•CNS Infection

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Outline

- Bacterial Meningitis
- Viral Meningitis and Encephalitis
- Brain Abscess
- Spinal & Epidural Abscess
- Tetanus, Botulism, Diptheria
- SARS-CoV-2 (COVID-19)

- Bacterial Meningitis

- **Pathogenic agents of bacterial meningitis according to age group and UD**

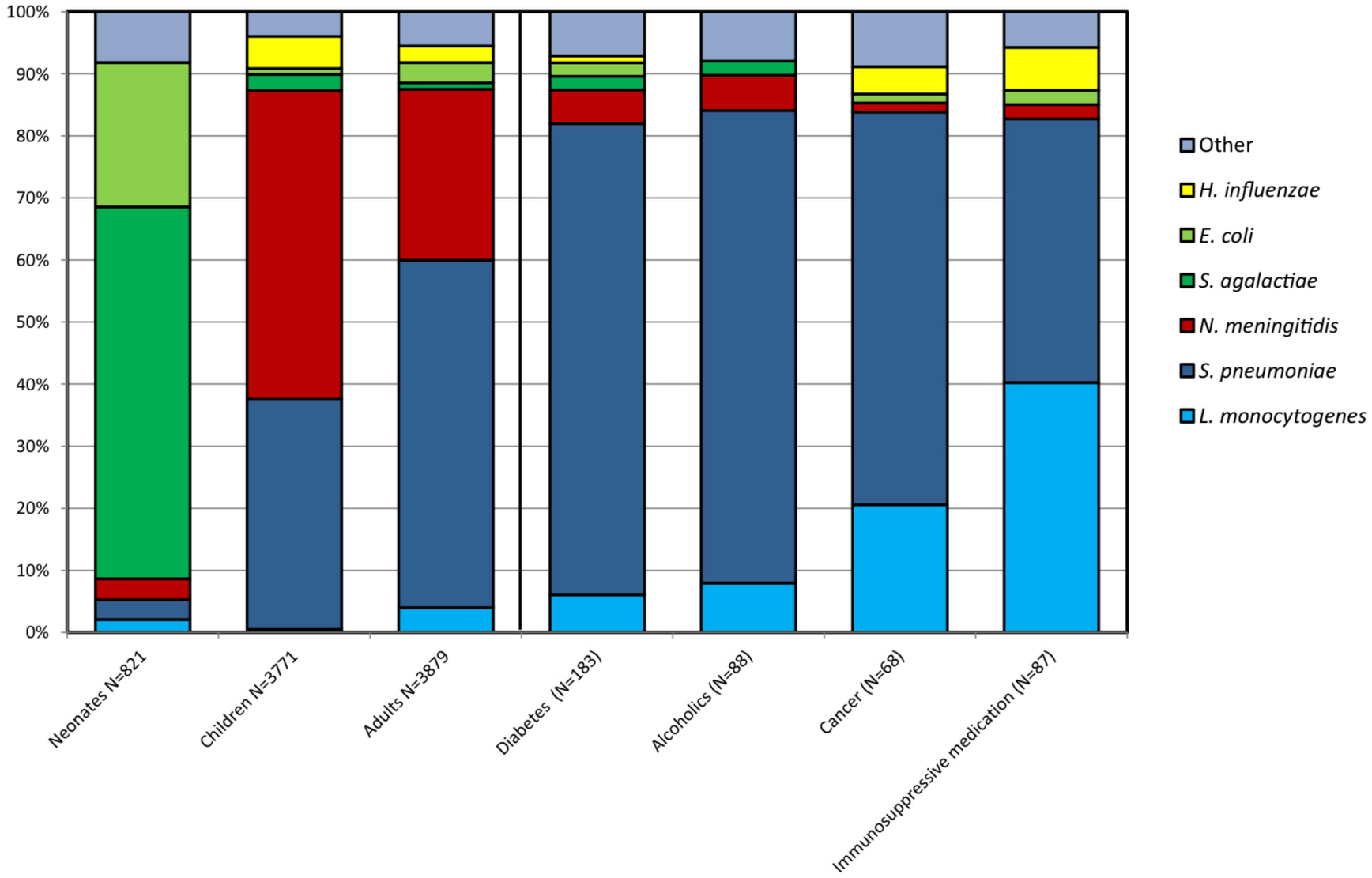


Fig. 1. Incidence of various pathogens in different age groups and with specific risk factors for bacterial meningitis [10,16,26–29]. Alcoholism was defined according to the diagnostics criteria of the National Institute on Alcohol Abuse and Alcoholism.

- C.N. van Ettekoven et al. / **Clinical Microbiology and Infection 23** (2017) 601e606

• Pathophysiology

•Bacterial Meningitis

Colonization

Survival within the bloodstream

Entry into the CNS

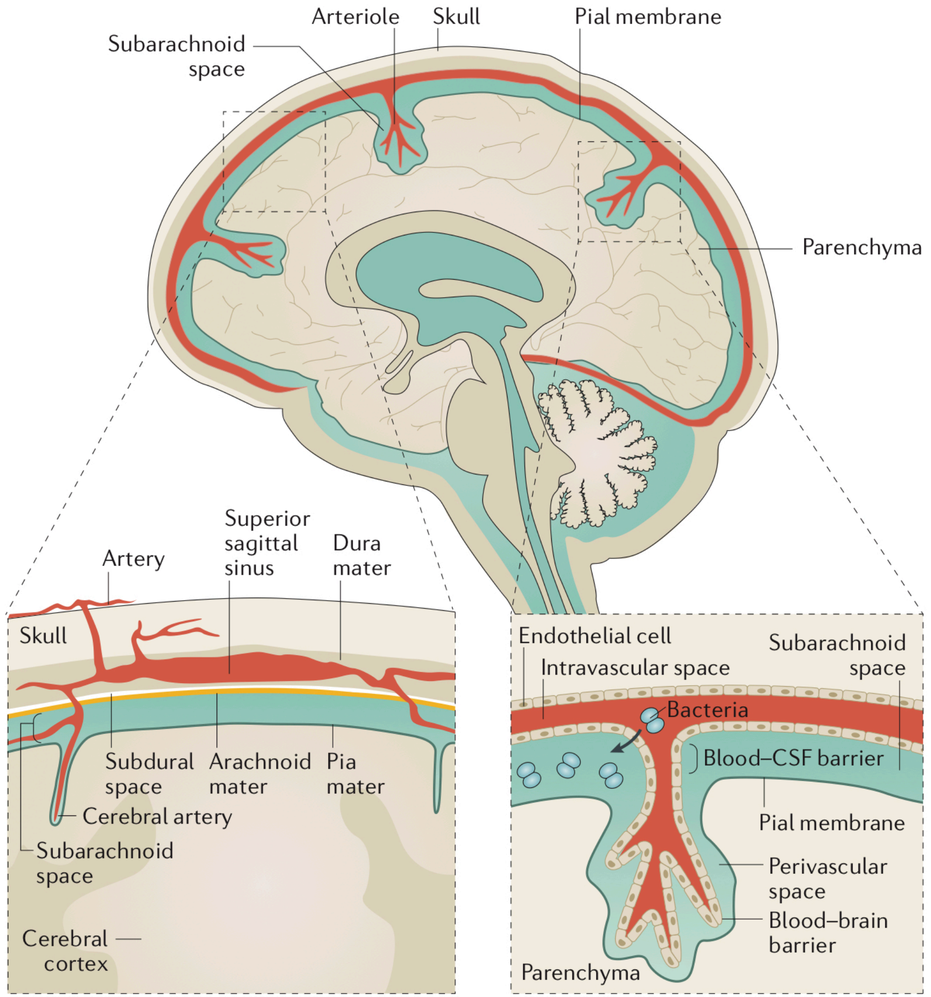


Figure 1 | **Anatomical considerations for the diagnosis of bacterial meningitis.** Mid-sagittal view of the brain showing the meninges: the dura mater, the subarachnoid mater and the pia mater. The meninges and cerebrospinal fluid (CSF) are in close anatomical relation with the cerebral cortex and brain parenchyma. Bacteria can reach the meninges through the blood–CSF barrier.

van de Beek, D., Brouwer, M., Hasbun, R. *et al.* Community-acquired bacterial meningitis. *Nat Rev Dis Primers* **2,** 16074 (2016).

• *S.pneumoniae*

- **Gram positive bacteria** , polysaccharide capsule
- S. pneumoniae belongs to the **α-hemolytic group** that characteristically produces a greenish color on blood agar because of the reduction of iron in hemoglobin
- S. pneumoniae invades the **bloodstream** and seeds other organs or **directly** reaches the cerebrospinal fluid (CSF) by local extension.

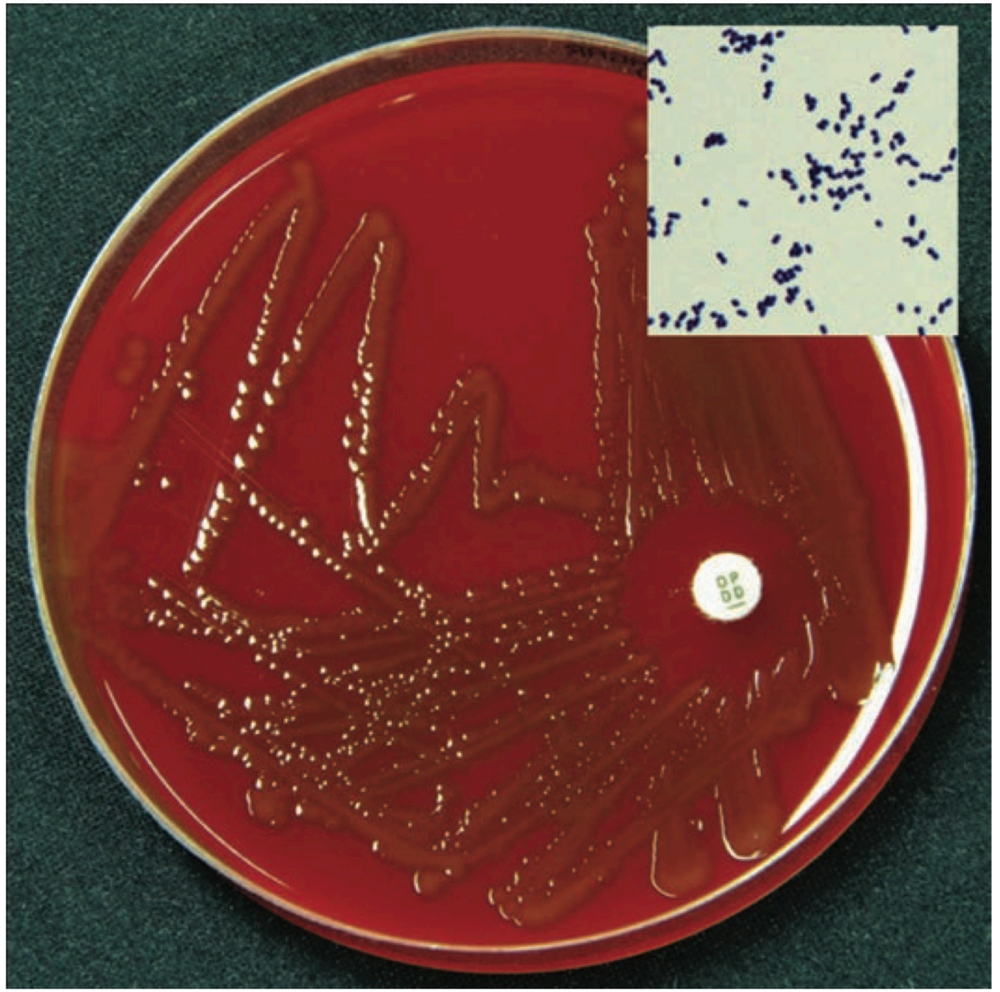
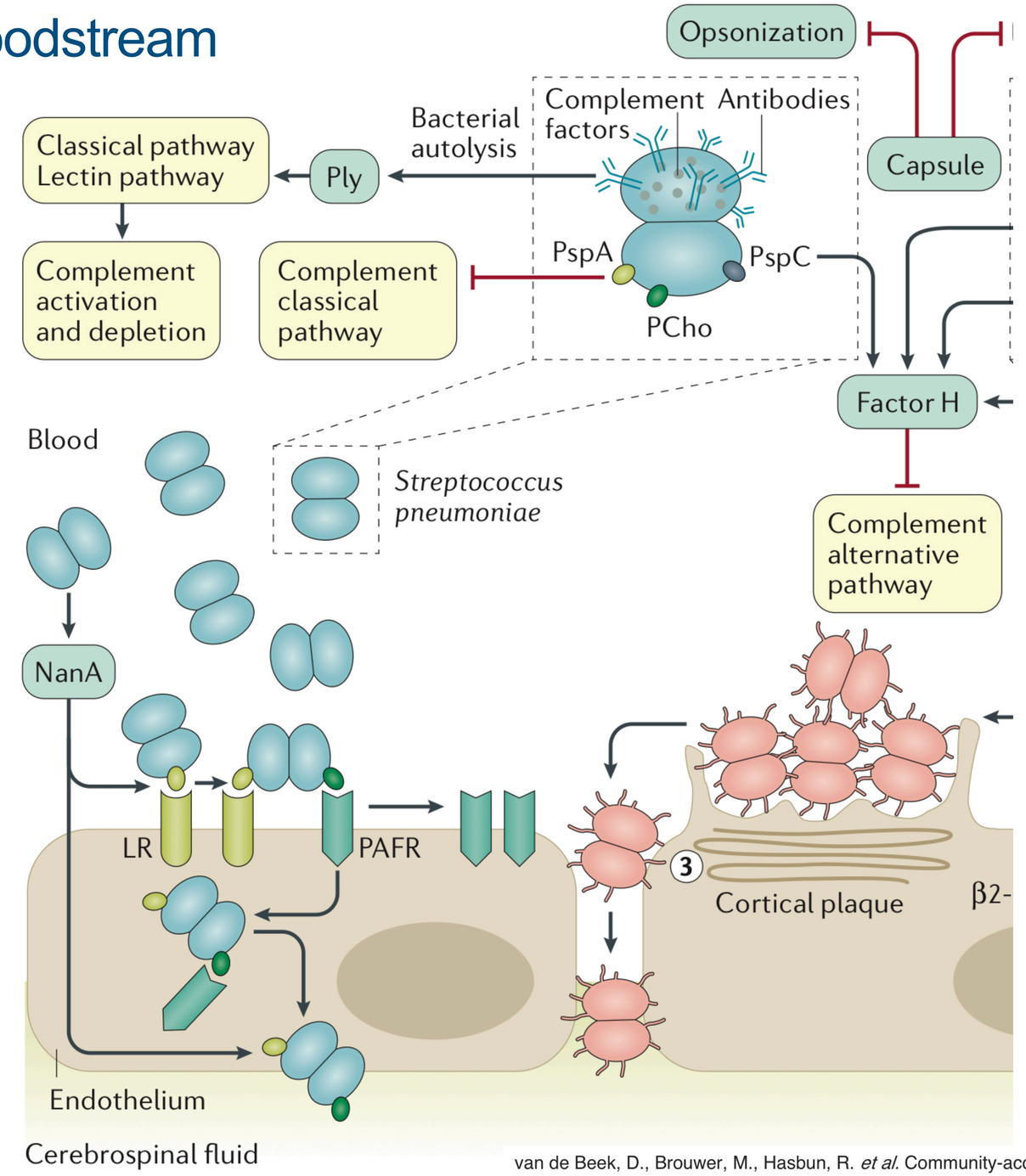


