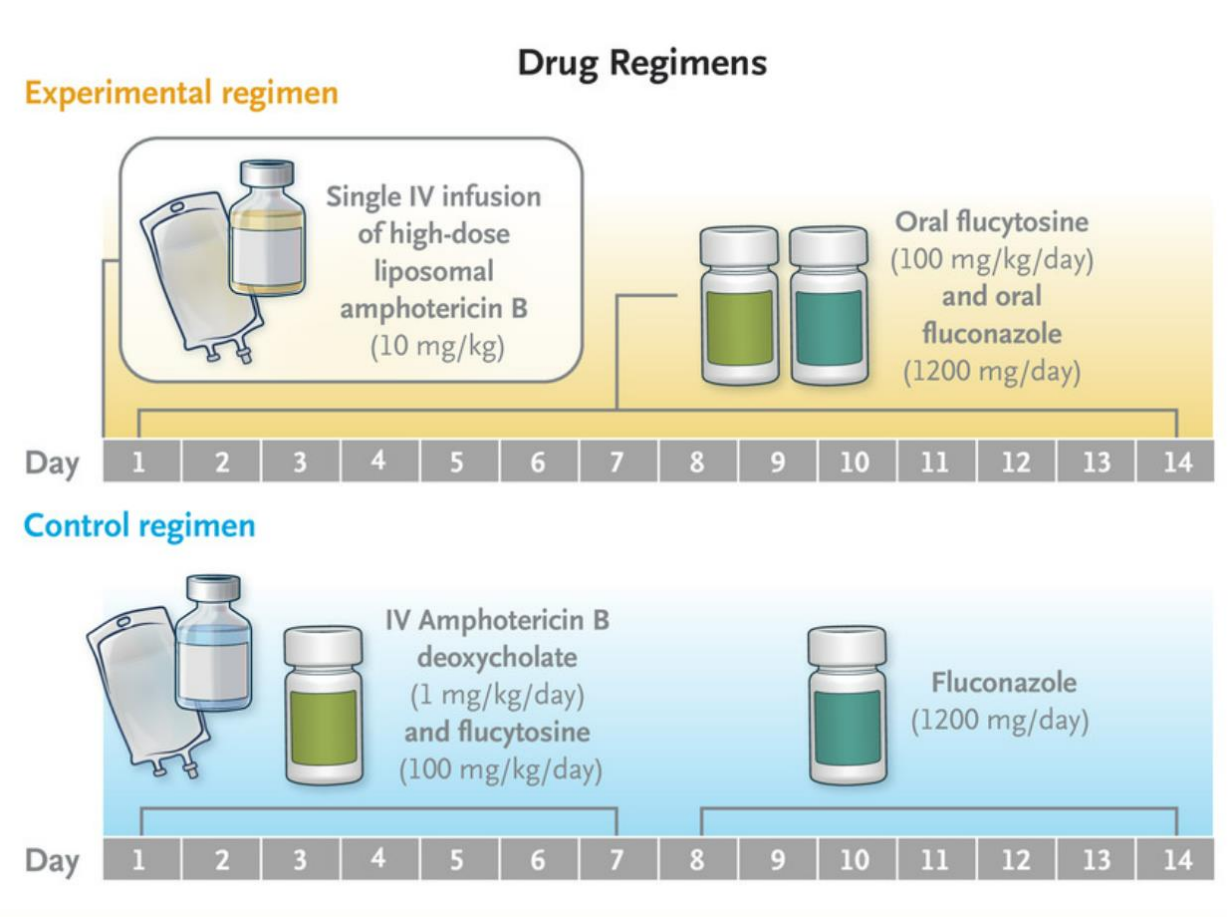
Hydrocephalus

More common in non-HIV

Clin Radiol. 2016 Jan;71(1):9-17.
J Fungi (Basel). 2023 May 19;9(5):594.

CRYPTOCOCCOSIS

Treatment: for HIV-associated cryptococcosis



CONCLUSIONS

Among HIV-positive adults with cryptococcal meningitis, a single high-dose infusion of liposomal amphotericin B plus oral therapy with flucytosine and fluconazole was non-inferior to the standard treatment and was associated with fewer adverse events.

Prevent IRIS

Delayed ART at least 4wk postinduction

Manage intracranial pressure

Repeat LP

Lumbar drain

Ventricular shunting

Mycoses. 2020 Aug;63(8):840-853.
J Neurol Sci. 2021 Mar 15;422:117325.
N Engl J Med. 2022 Mar 24;386(12):1109-1120

CRYPTOCOCCOSIS

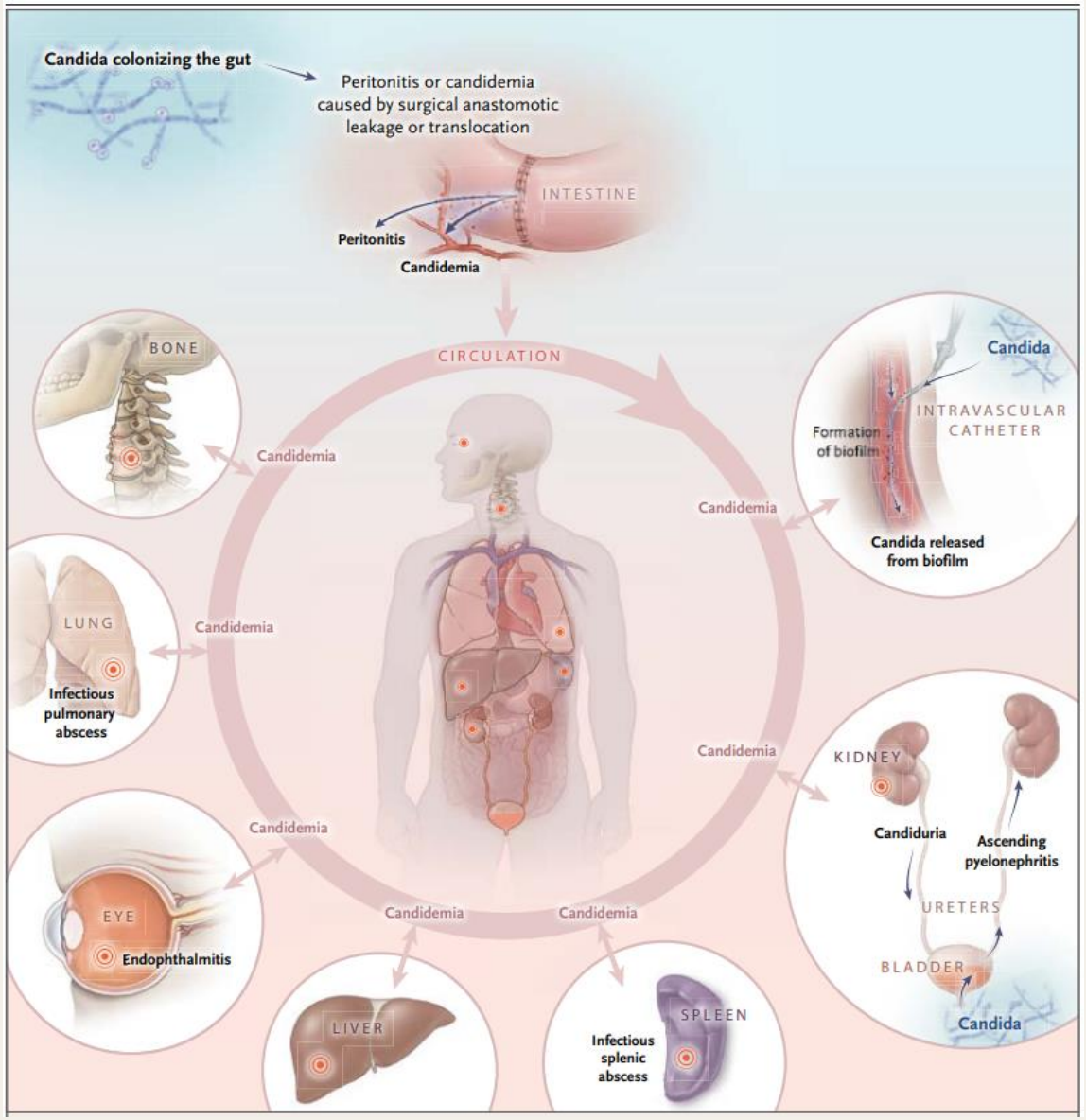
Treatment: for Non-HIV associated

Condition	Therapy of choice per phase		Duration
Meningitis and disseminated disease OR Moderate to severe non-CNS disease	Induction	Preferred: Liposomal AmB (3–4 mg/kg per day IV) or ABLC (5 mg/kg per day IV)[a] and Flucytosine (100 mg/kg per day in 4 divided doses).[b] *Alternative (in the absence of Flucytosine):* Lipid formulation of AmB	2 weeks (SOT) 4–6 weeks (Nontransplant, Non-HIV patients or in the absence of Flucytosine or with neurologic complications)
	Consolidation	Fluconazole p.o. 400–800 mg [6–12 mg/kg] daily *Salvage therapy in relapses:* Fluconazole 800–1200 mg p.o. daily OR Voriconazole 200- 400 mg p.o. daily OR Posaconazole 200 mg p.o. four times daily	8 weeks 10–12 weeks
	Maintenance	Fluconazole p.o. 200–400 mg daily	6–12 months
Mild to moderate non-CNS disease including pulmonary disease[c]	Therapy	Fluconazole p.o. 400 mg [6 mg/kg] daily	6–12 months
Pretransplant asymptomatic Pulmonary nodules	Therapy	Limited evidence [73]. Fluconazole p.o. (200–400 mg daily)	2 weeks before and 6–12 months after transplant