FIGURE 141-1 Pneumococci growing on blood agar, illustrating α hemolysis and optochin sensitivity (zone around optochin disk). *Inset:* Gram's stain, illustrating gram-positive diplococci. *(Photographs courtesy of Paul Turner, University of Oxford, United Kingdom.)*

David Goldblatt, Katherine L.O'Brient, Pneumococcal Infection,Harrison's Principle of Internal Medicine 20th Edition

Survival within the bloodstream



van de Beek, D., Brouwer, M., Hasbun, R. *et al.* Community-acquired bacterial meningitis. *Nat Rev Dis Primers* **2,** 16074 (2016).

- ***S.pneumoniae***

Host Defense Mechanism

- Innate Immunity : C-Reactive Protein bone phosphorylcholine inducing complement activation , TLR2, TLR4
- Acquired Immunity : B cells (antibodies)

TABLE 141-1 Clinical Risk Groups for Pneumococcal Infection

CLINICAL RISK GROUP	EXAMPLES
Asplenia or splenic dysfunction	Sickle cell disease, celiac disease
Chronic respiratory disease	Chronic obstructive pulmonary disease, bronchiectasis, cystic fibrosis, interstitial lung fibrosis, pneumoconiosis, bronchopulmonary dysplasia, aspiration risk, neuromuscular disease (e.g., cerebral palsy), severe asthma
Chronic heart disease	Ischemic heart disease, congenital heart disease, hypertension with cardiac complications, chronic heart failure
Chronic kidney disease	Nephrotic syndrome, chronic renal failure, renal transplantation
Chronic liver disease	Cirrhosis, biliary atresia, chronic hepatitis
Diabetes mellitus	Diabetes mellitus requiring insulin or oral hypoglycemic drugs
Immunocompromise/ immunosuppression	HIV infection, common variable immunodeficiency, leukemia, lymphoma, Hodgkin's disease, multiple myeloma, generalized malignancy, chemotherapy, organ or bone marrow transplantation, systemic glucocorticoid treatment for >1 month at a dose equivalent to ≥20 mg/d (children, ≥1 mg/kg per day)
Cochlear implants	…
Cerebrospinal fluid leaks	…
Miscellaneous	Infancy and old age; prior hospitalization; alcoholism; malnutrition; cigarette smoking; day-care center attendance; residence in military training camps, prisons, homeless shelters

Note: Groups for whom pneumococcal vaccines are recommended by the Advisory Committee on Immunization Practices can be found at *www.cdc.gov/vaccines /schedules/*.

David Goldblatt, Katherine L.O'Brient, Pneumococcal Infection,Harrison's Principle of Internal Medicine 20th Edition

• *S.pneumoniae*

Clinical Characteristic

- Fever 93% an altered mental status 94%
- Back Rigidity 57%
- Headache 41%
- Convulsion 11%
- Mortality 21%
- Neurologic Sequelae (Hearing loss 24%, Focal Neurodeficit 16%)

- Prognosis factor with poor outcome : Advance age , UD, History of headache, Presence of lung focus

Østergaard, C., Konradsen, H. B., & Samuelsson, S. (2005). Clinical presentation and prognostic factors of Streptococcus pneumoniae meningitis according to the focus of infection. *BMC infectious diseases*, *5*, 93. https://doi.org/10.1186/1471-2334-5-93

• *N.Meningitidis*

- **Gram-Negative aerobic diplococci** , capsule = virulence factor
- Phospholipid membrane : lipopolysaccharide and outer membrane proteins
- Genetic association with meningococcal disease is complement deficiency, increase risk 600-fold, may result in recurrent attacks

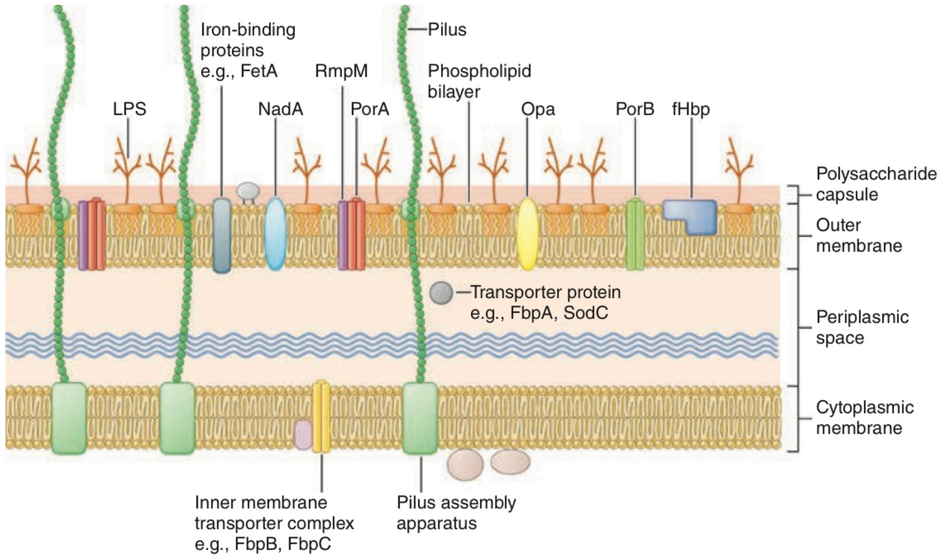
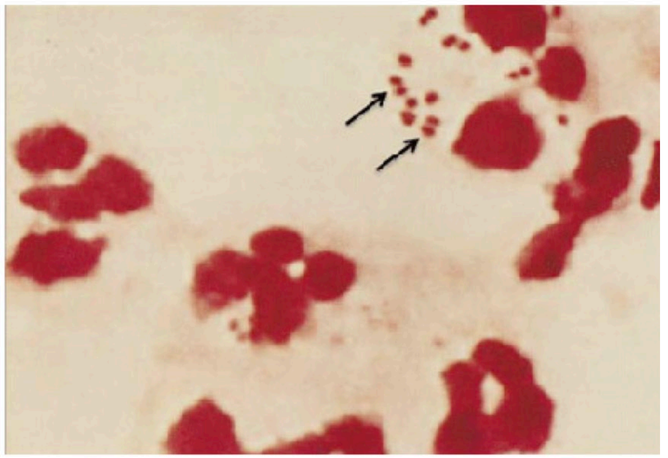


FIGURE 150-2 Cross-section through surface structures of *Neisseria meningitidis*. LPS, lipopolysaccharide. *(Reprinted with permission from M Sadarangani, AJ Pollard: Lancet Infect Dis 10:112, 2010.)*



N. meningitidis

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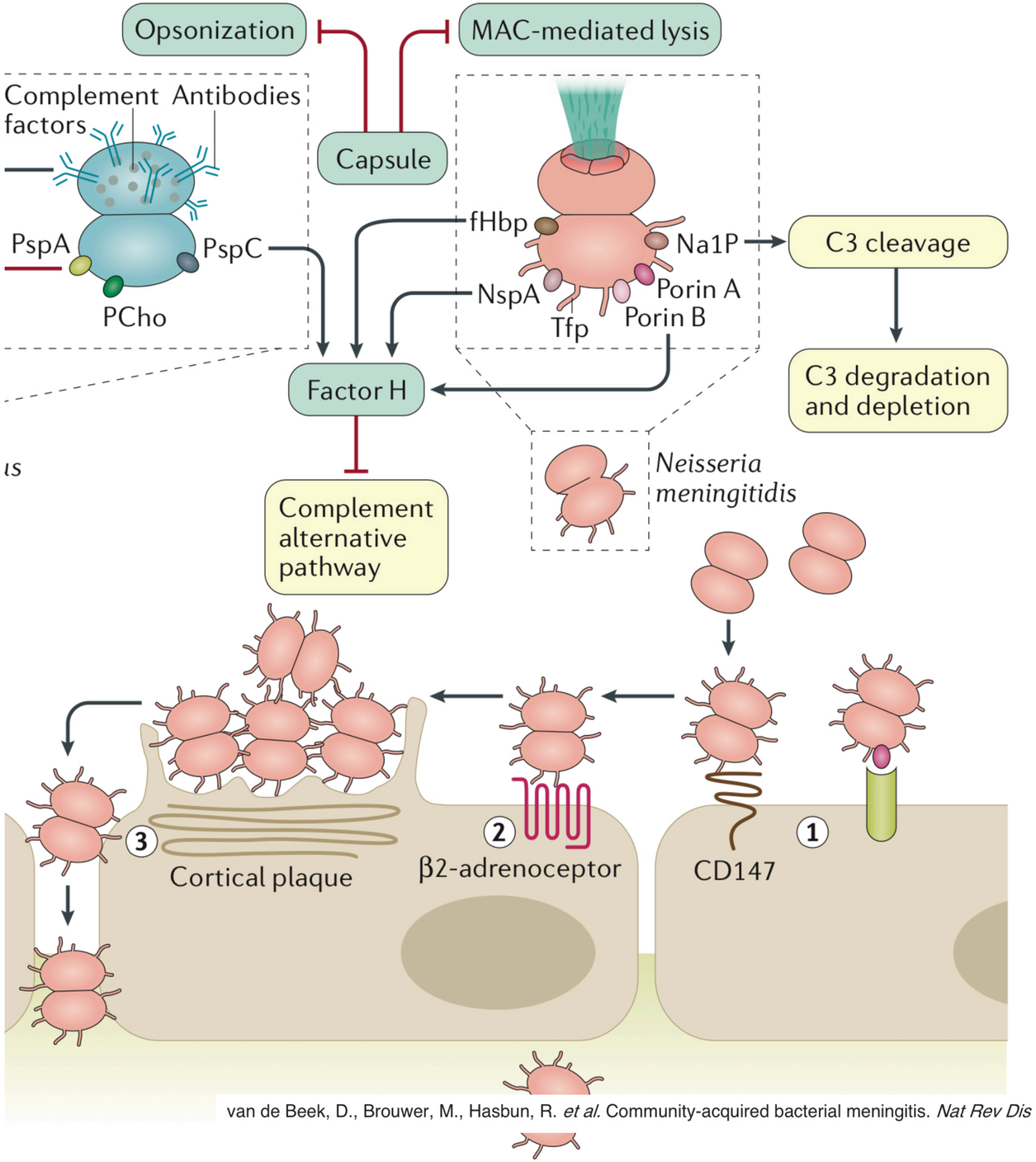
Survival within the bloodstream



van de Beek, D., Brouwer, M., Hasbun, R. *et al.* Community-acquired bacterial meningitis. *Nat Rev Dis Primers* **2,** 16074 (2016).

• *N.Meningitidis*

Clinical Characteristic

- Acute onset is characterized by severe headache, fever, nausea, vomiting, photophobia, and neck stiffness
- Neurological complications include seizures up to 40% cases.
- High mortality (50% when untreated)

Table 2

Complications of Meningococcal meningitis. High mortality rate in meningococcal meningitis is due to numerous potential complications.

Meningococcal meningitis	Fulminant meningococcemia
Early:-	
Seizures	Loss of skin, digits due to ischemic necrosis and infection
Raised intracranial pressure	
Hydrocephalus	
Cerebral venous thrombosis	Shock
Cerebral edema	Multiorgan failure
Hemiparesis	
Late:-	
Communicating hydrocephalus	
Subdural effusions in children	
Deafness	
Cranial nerve palsies	
Mental retardation	

- Generalized seizures occur early and are due to fever, metabolic derangement or toxic factors
- Focal seizures are more common after 4 to 10 days and are caused by arterial thrombosis, cortical vein thrombosis or abscess formation

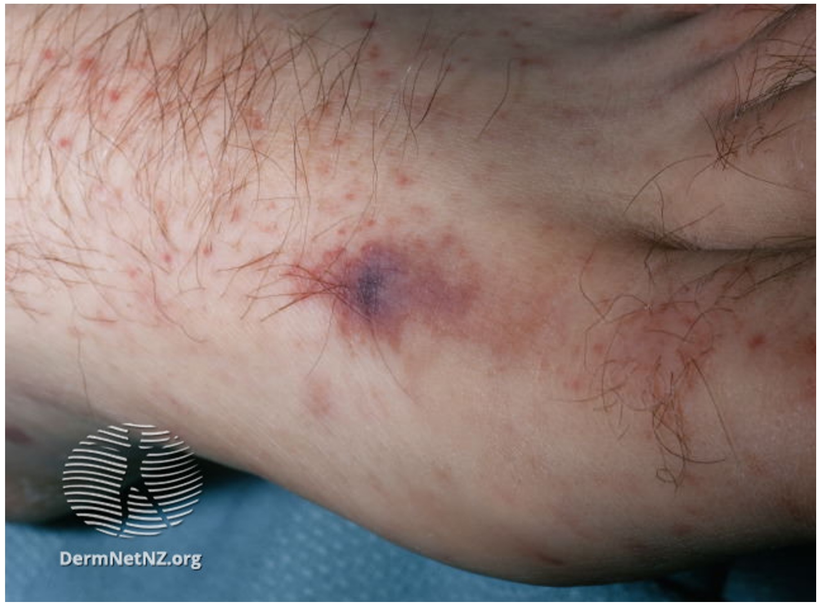
Johri, S., Gorthi, S. P., & Anand, A. C. (2005). Meningococcal Meningitis. *Medical journal, Armed Forces India*, *61*(4), 369–374.

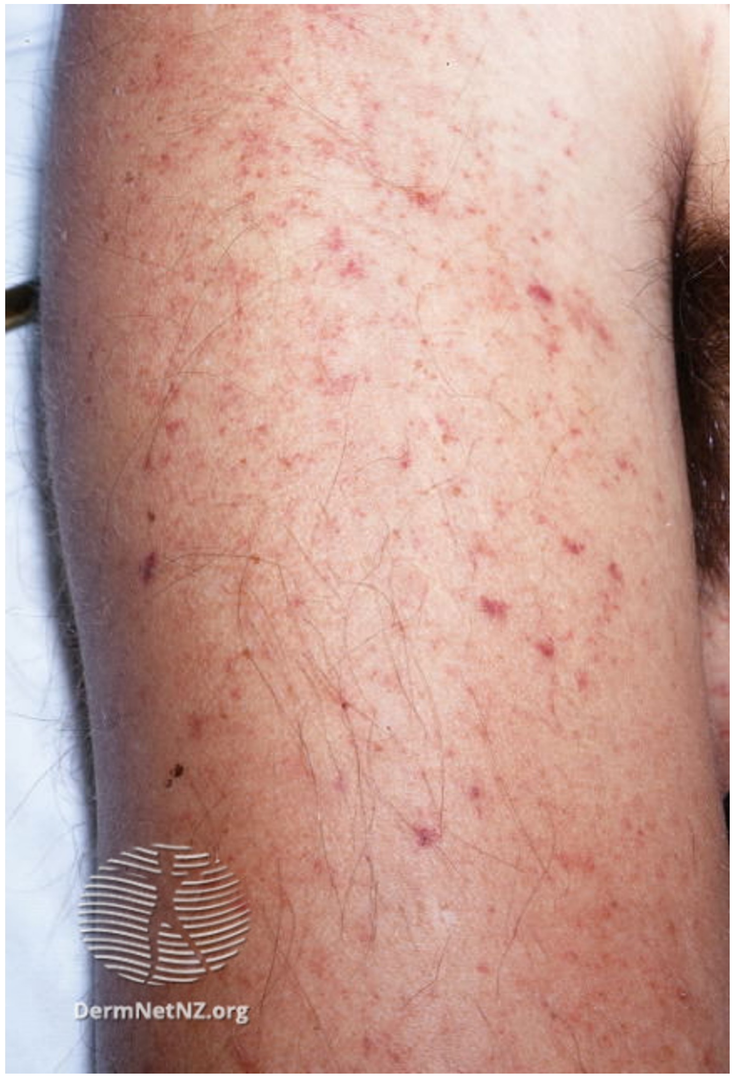
Simon Nadel, J. Simon Kroll, **Diagnosis and management of meningococcal disease**: the need for centralized care, FEMS Microbiology Reviews, Volume 31, Issue 1, January 2007, Pages 71–83, https://doi.org/10.1111/j.1574-6976.2006.00059.

• *N.Meningitidis*

Clinical Characteristic

- Diffuse eythematous maculopapular rash. As it evolves, petechiae and purpura appear primarily on the trunk and lower extremities





Prof Amanda Oakley, Dermatologist, Hamilton New Zealand. Reviewed and updated 18 February 2014.

Simon Nadel, J. Simon Kroll, **Diagnosis and management of meningococcal disease**: the need for centralized care, FEMS Microbiology Reviews, Volume 31, Issue 1, January 2007, Pages 71–83, https://doi.org/10.1111/j.1574-6976.2006.00059.

• *N.Meningitidis*

Prophylaxis

- Close contacts , increased risk for developing secondary disease
- Household contacts of the index cas
- Health care workers : Direct exposed to RS secretion

Table 3

Chemoprophylaxis against meningococcal disease

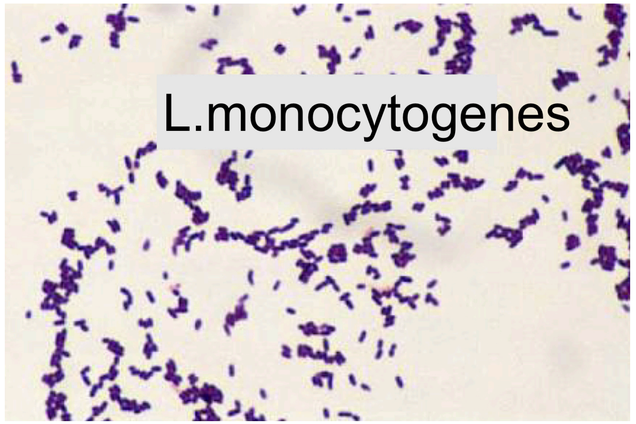
Drug and age group	Dosage
Rifampicin (oral)	
Children<1month	5mg/kg of body weight every 12 hr for 2 days
Children ≥ 1month	10 mg/kg every 12 hr for 2 days
Adults	600 mg every 12 hr for 2 days
Ciprofloxacin (oral)	500 mg given in a single dose (adults)
Ceftriaxone	
Children<15 yr	125 mg given in a single intramuscular dose
Children ≥ 15 yr/Adults	250 mg given in a single intramuscular dose
Oflaxacin (oral)	400 mg, given in a single dose (adults)
Azithromycin (oral)	500 mg, given in a single dose (adults)

Johri, S., Gorthi, S. P., & Anand, A. C. (2005). Meningococcal Meningitis. *Medical journal, Armed Forces India*, *61*(4), 369–374.

Andrew J.Pollard, Meningococcal Infection,Harrison's Principle of Internal Medicine 20th Edition

• *L.monocytogenes*

- L. monocytogenes is a facultatively anaerobic, nonsporulating, **gram- positive rod**
- Infections with L. monocytogenes follow ingestion of contaminated food that contains the bacteria at high concentrations
- L. monocytogenes induces its own internalization by cells
- Internalin-mediated entry , crossing BBB



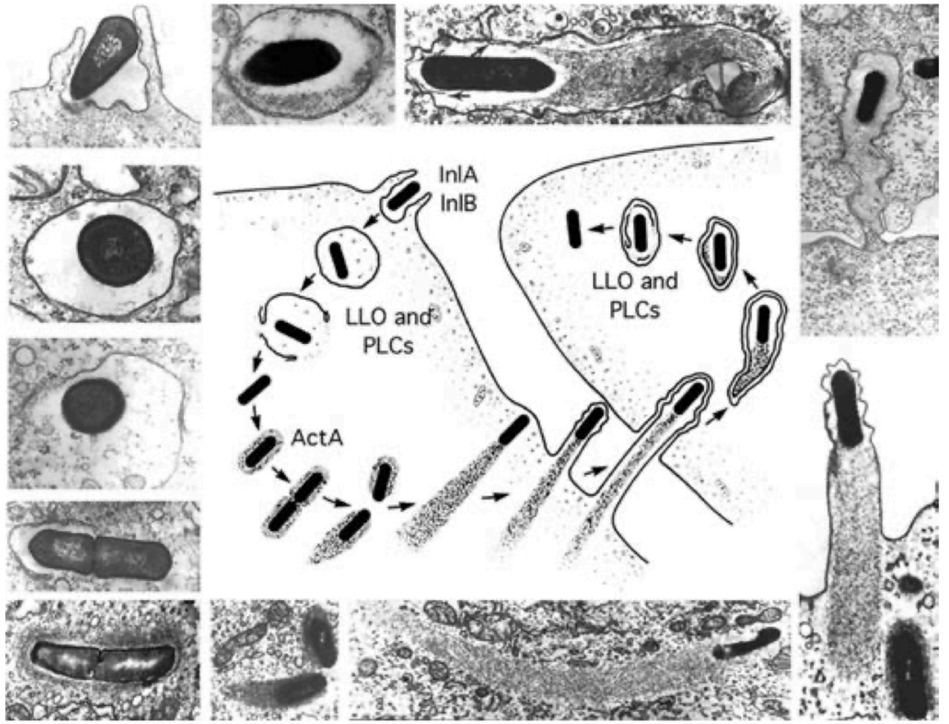


FIGURE 146-1 Stages in the intracellular life cycle of *Listeria monocytogenes.* The central diagram depicts cell entry, escape from a vacuole, actin nucleation, actin-based motility, and cell-to-cell spread. Surrounding the diagram are representative electron micrographs from which it was derived. ActA, surface protein mediating nucleation of host actin filaments to propel bacteria intra- and intercellularly; LLO, listeriolysin O; PLCs, phospholipases C; Inl, internalin. See text for further details. *(Adapted with permission from LG Tilney, DA Portnoy: J Cell Biol 109:1597, 1989. © Rockefeller University Press.)*

Elizabeth L.Hofmann, Daniel A.Portnoy, Listeria monocytogenes Infections, Harrison's Principle of Internal Medicine 20th Edition

• *L.monocytogenes*

Table 1. Clinical and laboratory characteristics at admission to the hospital for 30 adults with community-acquired *Listeria monocytogenes* meningitis.