Disseminated is considered involvement of >1 noncontiguous sites.
AmB, Amphotericin B; ABLC, Amphotericin B lipid complex; CNS, central nervous system; SOT, solid organ transplant recipients.
[a]6 mg/kg per day can be considered in relapses or with a high cryptococcal burden.
[b]A dosage reduction is required with renal impairment: creatinine clearance (CrCl) >50 ml/min, 100–150 mg/kg/day; CrCl 26–50 ml/min, 75 mg/kg/day; CrCl 13–25 ml/min, 37 mg/kg/day; CrCl < 13 ml/min, avoid flucytosine. Dose monitoring is also recommended in the first 72 h of therapy with a goal trough concentration of 20–40 mg/l; peak concentration should not exceed 100 mg/l.
[c]In the absence of diffuse pulmonary infiltrates.

Curr Opin Infect Dis. 2018 Aug;31(4):278-285.

CANDIDA



N Engl J Med. 2015 Oct 8;373(15):1445-56.

CANDIDA

Risk factor:

- HIV (CD4<200)
- Immunosuppression disease
- Previous treatment with antibiotics and corticosteroids
- Carrier of intravascular catheters
- Recent abdominal surgery
- Recent neurosurgery/insertion of CSF derivative systems (occur months after procedure)
- IVDU

Clinical manifestation:

- Subacute meningitis
- Microabscess (propensity for parieto-occipital)
- Vascular invasion (esp.basal ganglia) eg. cerebral infarction, mycotic aneurysm, SAH
- Postprocedure: eg. dysfunction of the shunt leading to hydrocephalus

J Neurol Sci. 2021 Mar 15;422:117325.
Diagn Microbiol Infect Dis. 2000 Jul;37(3):169-79.

CANDIDA

Investigation:

CSF profile: pleocytosis, low glucose, elevated protein
Fungal culture, Serum mannan/antimannan, β-D glucan, PCR
MRI: microabscess or meningeal enhancement

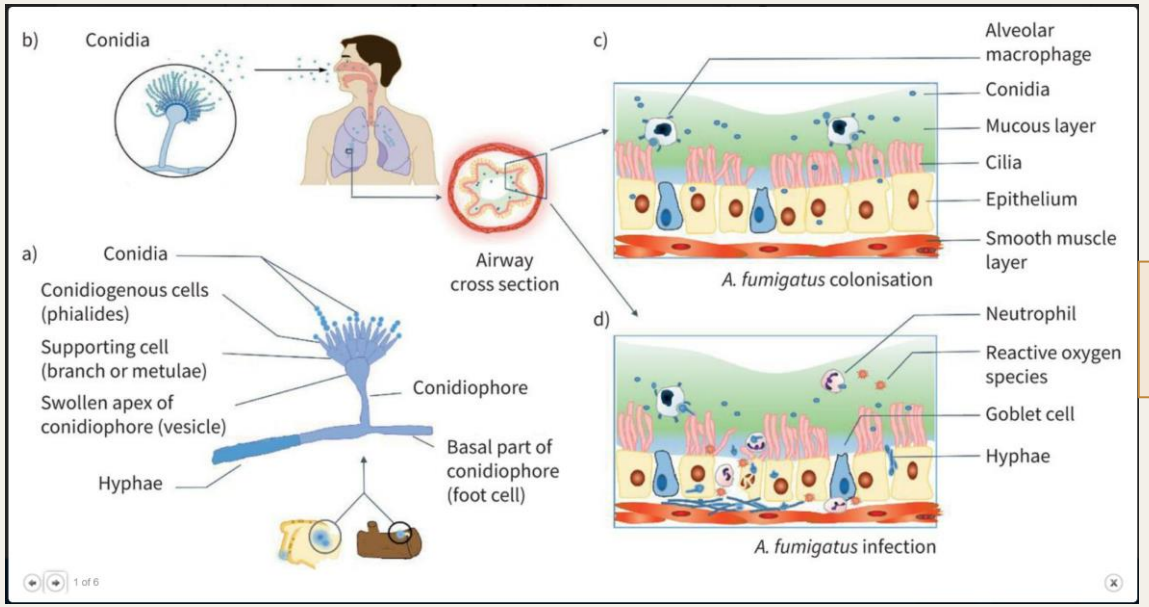
Treatment:

Initial treatment: **Liposomal AmB**, 5 mg/kg/d, +/- oral flucytosine, 25 mg/kg 4 times/d
Step-down therapy: **Fluconazole**, 400–800 mg/d (6–12 mg/kg/d)
Therapy should continue until all signs and symptoms and CSF and radiological abnormalities have resolved
Infected CNS devices should be **removed** if possible
Whom a ventricular device cannot be removed;

AmB deoxycholate 0.01 mg to 0.5 mg in 2 mL 5% dextrose in water through the device

J Neurol Sci. 2021 Mar 15;422:117325.
Clin Infect Dis. 2016 Feb 15;62(4):e1-50.
Diagn Microbiol Infect Dis. 2000 Jul;37(3):169-79.

ASPERGILLUS



Hematogenous spread

- Sinusitis → Direct invasion to CNS eg. Abscess
- Angioinvasion
  - Ischemic stroke
  - Hemorrhagic transformation
  - Mycotic aneurysms
  - SAH
  - Cerebral abscess

PLoS One. 2016 Apr 20;11(4):e0152475.
Eur Respir Rev. 2021 Nov 17;30(162):210103.

ASPERGILLUS

Risk factor: hematologic malignancy, prolonged neutropenia, chronic corticosteroid used

Clinical manifestation:

CNS: Brain abscess, cranial neuropathies, mycotic aneurysms, cerebral ischemic/hemorrhagic infarct/SAH
Pulmonary: Aspergilloma, Allergic bronchopulmonary aspergillosis, Tracheobronchial aspergillosis, Invasive pulmonary aspergillosis
Sinusitis
Eye: Endophthalmitis, periorbital cellulitis, vitritis, dacryocystitis

J Neurol Sci. 2021 Mar 15;422:117325.