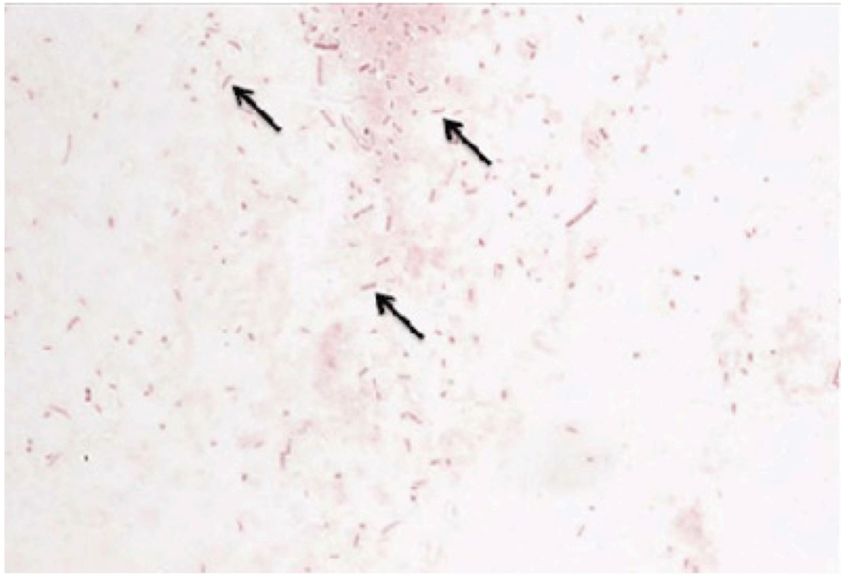
Variable	Patients (n = 30)
Age, mean years ± SD	65 ± 18
Male sex	15/30 (50)
Predisposing factors	
Immunocompromise	20/30 (67)
Pneumonia	1/30 (3)
Otitis or sinusitis	1/30 (3)
Pretreated with antimicrobials	5/30 (17)
Duration of symptoms <24 h	11/30 (37)
Seizures	2/30 (7)
Symptoms at presentation	
Headache	22/25 (88)
Nausea	20/24 (83)
Neck stiffness	22/30 (73)
Temperature ≥38°C	27/30 (90)
Score on Glasgow coma scale at presentation	
Median score ± SD	12 ± 3
<14 (indicating change in mental status)	21/30 (70)
≤8 (indicating coma)	3/30 (10)
Triad of fever, neck stiffness, and change in mental status	13/30 (43)
Laboratory findings[a]	
Indexes of CSF inflammation	
Opening pressure, median mm of water (range)	275 (150–400)
WBC count	
Median cells (range)	620 (24–16003)
<100 cells/mL	4/28 (13)
100–999 cells/mL	13/28 (46)
>999 cells/mL	11/28 (39)
Protein level, median g/L (range)	2.52 (1.1–19.3)
CSF/blood glucose ratio, median value (range)	0.30 (0.03–0.86)
CSF Gram stain results	
Negative	16/25 (60)
Gram-positive rod	7/25 (28)
Other[b]	2/25 (4)
Blood culture findings	
L. monocytogenes	12/26 (46)
Other[c]	2/26 (8)
Erythrocyte sedimentation rate, median mm per h (range)	39 (10–242)
C-reactive protein level, median value (range)	117 (4–467)
Thrombocyte count, median platelets/mL (range)	186 (4–653)
Hyponatremia	22/30 (73)

- immunosuppressive therapy, immunosenescence, diabetes, or malignancies

Matthijs C. Brouwer, Diederik van de Beek, Sebastiaan G. B. Heckenberg, Lodewijk Spanjaard, Jan de Gans, Community-Acquired Listeria monocytogenes Meningitis in Adults, Clinical Infectious Diseases, Volume 43, Issue 10, 15 November 2006, Pages 1233–1238,

• *H.influenza*

- H. influenzae is a small (1- × 0.3-μm) **gram-negative, variable shape**
- Airborne droplet or by direct contact with secretion or fomites
- Invasion and Hematogenous spread from RS tract to meninges
- Type b polysaccharide capsule , virulence factor avoid opsonization



H. influenzae

Timothy F.Murphy, Haemophilus and Moraxella Infection, Harrison's Principle of Internal Medicine 20th Edition

- ***H.influenza***

Clinical Characteristic

Clinical features on admission	
Fever (temp. >38°C)	82% (23/28)
Body temperature	39.1°C (38.2–39.7
Back rigidity	79% (27/34)
Altered mental status	67% (22/33)
Convulsions	10% (3/30)

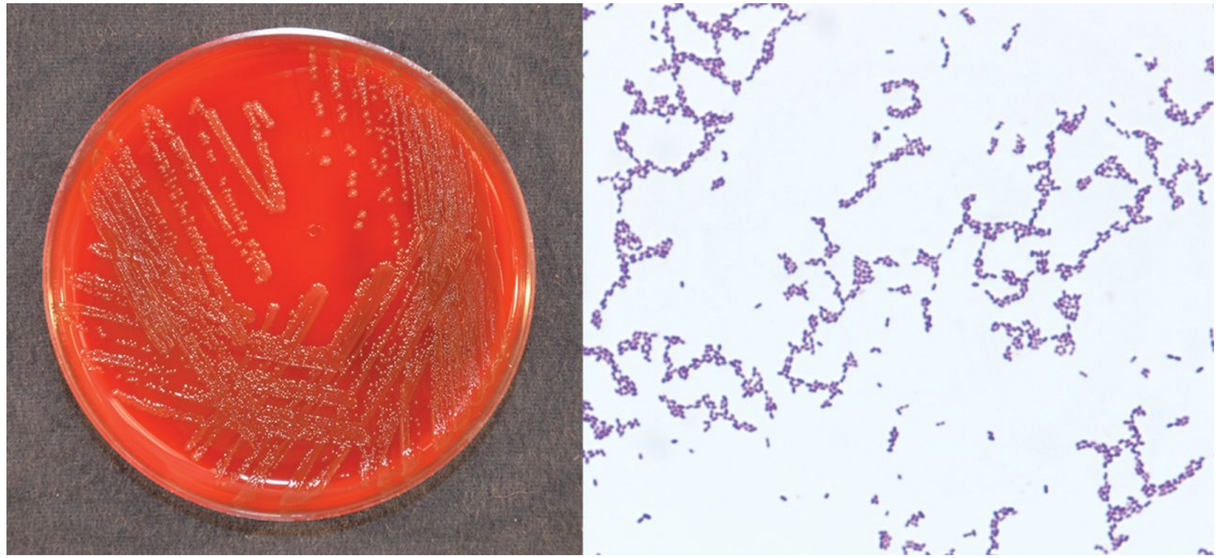
Percentage or medians (25/75 percentiles)	Adults (*n* = 36)
Gender (females, %)	63% (23/36)
Age	63 years (44–75)
Infected with *Hib*	11% (4/36)
Underlying diseases	17% (5/30)
Predisposing conditions	26% (8/31)
Focus of infection	
Otitis media	33% (12/36)
Pneumonia	17% (6/36)
Sinusitis	8% (3/36)
Unknown	47% (17/36)

Paraclinical findings	
CSF WBC (cells/μL)	3261 (1084–4244)
CSF protein (g/L)	2.9 (2.0–7.7)
CSF glucose (mmol/L)	2.2 (0.5–3.2)
CSF/blood glucose ratio	0.28 (0.14–0.38)
Blood WBC (10^9 cells/L)	15.0 (11.4–19.3)
Platelets (10^9 cells/L)	216 (169–305)
Blood sodium (mmol/L)	137 (135–139)
Blood glucose (mmol/L)	8.1 (6.6–10.3)
CRP (mg/L)	98 (39–190)
Positive CSF Gram staining	59% (17/29)
Positive CSF culture	97% (34/35)
Positive blood culture	58% (19/33)
Ampicillin non-susceptibility	7% (2/30)
type b	25% (1/4)
type non-b	4% (1/26)
Steroid therapy	10% (3/30)
Mechanical ventilation	27% (8/30)
Hearing loss	18% (5/28)
Neurological sequelae	4% (1/28)
Death	14% (5/36)

Clinical Microbiology and In
Volume 16, Issue 5, May 2010, Pages 43

• *S.suis*

- **Gram positive bacteria**, alpha hemolysis on sheep blood agar
- Pork consuming and pig rearing countries in SEA
- Deafness with or without vestibular dysfunction , direct infection of cochlea
- Enter perilymph via the cochlear aqueduct through lytic action of exotoxins



• van Samkar A, Brouwer MC, Schultsz C, van der Ende A, van de Beek D (2015) Streptococcus suis Meningitis: A Systematic Review and Meta-analysis. PLoS Negl Trop Dis 9(10): e0004191. doi:10.1371/journal.pn

Eric Gomez, Cassie C. Kennedy, Marcelo Gottschalk, Scott A. Cunningham, Robin Patel, Abinash Virk *Streptococcus suis*-Related Prosthetic Joint Infection and Streptococcal Toxic Shock-Like Syndrome in a Pig Farmer in the United States
DOI: 10.1128/JCM.02934-13

- ***S.suis***

Clinical Characteristic

Table 1. Clinical characteristics of patients with *S. suis* meningitis.

	n/N* (%)
Age[ab]	48.8 (SD 3.9)
Male	581/711 (82%)
Predisposing factors	
Alcoholism	60/322 (19%)
Diabetes mellitus	11/209 (5%)
Splenectomy	5/507 (1%)
Immunosuppressive medication	2/601 (0.3%)
Cancer	5/85 (6%)
Exposure to pigs/pork	395/648 (61%)
Clinical presentation	
Skin injury in the presence of pig/pork contact	78/384 (20%)
Headache	429/451 (95%)
Fever	514/528 (97%)
Neck stiffness	462/496 (93%)
Altered consciousness	35/113 (31%)
Classic meningitis triad[1]	4/43 (9%)
Nausea/vomiting	210/321 (65%)
Blood characteristics	
Leukocytes[ac]	17.4 (SD 0.9)
Thrombocytes[ad]	166.3 (SD 19.1)
Cerebrospinal fluid characteristics	
Leukocytes/mm3 [ae]	1920 (SD 757)
Protein (g/dL)[af]	2.4 (SD 0.8)
Glucose (mmol/L)[ag]	1.09 (SD 0.60)
Positive cultures	
Cerebrospinal fluid	758/913 (83%)
Blood	288/435 (66%)
Adjunctive dexamethasone	157/300 (52%)
Outcome	
Death	17/581 (3%)
Hearing loss	259/489 (53%)
Other sequelae	35/286 (12%)
Full recovery	116/320 (36%)

- Tan JH, Yeh BI, Seet CS. Deafness due to haemorrhagic labyrinthi tis and a review of relapses in Streptococcus suis meningitis. Singapore Med J. 2010;51:e30–e33.

• Bacterial Meningitis : Clinical manifestation

TABLE 3.2. Presenting clinical characteristics of adults with bacterial meningitis

Country	Netherlands [41]	France [42]	Spain [43]	Iceland [44]	Denmark [25
Observation period	1998–2002	2001–2004	1996–2010	1975–1994	1989–2010
No. of patients	696	60	295	119	172
Headache	87%	87%	—	—	58%
Nausea/vomiting	74%	—	45%	—	—
Neck stiffness	83%	—	69%	82%	65%
Rash	26%	—	20%	52%	—
Fever (>38.0°C)	77%	93%	95%	97%	87%
Altered mental status	69%	30%	54%	66%	68%
Coma	14%	—	7%	13%	16%
Focal neurologic deficits	34%	23%	15%	—	21%
Triad of fever, neck stiffness and altered mental status	44%	—	41%	51%	45%

- **Rapid onset and progression** of symptoms over hours
- Is typical and can be helpful to distinguish **Bacterial** from Viral infections

van de Beek D, Cabellos C, Dzupova O, Esposito S, Klein M, Kloek AT, Leib SL, Mourvillier B, Ostergaard C, Pagliano P, Pfister HW, Read RC, Sipahi OR, Brouwer MC; **ESCMID Study Group for Infections of the Brain (ESGIB). ESCMID guideline: diagnosis and treatment of acute bacterial meningitis.** Clin Microbiol Infect. 2016 May;22 Suppl 3:S37-62. doi: 10.1016/j.cmi.2016.01.007. Epub 2016 Apr 7. PMID: 27062097.

- Bacterial Meningitis : Diagnosis and Investigation

• Bacterial Meningitis : Diagnosis and Investigation

Table 22.2 CSF findings in acute and chronic meningitis and other CNS infectious conditions

Type of infection	Macroscopic appearance	Cells	Protein (mg/dL)	Glucose (mg/dL)	Other tests
Normal	Clear	<5 lymphocytes/mm^3	15–45	50–75	Negative test results
Bacterial meningitis (*S. pneumoniae*; *N. meningitides*; *L. monocytogenes*)	Cloudy or turbid	*Increased* (*commonly* > *200*) *Typically* >*90 % PMNs* Can be normal in meningococcemia	>100	Reduced (<40)	Gram stain, bacterial culture, and antigen tests may be positive
Viral meningitis (enteroviruses; herpes simplex; arboviral encephalitis)	Clear or rarely opalescent	Increased May have PMN predominance early in the course of infection; converts to lymphocytic predominance within 12–24 h	Usually <100	Normal	Gram stain, bacterial culture, and antigen tests negative PCR for HSV, VZV, arboviruses, and enteroviruses may be positive
Fungal meningitis (cryptococcus; histoplasmosis; coccidioidomycosis)	Cloudy or turbid	>100 (<50 %) Usual range 100–400 usually lymphocytic predominance May be normal in cryptococcal meningitis	100–900	< 40	Cryptococcus can be diagnosed from India ink preps, antigen tests, or culture; PCR
Tuberculous meningitis	Cloudy or turbid	Increased Typically >100 Usual range 100–400 PMN early but converts to lymphocytic predominance	100–900	<40	Acid-fast bacilli occasionally seen on CSF smear stained with Kinyoun or Ziehl-Neelsen stains

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

Table 1 Indications for CT head prior to LP

	IDSA guideline[13]	ESCMID guideline[14]
Immunosuppression	HIV infection, immunosuppressive therapy, post-transplantation	Severely immunocompromised state
Background of CNS disease	Mass lesion, stroke or focal CNS infection	No recommendation
Seizures	Seizures within a week prior to presentation	New onset seizures
Level of consciousness	GCS < 15	GCS < 10
Focal neurological deficit	Focal deficit including cranial nerve palsies	Focal deficit excluding cranial nerve palsies
Papilloedema	Indication for CT	No recommendation
Duration of symptoms	No recommendation	No recommendation

• Contraindication to LP

- Lateral shift of midline structure
- Loss of suprachiasmatic and basilar cisterns
- Obliteration of 4 th ventricle
- Obliteration of superior cerebellar cistern
- Obliteration of quadrigeminal plate cistern
- Posterior fossa mass

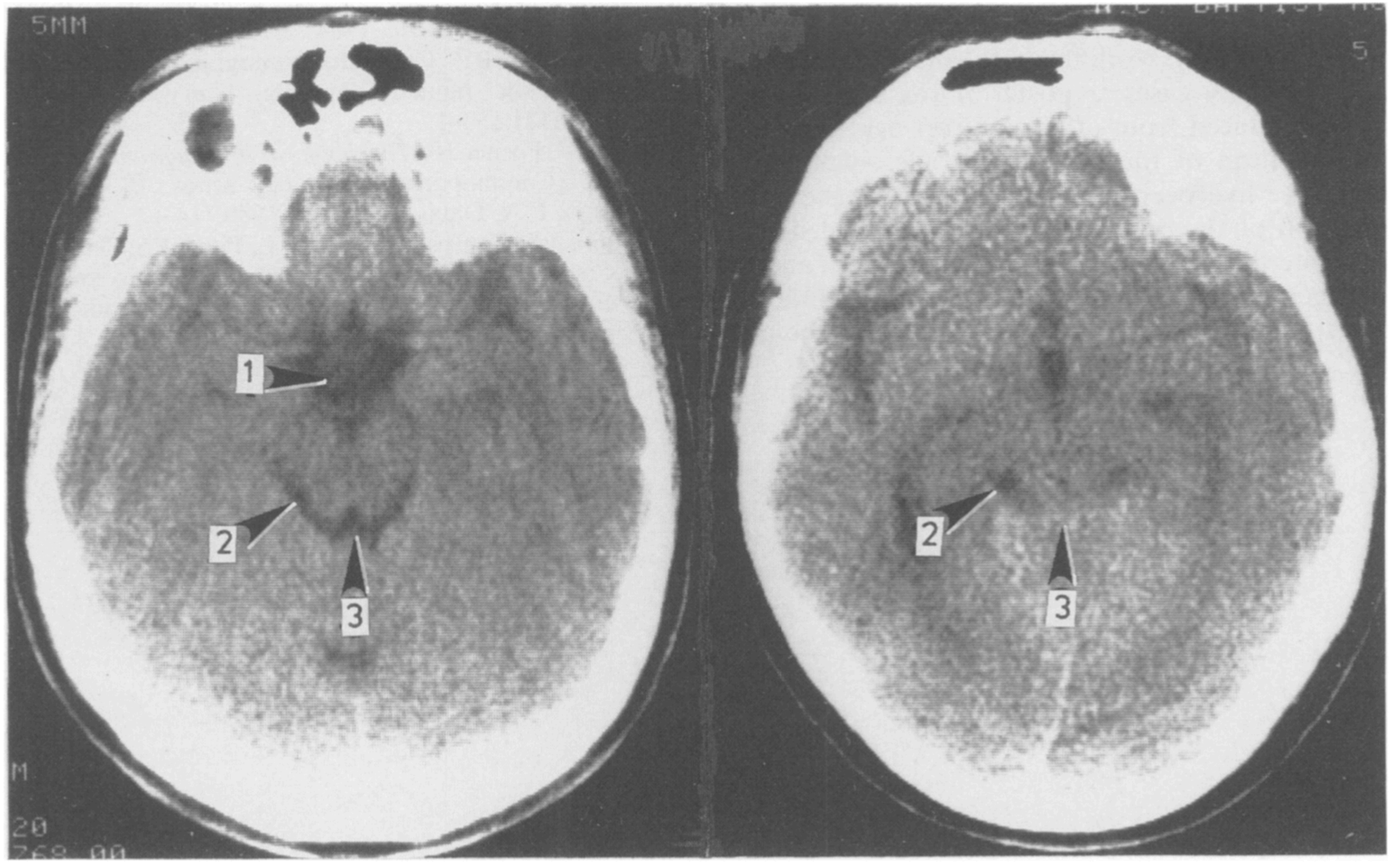


Fig 2 (*left*) *Normal uninfused CT scan demonstrating the basilar cisterns* (*1 = suprasellar cistern, 2 = ambient cistern, 3 = quadrigeminal plate cistern*), *and* (*right*) *an example of upward transtentorial herniation with obliteration of the quadrigeminal plate cistern* (*3*) *and sparing of the ambient cistern* (*2*).

Gowe

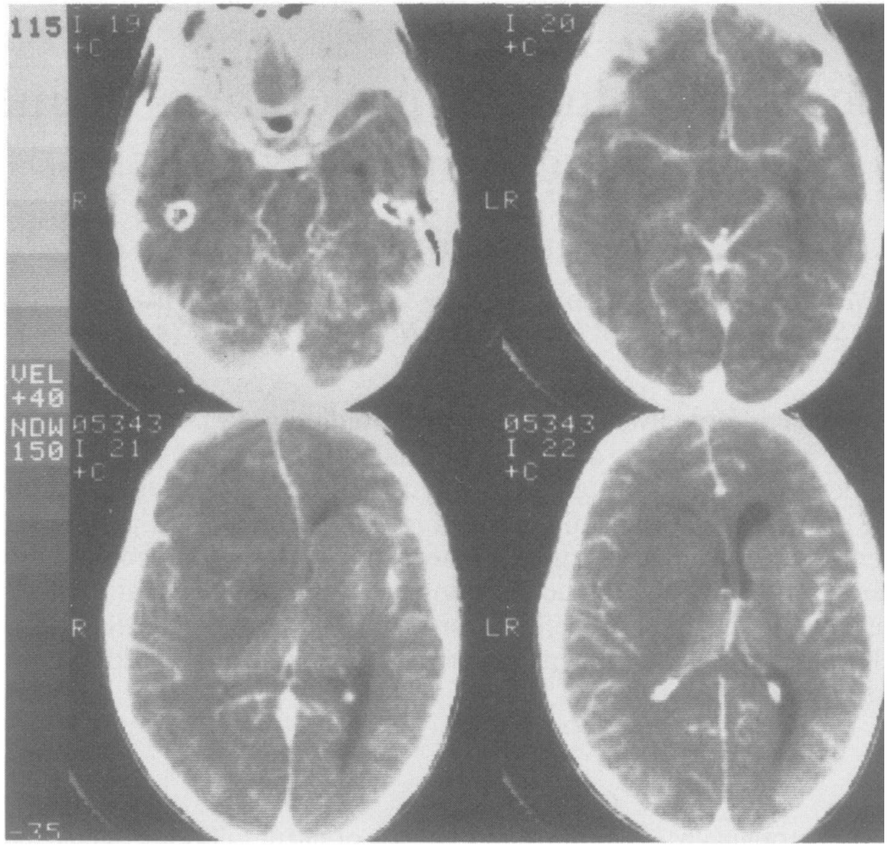


Fig 1 *Infused CT scan that demonstrates midline shift and uncal herniation with displacement of the right posterior cerebral artery.*

- Journal of Neurology, Neurosurgery,and Psychiatry 1987;50:1071-1074

• Bacterial Meningitis : Treatment

TABLE 4.1. Empiric antibiotic in-hospital treatment for community-acquired bacterial meningitis [3]

Patient group	Standard treatment: Reduced *Streptococcus pneumoniae* antimicrobial sensitivity to penicillin	Standard treatment: *S. pneumoniae* susceptible to penicillin	Intravenous dose[a]
Neonates <1 month old	Amoxicillin/ampicillin/penicillin plus cefotaxime, or amoxicillin/ampicillin plus an aminoglycoside		Age <1 week: cefotaxime 50 mg/kg q8h; ampicillin/amoxicillin 50 mg/kg q8h; gentamicin 2.5 mg/kg q12h Age 1–4 weeks: ampicillin 50 mg/kg q6h; cefotaxime 50mg/kg q6–8h; gentamicin 2.5 mg/kg q8h; tobramycin 2.5 mg/kg q8h; amikacin 10 mg/kg q8h
Age 1 month to 18 years	Cefotaxime or ceftriaxone plus vancomycin or rifampicin	Cefotaxime or ceftriaxone	Vancomycin 10–15 mg/kg q6h to achieve serum trough concentrations of 15–20 µg/mL; rifampicin 10 mg/kg q12h up to 600 mg/day; cefotaxime 75 mg/kg q6–8h; ceftriaxone 50 mg/kg q12h (maximum 2 g q12h)
Age >18 and <50 years	Cefotaxime or ceftriaxone plus vancomycin or rifampicin	Cefotaxime or ceftriaxone	Ceftriaxone 2 g q12h or 4 g q24h; cefotaxime 2 g q4–6 h; vancomycin 10–20 mg/kg q8–12h to achieve serum trough concentrations of 15–20 µg/mL; rifampicin 300 mg q12h
Age >50 years, or Age >18 and <50 years plus risk factors for *Listeria monocytogenes*[a]	Cefotaxime or ceftriaxone plus vancomycin or rifampicin plus amoxicillin/ampicillin/penicillin G	Cefotaxime or ceftriaxone plus amoxicillin/ampicillin/ penicillin G	Ceftriaxone 2 g q12h or 4 g q24h; cefotaxime 2 g q4–6h; vancomycin 10–20 mg/kg q8–12h to achieve serum trough concentrations of 15–20 µg/mL; rifampicin 300 mg q12h, amoxicillin or ampicillin 2 g q4h

[a]Diabetes mellitus, use of immunosuppressive drugs, cancer and other conditions causing immunocompromise.

van de Beek D, Cabellos C, Dzupova O, Esposito S, Klein M, Kloek AT, Leib SL, Mourvillier B, Ostergaard C, Pagliano P, Pfister HW, Read RC, Sipahi OR, Brouwer MC; **ESCMID Study Group for Infections of the Brain (ESGIB). ESCMID guideline: diagnosis and treatment of acute bacterial meningitis.** Clin Microbiol Infect. 2016 May;22 Suppl 3:S37-62. doi: 10.1016/j.cmi.2016.01.007. Epub 2016 Apr 7. PMID: 27062097.