ASPERGILLUS

Investigation:

CT/MRI: ring enhancing lesion, cerebral ischemic/hemorrhagic infarct/SAH, mycotic aneurysms

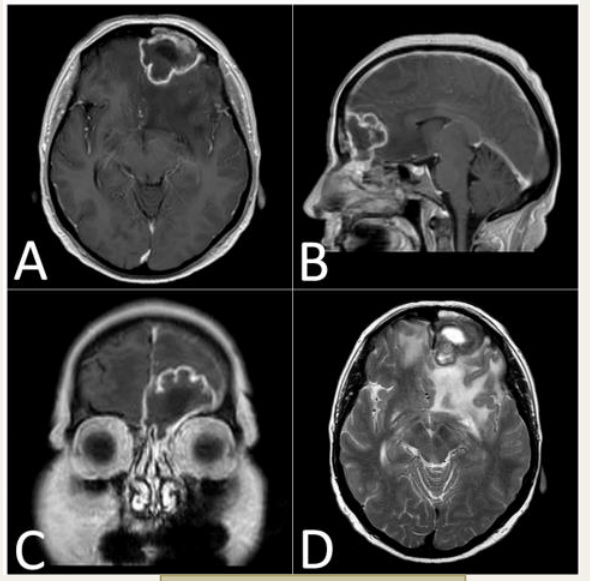
Tissue biopsy: branching septate hyphae

Serum galactomannan

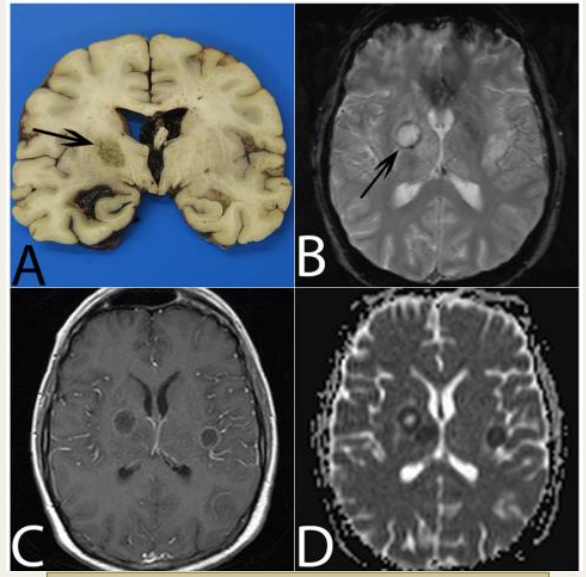
Treatment:

Voriconazole* 6mg/kg x day 1 then 4mg/kg at least 6-12wk

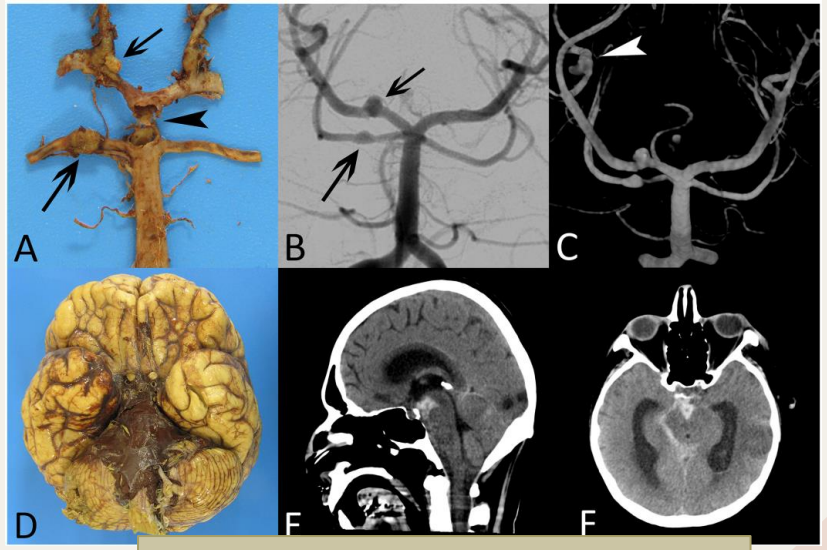
Liposomal Amphotericin B (for those intolerant or refractory to voriconazole)



Frontal abscess



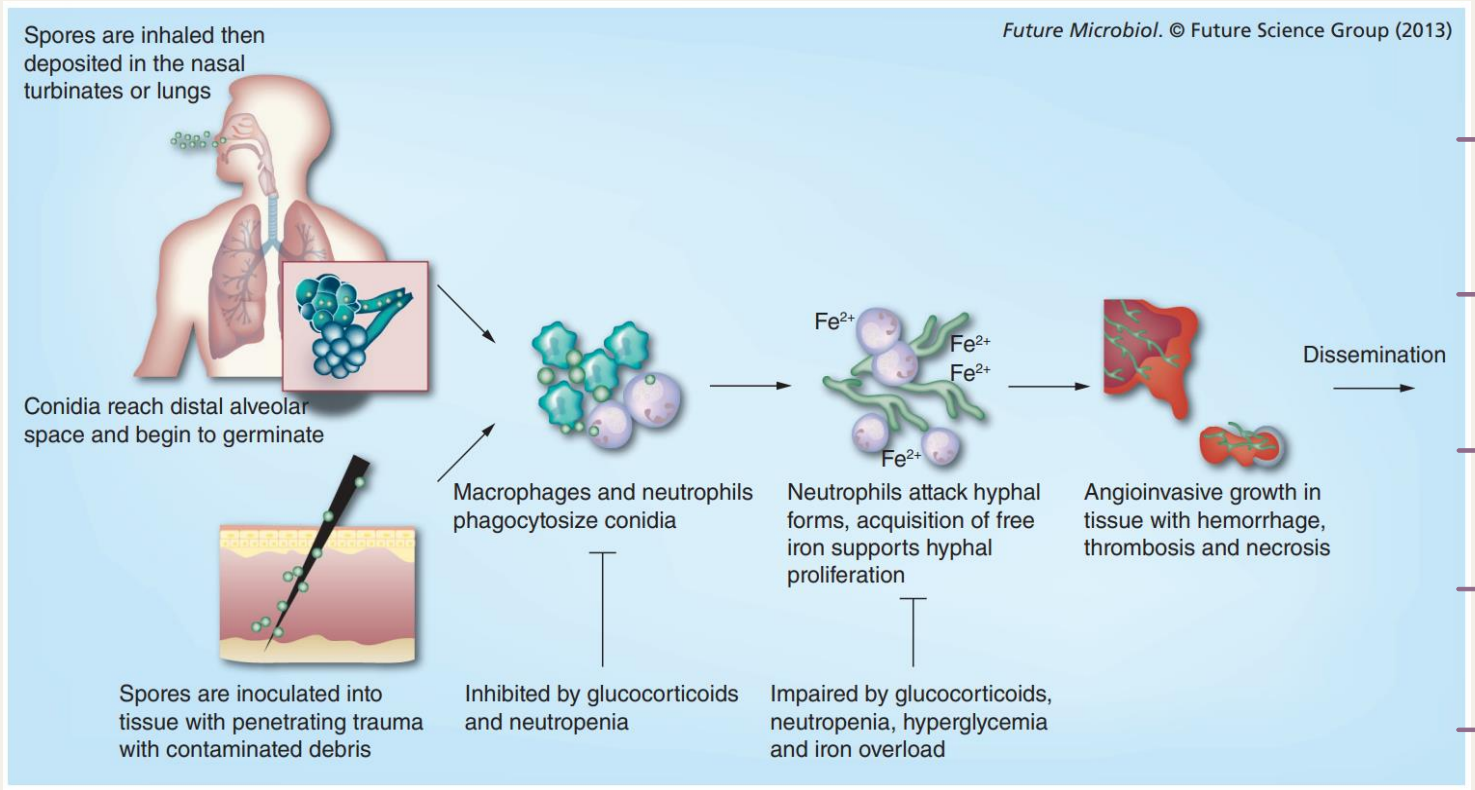
Thalamolenticular abscess



Ruptured mycotic aneurysm, SAH

PLoS One. 2016 Apr 20;11(4):e0152475.
Clin Infect Dis. 2016 Aug 15;63(4):e1-e60.

MUCORMYCOSIS



- **Rhinocerebral**
  - **Paranasal sinusitis**
  - **Orbital infection**
  - **Intracranial and vascular invasion**
    Arterial thrombosis, Cavernous sinus thrombosis, Cerebral hemorrhage, Mycotic aneurysms
- **Pulmonary**
- **Cutaneous**
- **Gastrointestinal**
- **Disseminated**

J Neurol Sci. 2021 Mar 15;422:117325.
Future Microbiol. 2013 Sep;8(9):1163-75.
Clin Infect Dis. 2012 Feb;54 Suppl 1:S23-34

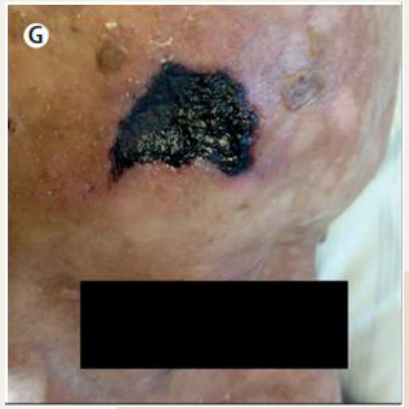
MUCORMYCOSIS

Rhizopus, Mucor, Lichtheimia
Localized **sinopulmonary disease**, tissue necrosis resulting from **angioinvasion** and **subsequent thrombosis**

Risk factor: HIV, HSCT, chronic corticosteroid used, DKA, prolonged voriconazole used, iron overload and chelation therapy

Clinical manifestation:

- **Rhinocerebral**: sinusitis invade to cranium occurs through orbital apex or cribiform plate (facial pain or numbness, unilateral orbital edema, multiple cranial neuropathies, proptosis, external ophthalmoplegia, visual loss or blurry vision)
- Pulmonary
- Cutaneous
- Gastrointestinal
- Disseminated



J Neurol Sci. 2021 Mar 15;422:117325.
Clin Infect Dis. 2012 Feb;54 Suppl 1:S23-34

MUCORMYCOSIS

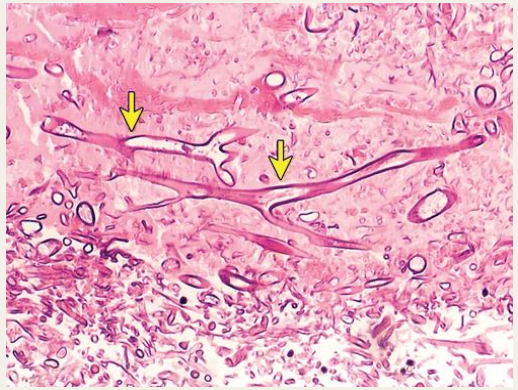
Investigation:

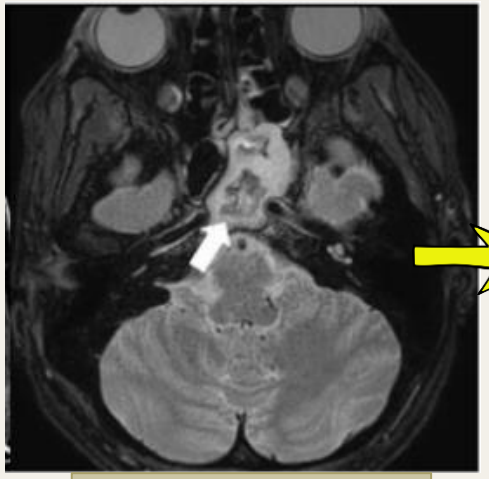
CT/MRI:

- Stage I: Paranasal sinusitis
- Stage II: Orbital infection
- Stage III: Intracranial and vascular invasion
  eg. Arterial thrombosis, Cavernous sinus thrombosis, Cerebral hemorrhage and mycotic aneurysms

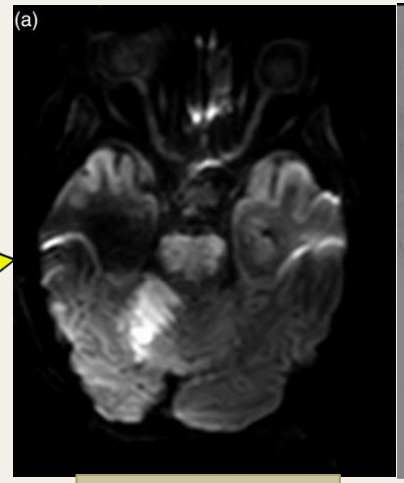
Tissue biopsy:

- non-septate/pauci-septate, ribbon-like hyphae

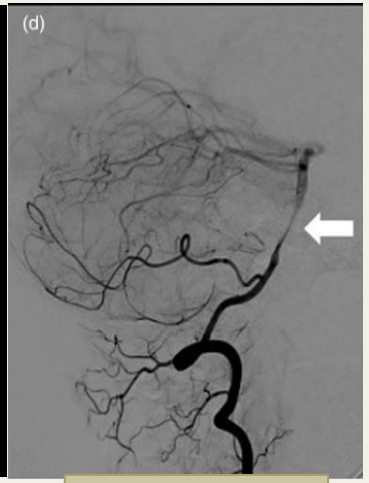




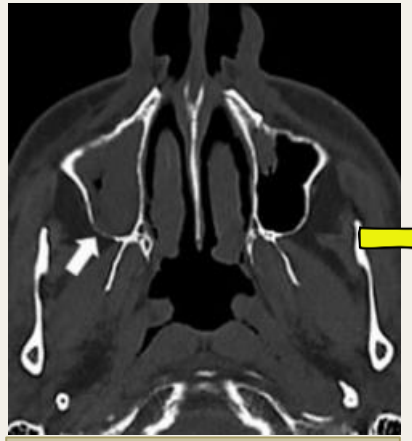
Sphenoid sinusitis



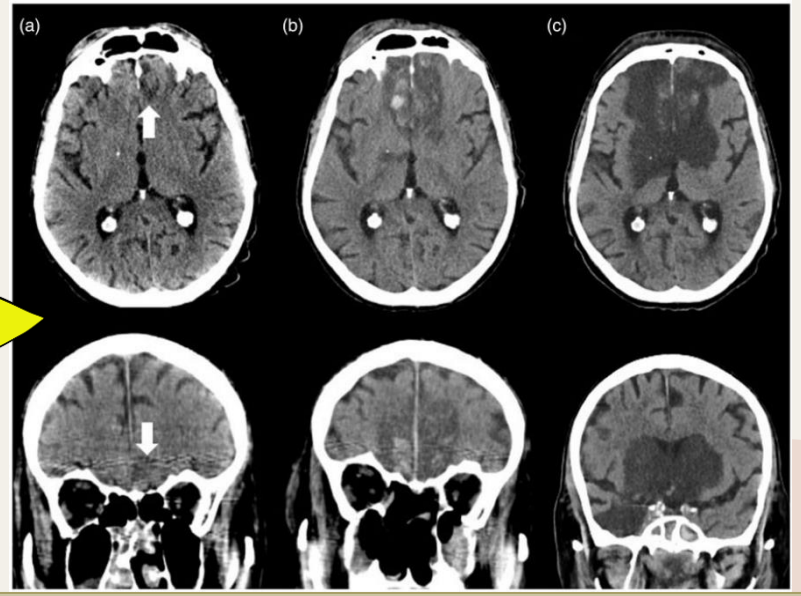
Rt.cerebellar infarction



Basilar artery stricture

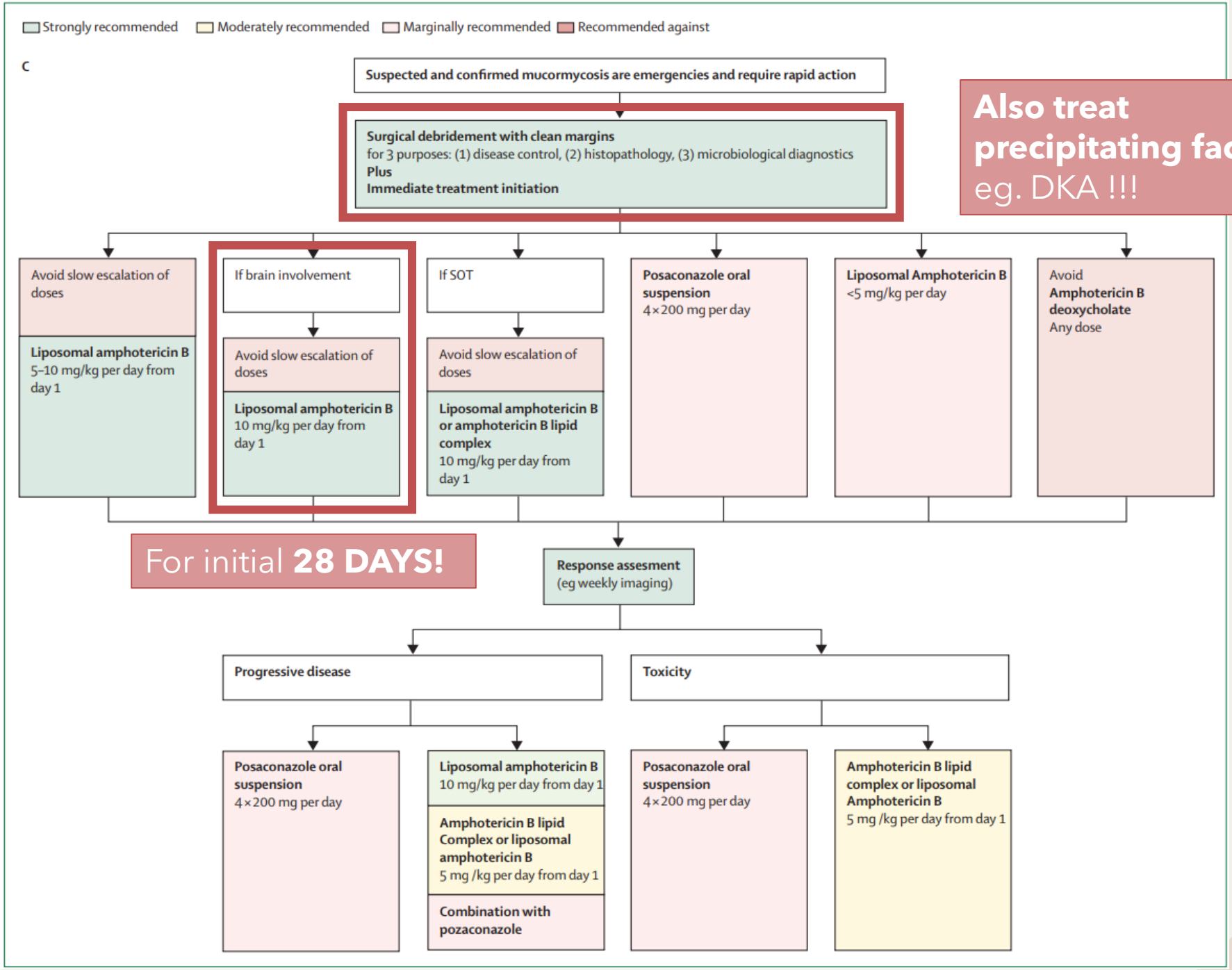


Rt.maxillary sinusitis



Frontal infarction with hemorrhagic transformation

Acta Radiol. 2022 Feb;63(2):232-244.



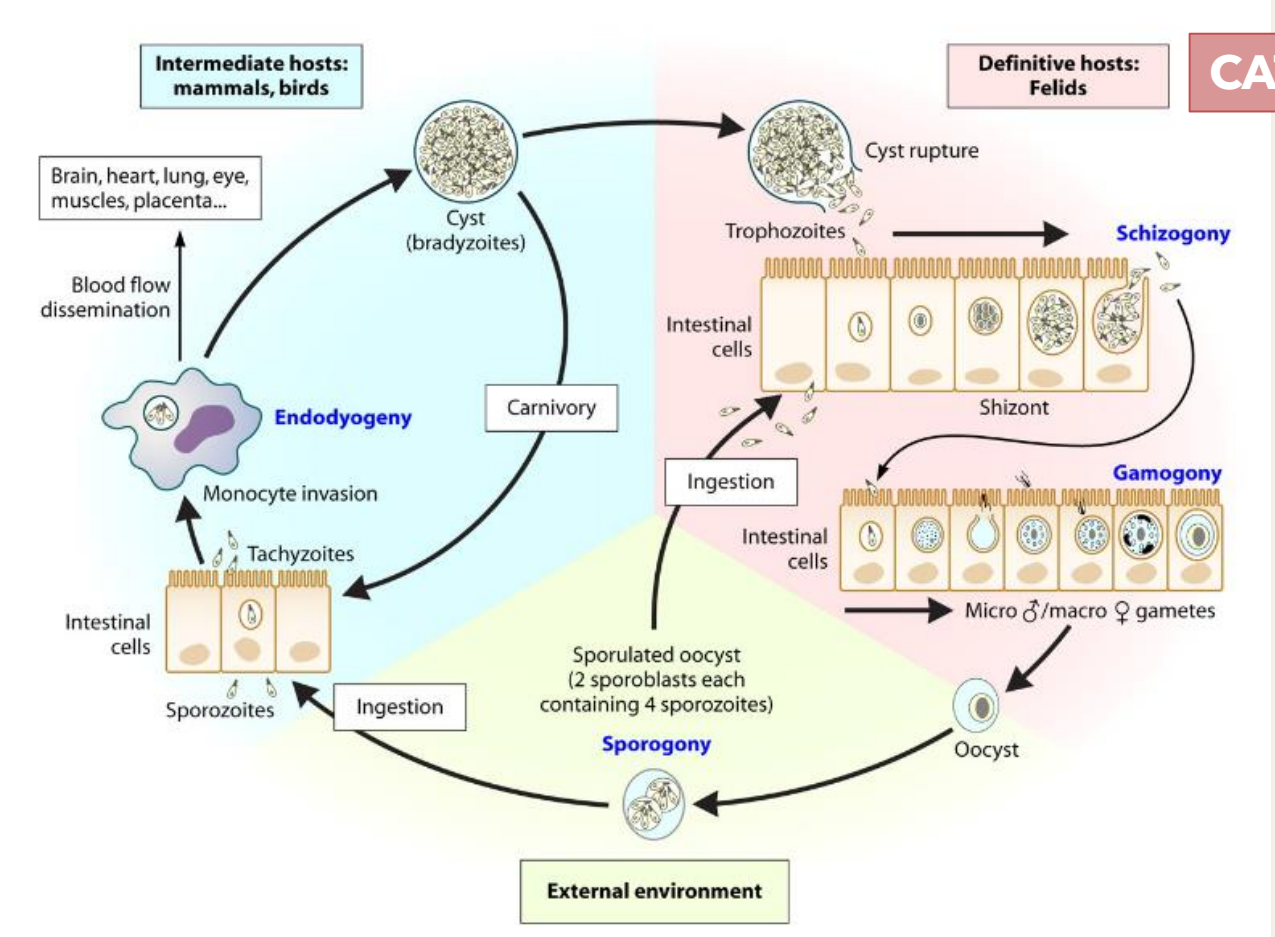
For initial **28 DAYS!**

Also treat precipitating factor
eg. DKA !!!

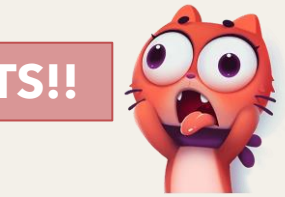
Lancet Infect Dis. 2019 Dec;19(12):e405-e421

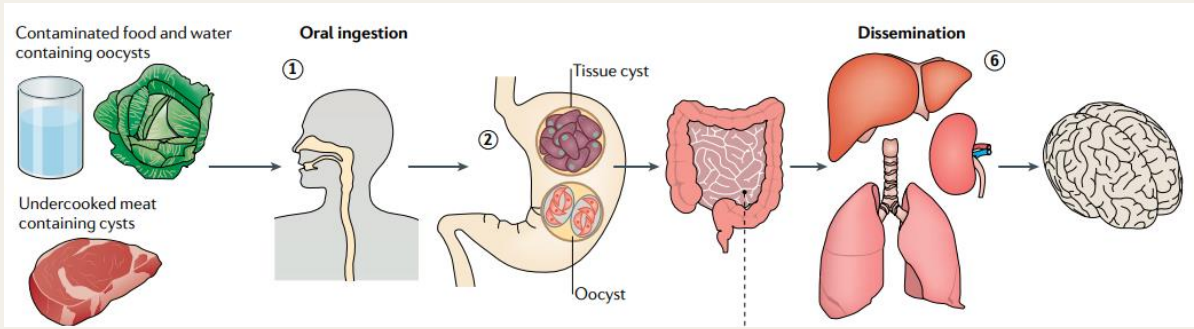

PARASITE
Toxoplasmosis

TOXOPLASMOSIS



CATS!!





Nat Rev Microbiol. 2021 Jul;19(7):467-480.
Clin Microbiol Rev. 2012 Apr;25(2):264-96.

TOXOPLASMOSIS

Bradyzoites survive intracellularly and reactivate during periods of immune suppression and can convert to active, proliferative tachyzoites, which can infect any CNS cell

Risk factor: HIV (CD4<200), HSCT, solid organ transplantation

Clinical manifestation:

Cerebral abscess

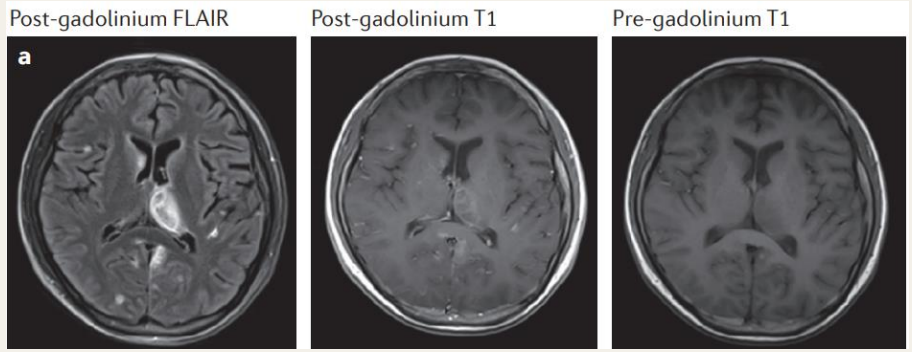
- tends to localize in the basal ganglia, may present with parkinsonism, hemichorea, hemiballismus, hemidystonia, rubral tremor

Diffuse encephalitis

Chorioretinitis: posterior uveitis, well-circumscribed and grayish yellow on fundoscopy

Nat Rev Neurol. 2016 Oct 27;12(11):662-674.