Microorganism	Standard treatment	Alternatives	Duration
Streptococcus pneumoniae			
Penicillin susceptible (MIC <0.1 µg/mL)	Penicillin or amoxicillin/ampicillin	Ceftriaxone, cefotaxime, chloramphenicol	10–14 days
Penicillin resistant (MIC >0.1 µg/mL), third-generation cephalosporin susceptible (MIC <2 µg/mL)	Ceftriaxone or cefotaxime	Cefepime, meropenem, moxifloxacin[b]	10–14 days
Cephalosporin resistant (MIC ≥2 µg/mL)	Vancomycin *plus* rifampicin, or vancomycin *plus* ceftriaxone or cefotaxime, or rifampicin *plus* ceftriaxone or cefotaxime[c]	Vancomycin *plus* moxifloxacin,[b] linezolid	10–14 days
Neisseria meningitidis			
Penicillin susceptible (MIC <0.1 µg/mL)	Penicillin or amoxicillin/ampicillin	Ceftriaxone, cefotaxime, chloramphenicol	7 days
Penicillin resistant (MIC ≥0.1 µg/mL)	Ceftriaxone or cefotaxime	Cefipime, meropenem, ciprofloxacin or chloramphenicol	7 days
Listeria monocytogenes	Amoxicillin or ampicillin, penicillin G[d]	trimethoprim-sulfamethoxazole, moxifloxacin,[b] meropenem, linezolid	At least 21 days
Haemophilus influenzae			
β-Lactamase negative	Amoxicillin or ampicillin	Ceftriaxone, cefotaxime or chloramphenicol	7–10 days
β-Lactamase positive	Ceftriaxone or cefotaxim	Cefepime, ciprofloxacin, chloramphenicol	7–10 days
β-Lactamase negative ampicillin resistant	Ceftriaxone or cefotaxime *plus* meropenem	Ciprofloxacin	7–10 days
Staphylococcus aureus			
Methicillin sensitive	Flucloxacillin, nafcillin, oxacillin	Vancomycin, linezolid, rifampicin,[e] fosfomycin,[e] daptomycin[b]	At least 14 days
Methicillin resistant	Vancomycin[f]	Trimethoprim/sulfamethoxazole, linezolid, rifampicin,[e] fosfomycin,[e] daptomycin	At least 14 days
Vancomycin resistant (MIC >2.0 µg/mL)	Linezolid[f]	Rifampicin,[e] fosfomycin,[e] daptomycin[b]	At least 14 days

[a]Recommendations must be in accordance with the results of the susceptibility
[b]Based on case reports.
[c]Ceftriaxone dose 2 g q12h and cefotaxime 2–3g q6h.
[d]Adding an aminoglycoside can be considered.
[e]Must not be used in monotherapy.
[f]Addition of rifampicin can be considered.

Trauma: skull fracture	*S. pneumoniae*; *H. influenzae*; Group B Streptococcus	Vancomycin 15 mg.kg IV q8–12 h *plus* ceftriaxone 2 g IV q12h
Trauma: penetrating	*Staphylococcus aureus*, coagulase-negative staphylococcu, *Enterobacteriaceae*, *Pseudomonas* spp.	Vancomycin 15 mg.kg IV q8–12 h *plus* cefepime 2 g IV q8h
Meningitis associated with shunts	*S. aureus*, coagulase-negative staphylococcus, *Enterobacteriaceae*, *Pseudomonas* spp.	Vancomycin 15 mg.kg IV q8–12 h *plus* cefepime 2 g IV q8h
Neurosurgery (e.g., craniotomy)	*S. aureus*, coagulase-negative staphylococcus, *Enterobacteriaceae*, *Pseudomonas* spp.	Vancomycin 15 mg.kg IV q8–12 h *plus* cefepime 2 g IV q8h

• Adjunctive Dexamethasone Treatment

- The release of bacterial cell-wall components by **bactericidal antibiotics** leads to the production of the **inflammatory cytokines** IL-1β and TNF-α
- Dexamethasone exerts its beneficial effect by **inhibiting the synthesis** of IL-1β and TNF-α at the level of mRNA, decreasing CSF outflow resistance, and stabilizing the blood-brain barrier
- H. influenzae, S. pneumoniae, and N. meningitidis have demonstrated its efficacy in decreasing meningeal inflammation and neurologic sequelae such as the incidence of sensorineural hearing loss

Karen L. Roos, Kenneth L.Tyler, **Acute meningitis**, Harrison's Principle of Internal Medicine 20th Edition

• Adjunctive Dexamethasone Treatment

Cochrane meta-analysis, corticosteroids were found to **decrease overall hearing loss and neurologic sequelae**, but did **not reduce mortality**

A subgroup analysis : **reduced mortality in pneumococcal meningitis** but not in meningitis due to other pathogens

High-income countries with a **high** standard of medical care

- Dexamethasone 10 mg IV q 6 hr x 4 day
- Timing : 15-20 mins before first dose of ATB (can still be up to 4 hrs)
- (Prevent the inflammatory response resulting from bacteriolysis)

- stopped if the patient is discovered not to have bacterial meningitis or if the bacterium causing the meningitis is a species other than H. influenzae or S. pneumoniae

• Brouwer MC, McIntyre P, Prasad K, van de Beek D. Corticosteroids for acute bacterial meningitis. Cochrane Database Syst Rev 2013;6: CD004405

• Vaccination

ตารางที่ 1. คำแนะนำการให้วัคซีนป้องกันโรคสำหรับผู้ใหญ่และผู้สูงอายุ
สมาคมโรคติดเชื้อแห่งประเทศไทย ปี พ.ศ. 2561

Vaccines[1]	Age groups (years)		
	19 – 26 years	27 – 64 years	≥ 65 years
Tetanus, diphtheria, pertussis vaccine (Td or Tdap)[2]	Boost with 1 dose of Td every 10 years (eg. at age 20, 30, 40, 50, 60…..)		
	Substitute one-time of Td with Tdap[3]		
Varicella vaccine[4]	2 doses (consider Anti-VZV IgG test before vaccination)		
Measles, mumps, rubella (MMR) vaccine[5]	2 doses(age ≤ 40 years)		
Human Papillomavirus (HPV) vaccine	3 doses (female)[6]		
	3 doses (male)[7]		
Inactivated influenza vaccine[8]	1 dose annually[9]		
Hepatitis A vaccine[10]	2 doses	2 doses (consider anti HAV IgG test before vaccination)	
Hepatitis B vaccine[11]	3 doses (consider Anti-HBs, Anti-HBc and HBsAg test before vaccination)		
23-valent pneumococcal polysaccharide vaccine (PPV-23)[12]			1 dose
13-valent pneumococcal conjugate vaccine (PCV-13)[13]			1 dose
Dengue vaccine[14]	3 doses (age ≤ 45 years)		
Live-attenuated zoster vaccine[15]			1 dose (age ≥ 60 years)

Recommended vaccine	Optional vaccine (considered in specific conditions: ตารางที่ 2)	Not recommended	Contraindication

ตารางที่ 2. คำแนะนำการให้วัคซีนป้องกันโรคสำหรับผู้ใหญ่และผู้สูงอายุที่มีโรคประจำตัว สตรีตั้งครรภ์และบุคลากรทางการแพทย์ สมาคมโรคติดเชื้อแห่งประเทศไทย ปี พ.ศ. 2561

Vaccines[1]	Conditions								
	Pregnancy	Health-care workers	Heart disease COPD, chronic kidney disease, diabetes	Cirrhosis	Anatomic or functional asplenia	HIV infection (CD4+ ≥ 200 cells/uL)	Severe immune suppressive state[17]	Organ/ bone marrow transplantation[18]	Hajj/Umrah Pilgrim[19]
23-valent pneumococcal polysaccharide vaccine(PPV-23)[12]			1 dose		1 dose with revaccination	1 dose with revaccination		1 dose with revaccination	
13-valent pneumococcal conjugate vaccine (PCV-13)[13]			1 dose		1 dose	1 dose		1 dose	
Meningococcal polysaccharide or conjugate vaccine[16]					1 dose with revaccination				1 dose with revaccination
Dengue vaccine									
Live-attenuated zoster vaccine[15]									

Recommended vaccine	Optional vaccine (considered in specific conditions: ตารางที่ 2)	Not recommended	Contraindication

- **Viral Meningitis and Encephalitis**

Virus	Disease	Major site of latency	Mode of Transmission
Alpha subfamily			
HSV-1	• Oral herpes Encephalitis	Sensory ganglion	Direct contact with lesion
HSV-2	• Genital herpes Meningitis	Sensory ganglion	Direct contact with lesion
VZV	Chickenpox	Sensory ganglion	Aerosols
Gamma subfamily			
EBV	IM, Burkett lymphoma, NPCA	B cells	Saliva
Beta Subfamily			
CMV	Congenital : Hepatitis/Pneumonia	Monocytes, Lymphocytes	Body fluid, Transplants, Transplacental
HHV-6	Roseola	T cells and B cells	Aerosols

- Enveloped DNA VIruses Clinical Gate

• Herpes simplex virus type 1 and type 2

- Large DS DNA core
- Complex capsid
- Bilayered lipid envelope

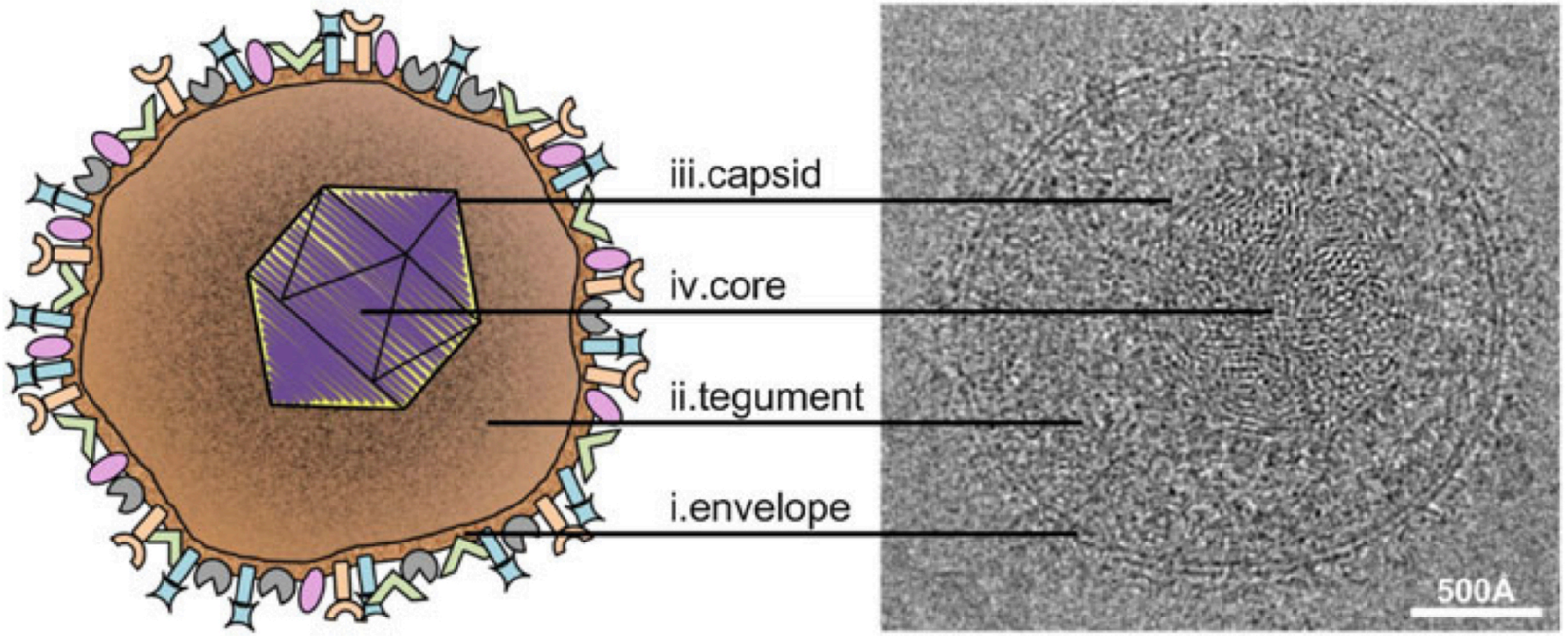


Fig. 6.1 Structure of the HSV-1 virion. The diagram at *left* depicts the four major structural components of the HSV-1 virion: (i) the outer envelope studded with various glycoproteins, (ii) the proteinaceous tegument layer, and (iii) the icosahedral capsid that houses (iv) the dsDNA core. Corresponding features in a cryo-electron micrograph of a virion are indicated at *right*. Bar = 500 Å

• Herpes simplex virus type 1 and type 2

- HSV-1 : Oral/Ocular mucosa , HSV-2 : Genital
- The most common neurologic manifestation of HSV-1 is encephalitis and of HSV-2 is meningitis
- 1ry infection : Asymptomatic/Vesicular rash at the site of exposure >> sensory neuron > Trigeminal/Sacral ganglion

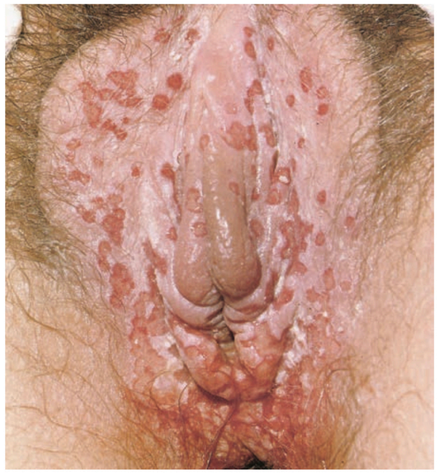


FIGURE 187-1 Genital herpes: primary vulvar infection, with multiple, extremely painful, punched-out, confluent, shallow ulcers on the edematous vulva and perineum. Micturition is often very painful. Associated inguinal lymphadenopathy is common. *(Reprinted with permission from K Wolff et al: Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology, 5th ed. New York, McGraw-Hill, 2005.)*

Lawrence Corey, Herpes Simplex Virus Infection, Harrison's Principle of Internal Medicine 20th Edition

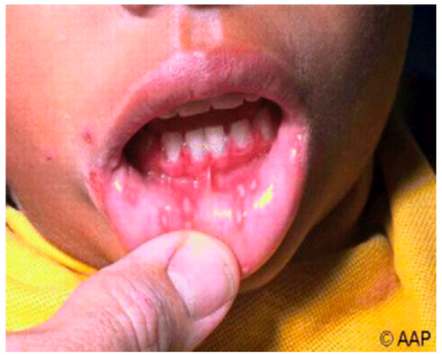


Figure 1. Herpes simplex stomatitis. Reprinted with permission from Pickering LK, Baker CJ, Kimberlin DW, Long SS, eds. *Red Book: 2012 Report of the Committee on Infectious Diseases*. 29th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2012:398–408.