TOXOPLASMOSIS



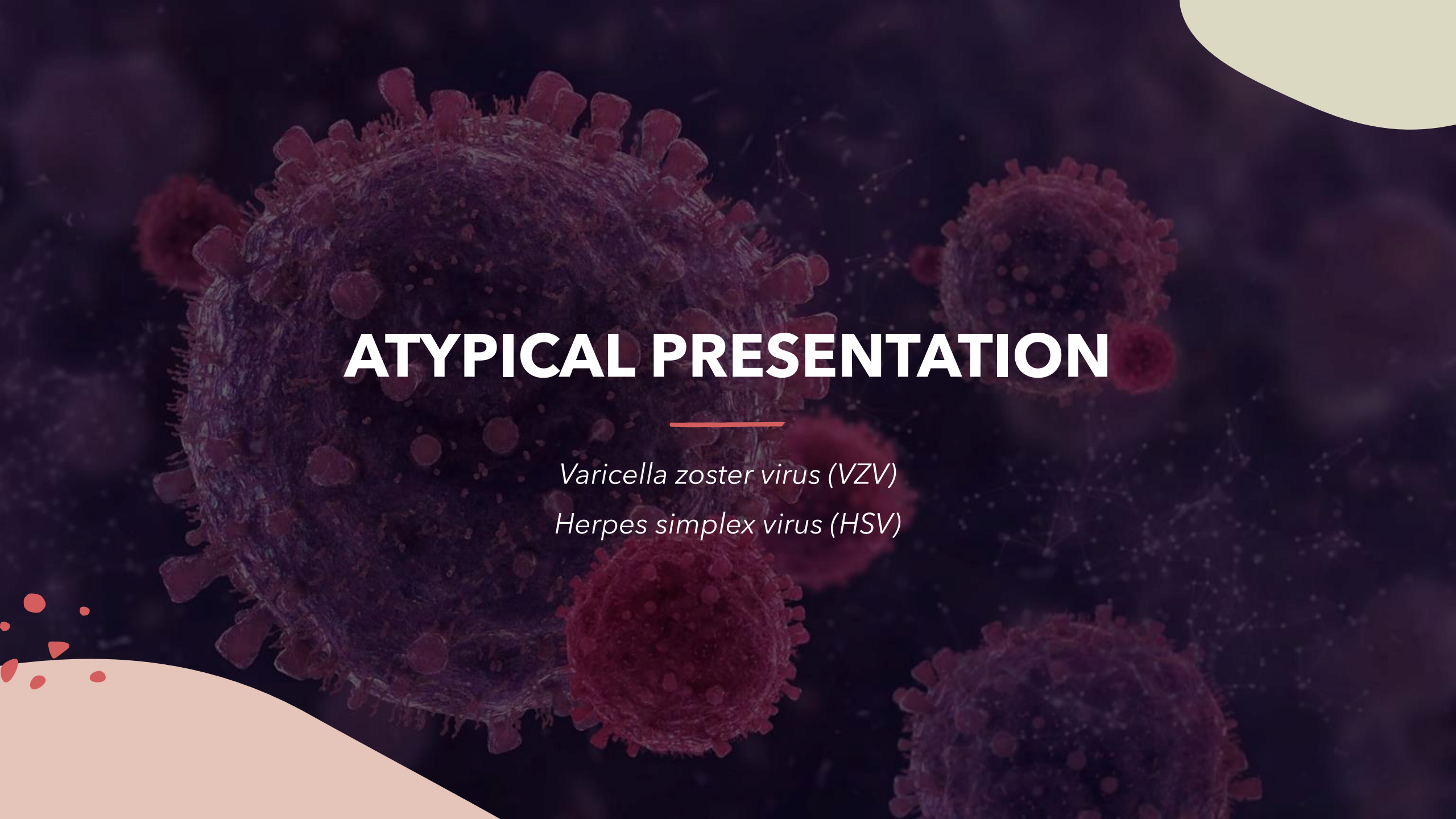
Investigation:

PCR of serum and CSF
CSF profile: mononuclear pleocytosis, elevated protein level, normal or reduced glucose
MRI: multiple ring-enhancing brain lesion often located on basal ganglia, thalamus, dentate nucleus

Treatment:

Induction therapy (beyond 1-2wk after clinical resolution)	Maintenance therapy (CD4<100)
- Pyrimethamine 200mg on the first day, then 75–100mg/d - Sulfadiazine 1–1.5g qid - Folinic acid 10–50mg/d	- Pyrimethamine 25–50mg/d - Sulfadiazine 0.5–1.0g qid - In addition, supplementary folinic acid 10–50mg/d

Nat Rev Neurol. 2016 Oct 27;12(11):662-674.

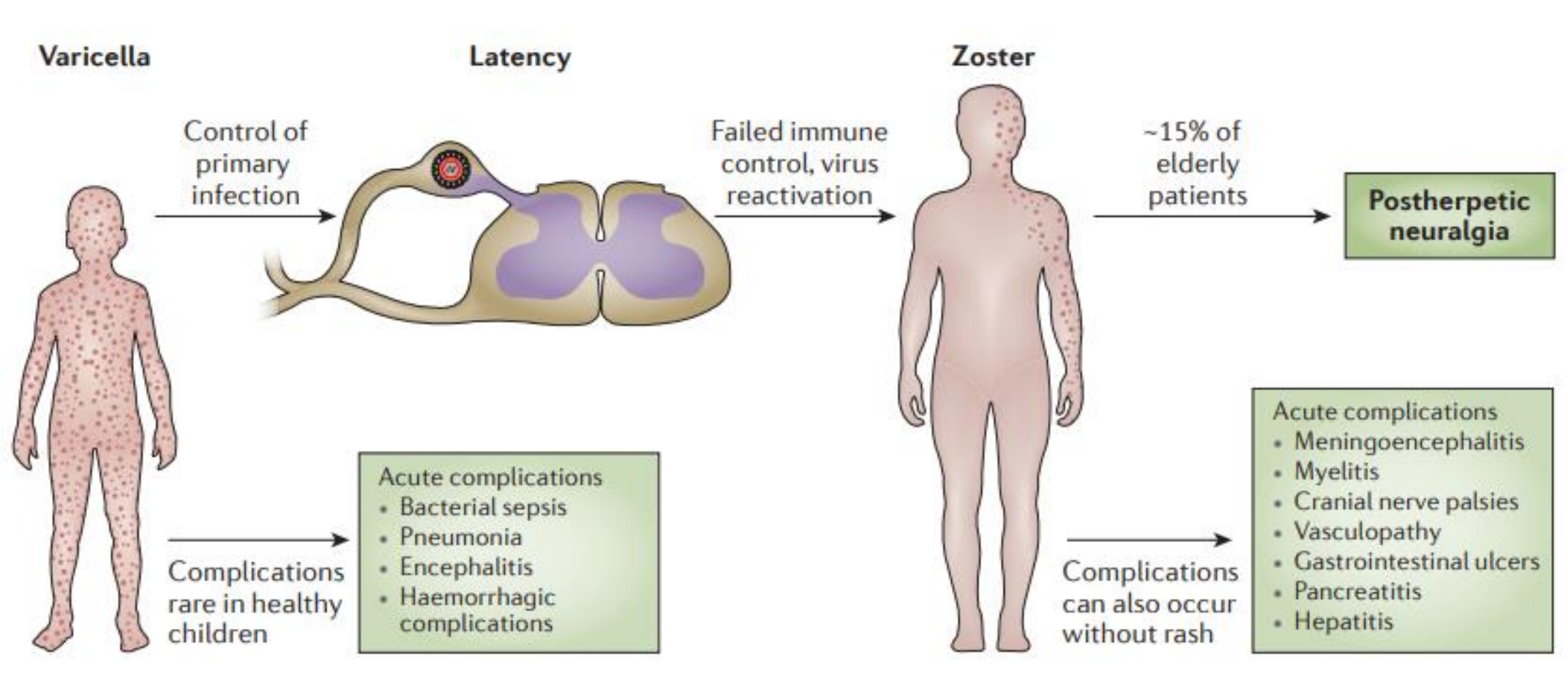


ATYPICAL PRESENTATION

Varicella zoster virus (VZV)

Herpes simplex virus (HSV)

VARICELLA ZOSTER VIRUS (VZV)

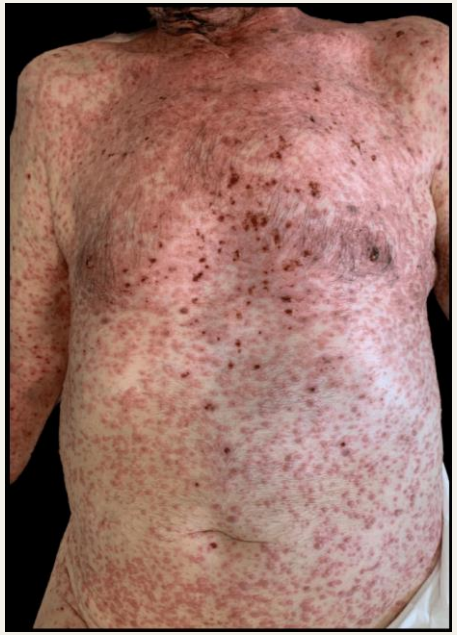


Nat Rev Dis Primers. 2015 Jul 2;1:15016.

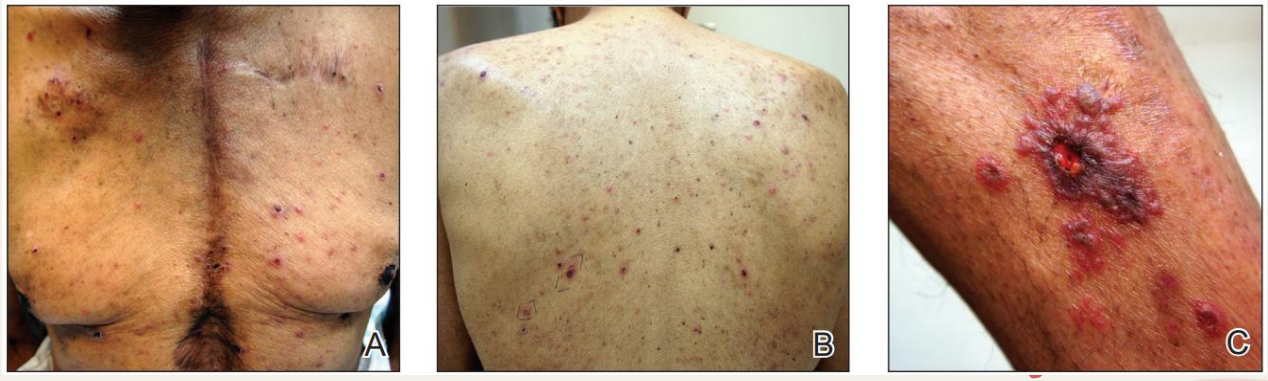
VARICELLA ZOSTER VIRUS (VZV)

ATYPICAL Clinical manifestation:

- Neurological complication
  - Vasculopathy, Aseptic meningoencephalitis, Transverse myelitis
- Pulmonary complication
  - VZV pneumonitis, VZV pneumonia
- Cutaneous complication
  - Staphylococcal and streptococcal toxic shock syndromes,
  - Bacterial superinfection,
  - Bullous or hemorrhagic varicella,
  - Purpura fulminans,
  - Varicella-associated necrotizing fasciitis
- Maternal and Fetal varicella syndrome
- Recurrent VZV infection



Disseminated papules and vesicles with an erythematous base located on the trunk.



Diffuse vesicle on chest and back

hemorrhagic,
necrotic, vesiculobullous
lesion with surrounding vesicles

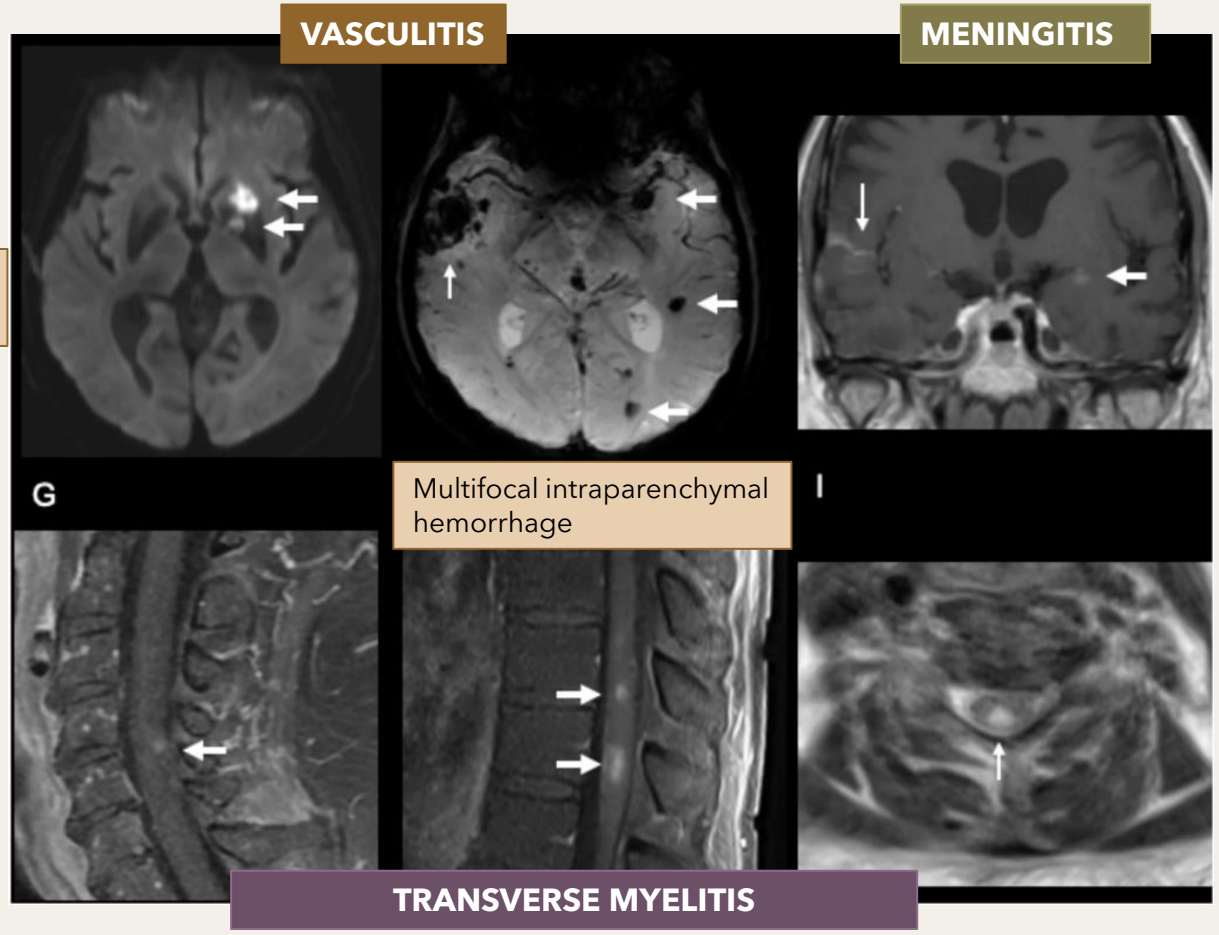
Cureus. 2023 Jan 4;15(1):e33359.
Cutis. 2017 Nov;100(5):321;324;330.
J Infect Dis. 2002 Oct 15;186 Suppl 1:S91-8.

VARICELLA ZOSTER VIRUS (VZV)

	Large vessel vasculopathy	Small vessel vasculopathy	Aseptic meningitis	Myelitis
Demographic	Elderly, immunocompetent	Immunocompromised	Immunocompetent and immunocompromised	Immunocompetent and immunocompromised
Presentation	Acute focal neurologic deficits	Altered mental status, headaches, focal deficits, seizures	Headache, fevers, altered mental status	Weakness, sensory abnormalities
Rash	Trigeminal distribution	Often absent	Can be absent	Frequently a rash
MRI findings	Multifocal hyperintense lesions on T2-weighted FLAIR images; typically affect large arteries of anterior or posterior circulation	Multifocal infarcts; typically affect branches of large cerebral arteries or small cerebral arteries	Normal	Increased T2 signal lesions in the cord in association with cord swelling
CSF findings	• Often with lymphocytic pleocytosis, elevated protein, and normal glucose, but can be absent • Detection of anti-VZV antibody in CSF may be more sensitive than VZV PCR	• Often with mild pleocytosis, normal to mild elevation of CSF protein, but can be absent • Detection of anti-VZV antibody in CSF may be more sensitive than VZV PCR	• Lymphocytic pleocytosis, elevated protein, normal glucose in CSF • VZV DNA can correlate with severity	• Lymphocytic pleocytosis with elevated protein and normal glucose in 75% of cases

Transpl Infect Dis. 2019 Apr;21(2):e13038.