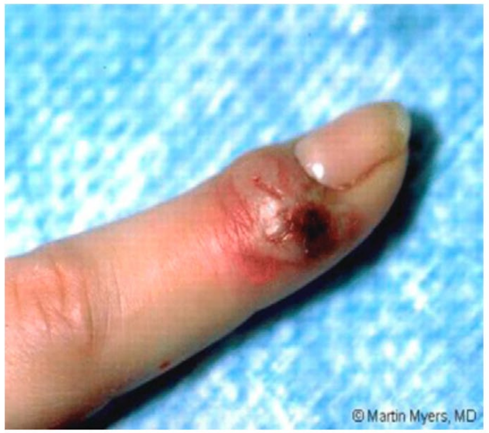
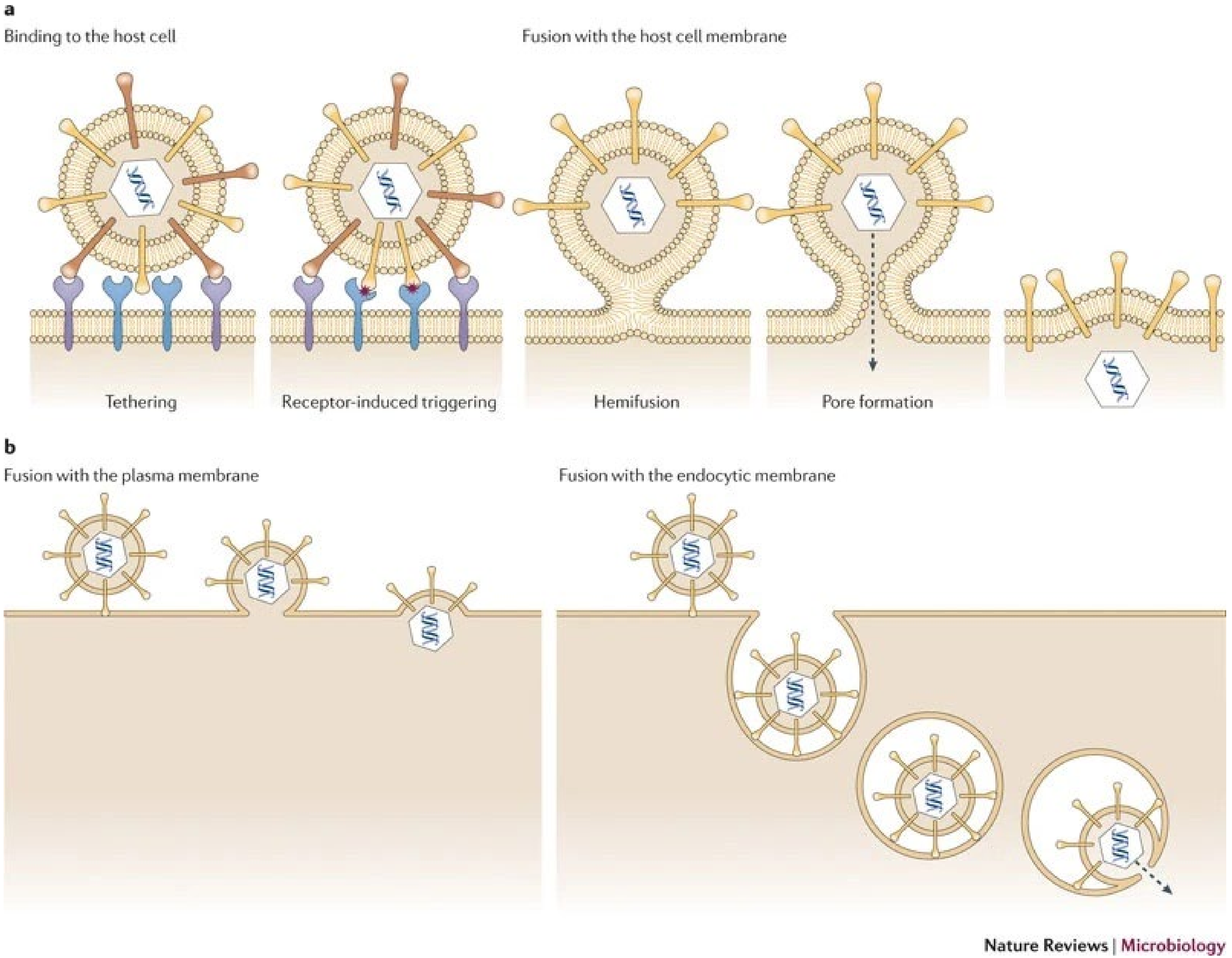


Figure 2. Herpetic whitlow. Reprinted with permission from © Myers, MD.

Herpes Simplex Viruses 1 and 2 February 2015 Pediatrics in Review 36(2):86-90

- CONTINUUM 2018;24(5, NEUROINFECTIOUS DISEASE):1349–1369



Connolly SA, Jackson JO, Jardetzky TS, Longnecker R. **Fusing structure and function: a structural view of the herpesvirus entry machinery.** Nat Rev Microbiol. 2011 May;9(5):369-81. doi: 10.1038/nrmicro2548. Epub 2011 Apr 11. PMID: 21478902; PMCID: PMC32

• Herpes simplex virus type 1 and type 2

•Pathogenesis

- 1/3 result from primary infection
- 2/3 had preexisting antibodies
- HSV may gain access to the CNS by several proposed mechanisms
  - Direct spread through the olfactory or trigeminal nerves
  - Hematogenous dissemination of distant lesions
- The predilection for orbitofrontal and temporal cortex suggests that direct extension through the cranial nerves may be most likely

• Herpes Simplex Virus Encephalitis

•Clinical symptom and signs of HSE

- Seizures (32%)
- Abnormal behavior (23%)
- Loss of consciousness (13%)
- Confusion or disorientation (13%)
  - Other common presenting findings include fever, autonomic dysfunction, and dysphagia

• CONTINUUM 2018;24(5, NEUROINFECTIOUS DISEASE):1349–1369

• Herpes Simplex Virus Encephalitis

•DIAGNOSIS

- HSV infection requires CSF analysis to evaluate for cell count, protein, glucose, and viral DNA.
- Polymerase chain reaction (PCR) testing has become the gold standard
- **HSV PCR** has a sensitivity of 96% and specificity of 99%
  - **26%** of patients (whether healthy or immunocompromised) with HSV encephalitis had a **normal CSF white blood cell count** (less than 5 cells/mm3)

- **When suspicion is high, patients should <u>continue</u> treatment** and HSV PCR should be repeated in 3 to 7 days
- Persistent PCR positivity may require prolonged duration of therapy

- CONTINUUM 2018;24(5, NEUROINFECTIOUS DISEASE):1349–1369
- Saraya AW, Wacharapluesadee S, Petcharat S, et al. Normocellular CSF in herpes simplex encephalitis. BMC Res Notes 2016;9:95. doi:10.1186/s13104-016-1922-9.

• Herpes Simplex Encephalitis

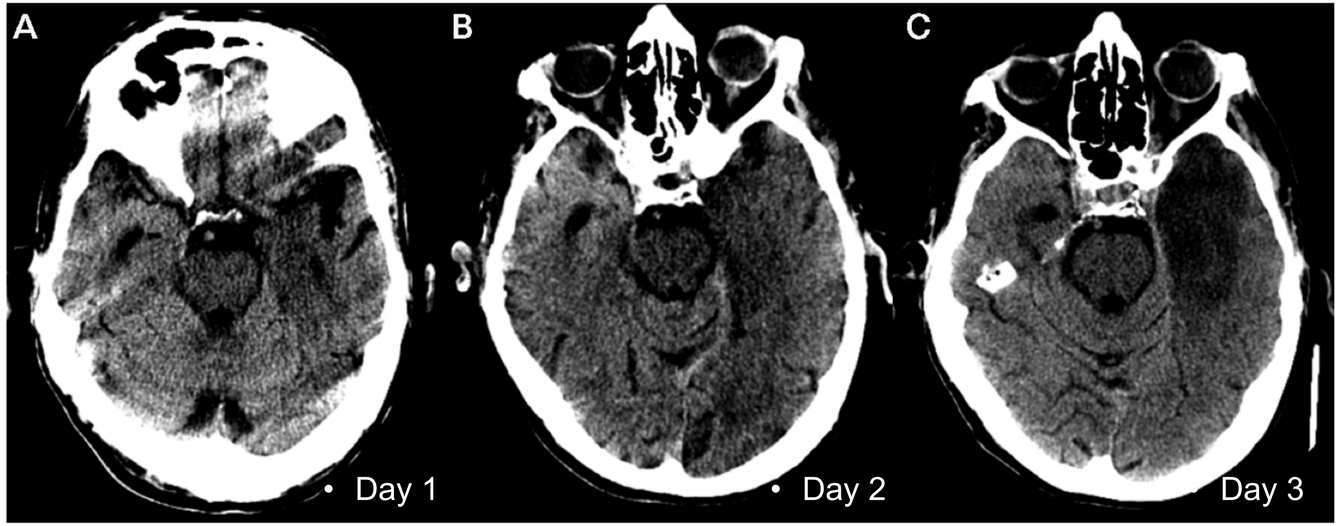


FIGURE 5-2

Imaging of the patient in CASE 5-1. Axial noncontrast head CT demonstrates progressive hypodensity (edema) in the left medial temporal lobe over a 3-day course. *A*, Day 1 demonstrates only mild left medial temporal lobe hypodensity. *B*, Day 2 demonstrates progressive hypodensity in the medial temporal lobe with effacement of the temporal horn of the lateral ventricle. *C*, Day 3 demonstrates a large area of edema in the medial and anterior left temporal lobe. These images illustrate classic findings of untreated herpes virus encephalitis.