VARICELLA ZOSTER VIRUS (VZV)



Treatment:

Decrease in immunosuppression and intravenous acyclovir for 10-14 days

Foscarnet, cidofovir, and brincidofovir have been used for acyclovir-resistant strains

Corticosteroid remain controversy

J Neurol Sci. 2022 Jun 15;437:120262.
Transpl Infect Dis. 2019 Apr;21(2):e13038.

HERPES SIMPLEX VIRUS (HSV)

ATYPICAL clinical manifestation:

HSV-2 is more common than in immunocompetent host

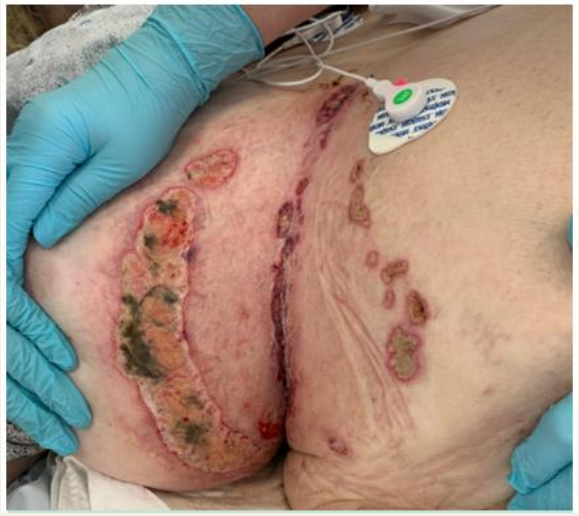
Generalized HSV infection

- More generalized cutaneous manifestation
- Esophagitis
- Hepatitis
- Pneumonia
- Encephalitis

Relapsed Herpes simplex Encephalitis

Table 1. Literature review about disseminated herpes simplex virus infections in neonates and adults

Predesposition	Leading site of involvement	Virus type
Neonate	Hepatitis	I
Healthy adult	Hepatitis	I/II
Pregnancy	Hepatitis	II
Transplantation (liver/heart/kidney)	Hepatitis	I/II
Post-thymektomy (invasive thymoma)	Hepatitis	II
Vulvo-vaginitis	Hepatitis, spleenitis	II
Pemphigus vulgaris	Hepatitis	I
HIV	Hepatitis, spleenitis	II
Steorid use for upper airway obstruction	Hepatitis	I
Leukemia (ALL)	Hepatitis/pneumonitis	II
Plasmocytoma	Hepatitis	II
Cold (previous weeks)	Hepatitis	I



Linear ulcer with scattered areas of necrotic base

Am J Med. 2022 Mar;135(3):327-330
Pathol Res Pract. 2005;201(2):123-9.

HERPES SIMPLEX VIRUS (HSV)

Relapsed Herpes Simplex Encephalitis

fail to completely suppress or fully eradicate HSV from CSF hence they are presumed to be at greater risk for relapse of HSE

Risk factor: Corticosteroid

Investigation:

CSF profile: lymphocytic pleocytosis, low to normal glucose, elevated protein

CSF for PCR HSV

MRI

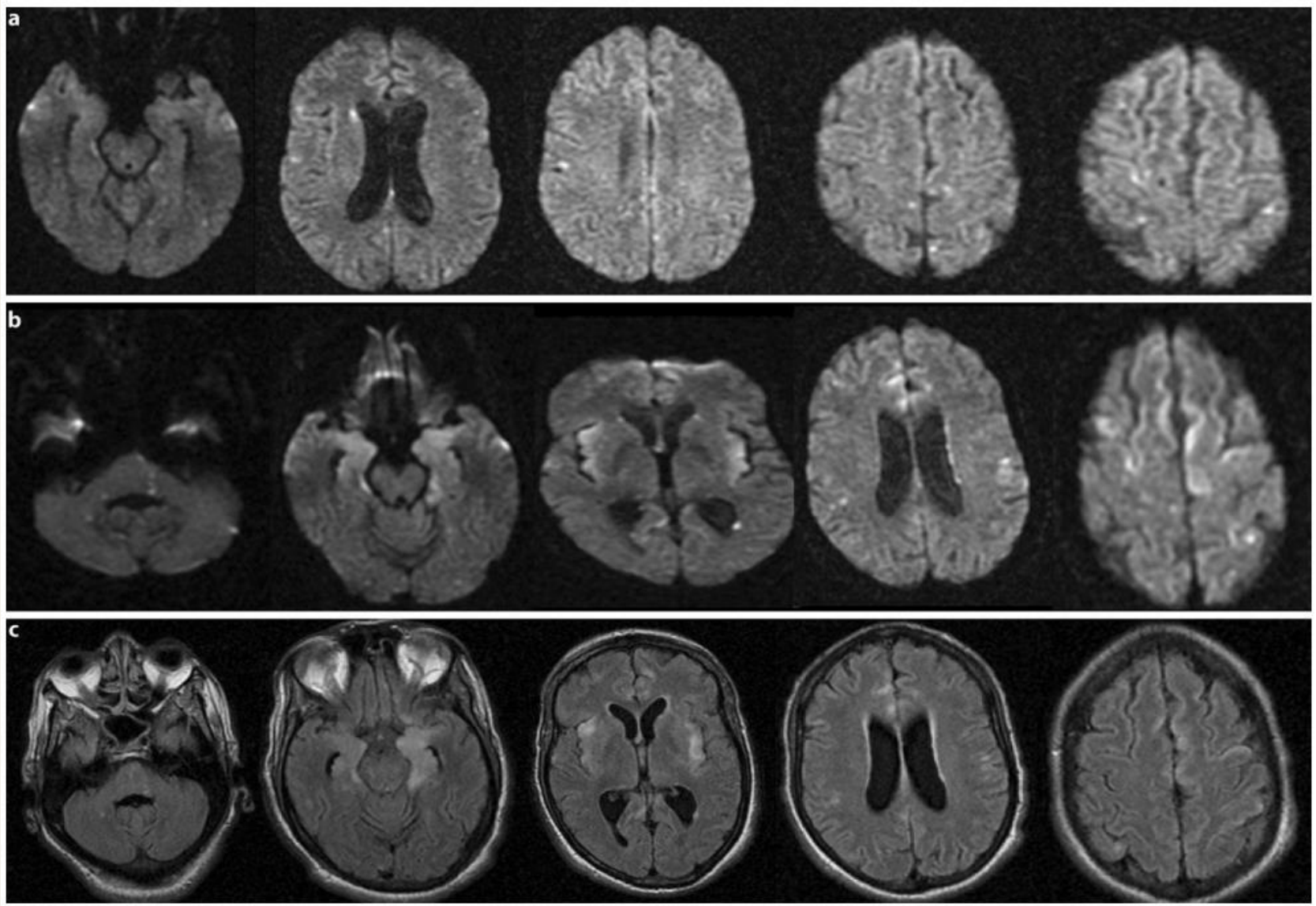
Prevention:

No studies evaluating the potential role of antiviral prophylaxis for the prevention of relapse of HSE.

Immunocompetent patients with HSV encephalitis will typically have a **negative CSF HSV PCR after 14 days of acyclovir treatment**

IDCases. 2019 Aug 20;18:e00626.

HERPES SIMPLEX VIRUS (HSV)



At 5 and 6 weeks: bilateral multiple small (<5 mm) punctate foci of diffusion abnormalities at the grey-white matter junction in cerebral hemispheres.

The DWI (b) and fluid-attenuated inversion recovery (FLAIR)

At 8 weeks:additional punctate foci at the grey-white matter junction in cerebral hemispheres, pons and cerebellum, few poorly defined larger areas of cortical-subcortical hyperintensities in both hemispheres, and bilateral extensive hyperintensities in hippocampi, insula and cingulate gyri

Clin Neuroradiol. 2017 Jun;27(2):231-234.


THANK YOU :)