•MRI classic imaging findings

•Hemorrhage, necrosis, and edema in the medial temporal lobes and may extend to affect other limbic areas, including the insula, cingulate, and inferolateral frontal cortex

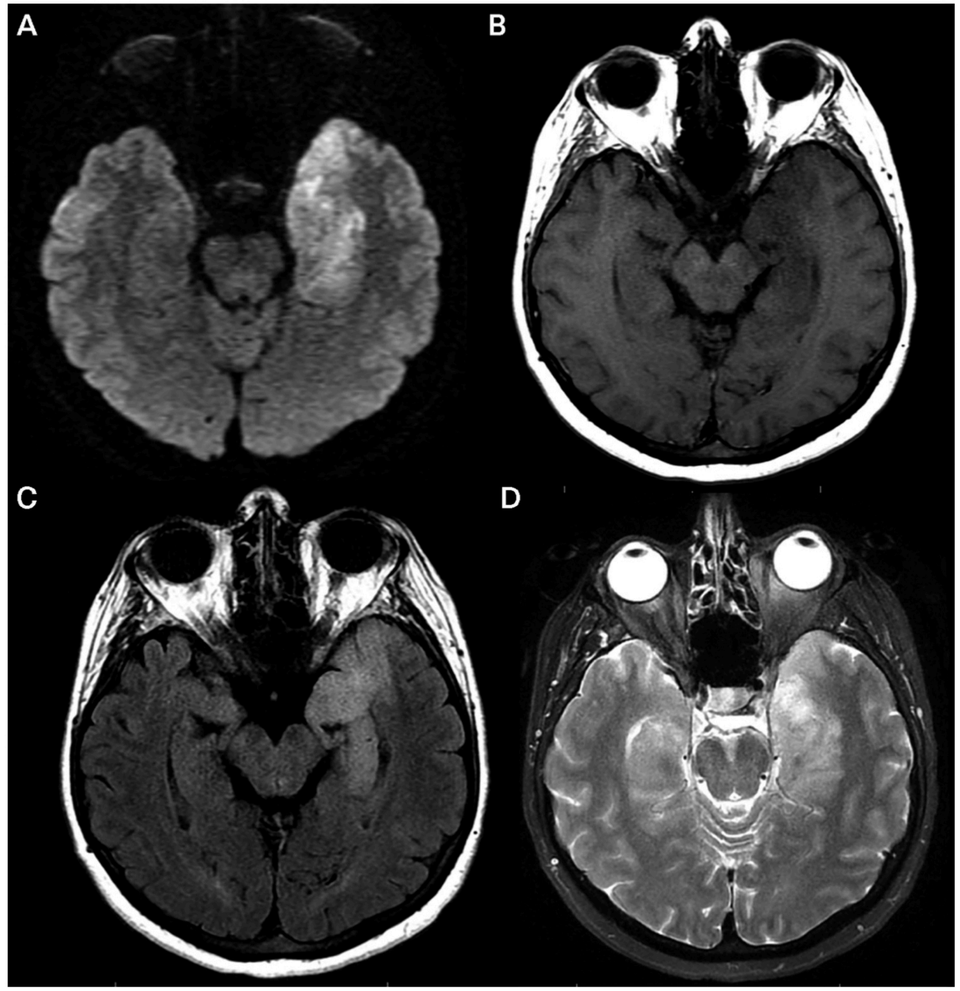


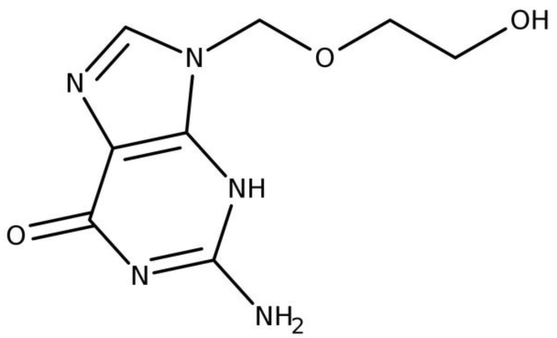
FIGURE 5-3

Classic MRI findings of herpes simplex virus encephalitis. *A*, Axial diffusion-weighted MRI shows restricted diffusion in the left medial temporal lobe (confirmed with apparent diffusion coefficient map [not shown]). *B*, Axial noncontrast T1-weighted MRI shows concurrent hypointensity within the same area. Fluid-attenuated inversion recovery (FLAIR) (*C*) and T2-weighted (*D*) images show a large area of hyperintensity, representing edema within the left temporal lobe.

• CONTINUUM 2018;24(5, NEUROINFECTIOUS DISEASE):1349–1369

• Herpes Simplex Encephalitis

•Prognosis

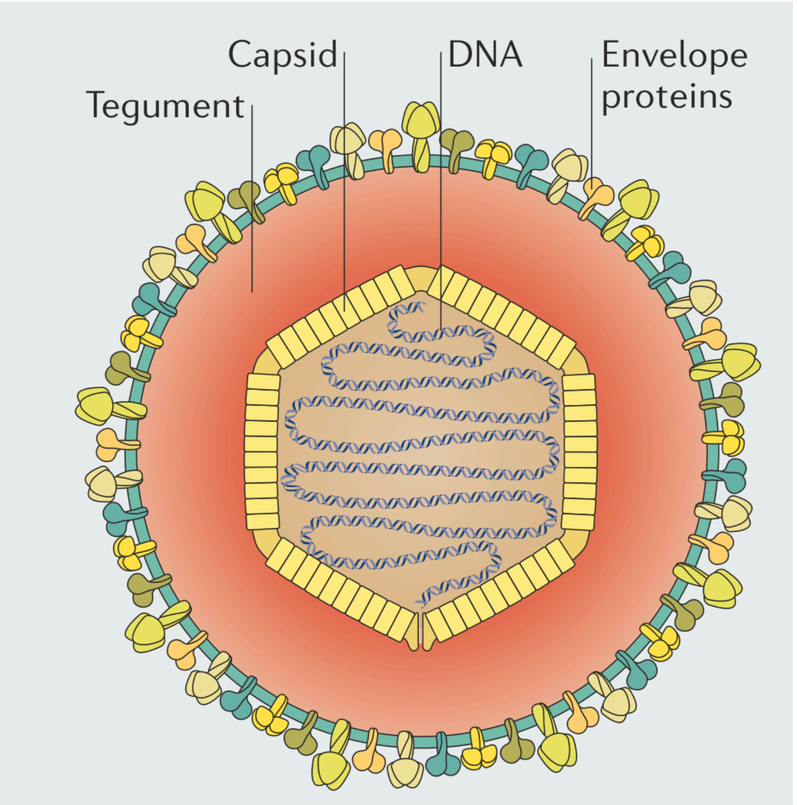


- 70% Mortality (absence of antiviral)
- 10-30% Mortality (appropriate Acyclovir Treatment)
- Negative prognostic factor
  - •Older age
  - •Coma/Lower level of consciousness
  - •Delay in acyclovir administration
  - •Severe EEG abnoamalities

- Acyclovir 10 mg/my IV q 8 hr for 14-21 days
- Should be initiated as soon as the diagnosis is considered, to prevent extensive replication and subsequent CNS damage

• Varicella zoster encephalitis

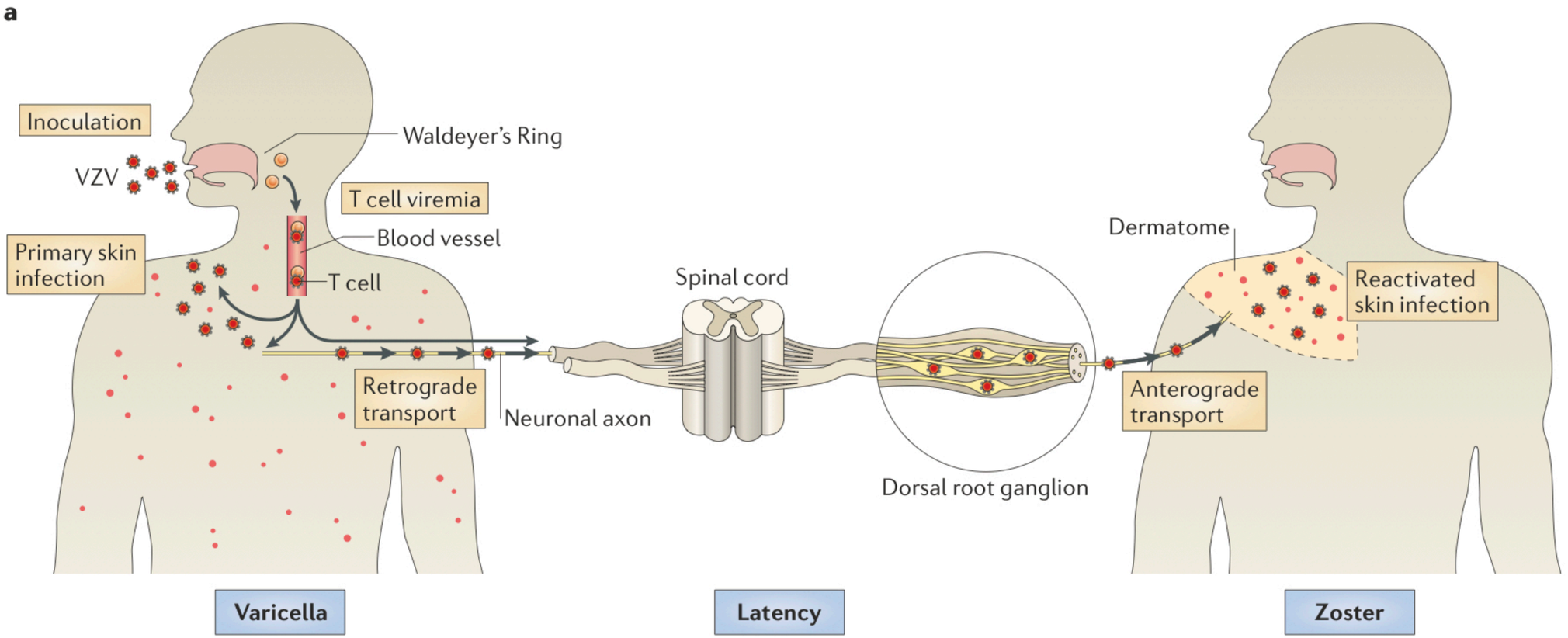
- 2nd most common encephalitis in KCMH
- VZV Persist in DRG after primary infection with chickenpox
- All neurologic disorders produced by VZV can occur in the absence of rash
- **Reactivate episodically**, but immune system typically suppresses before symptom occur
  - Sensory Nerve >> Skin >> Epithelial cells>> Vesicular lesion (Dermatome)
  - Hematogenous spread



- Saraya et al. BMC Neurology 2013, 13:150

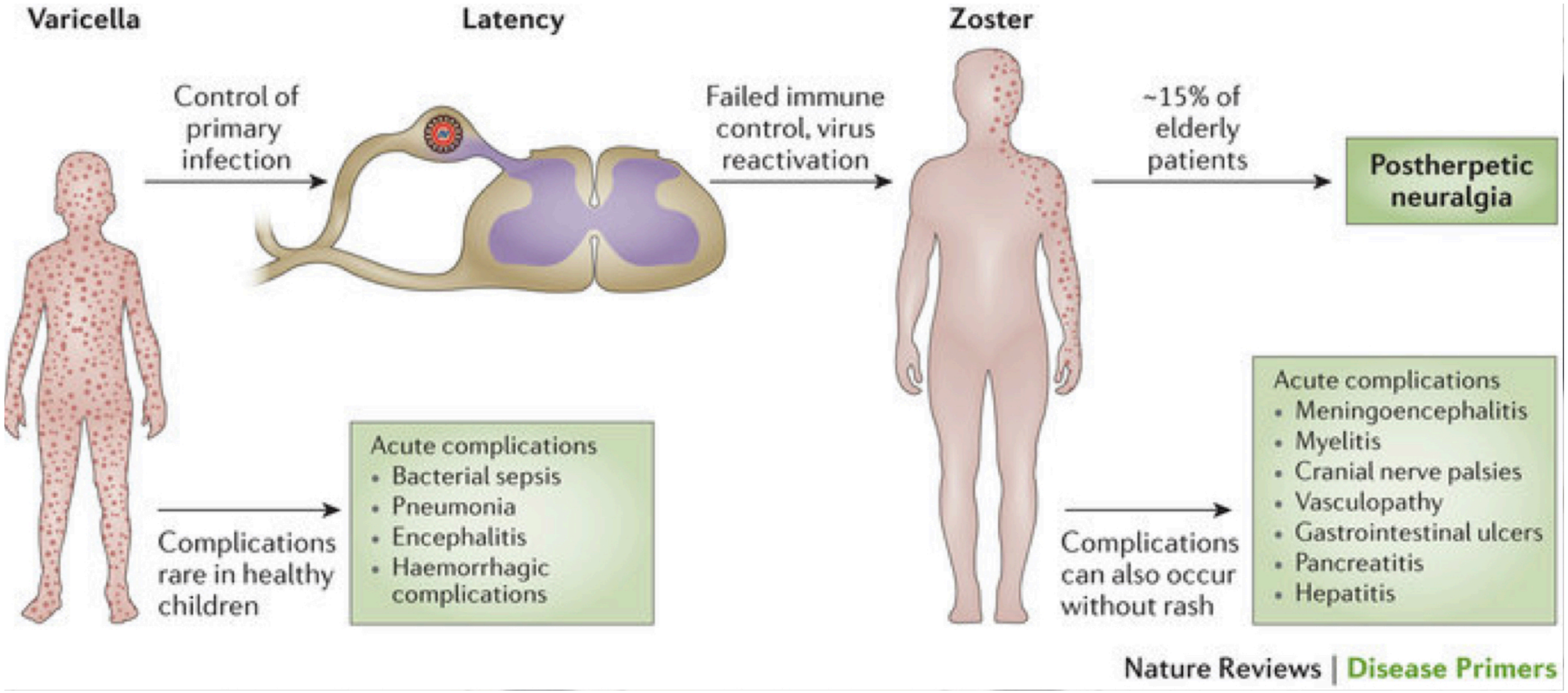
Zerboni, L., Sen, N., Oliver, S. *et al.* **Molecular mechanisms of varicella zoster virus pathogenesis**. *Nat Rev Microbiol* **12,** 197–210 (2014). https://doi.org/10.1038/nrmicro3215

• VZV Infection

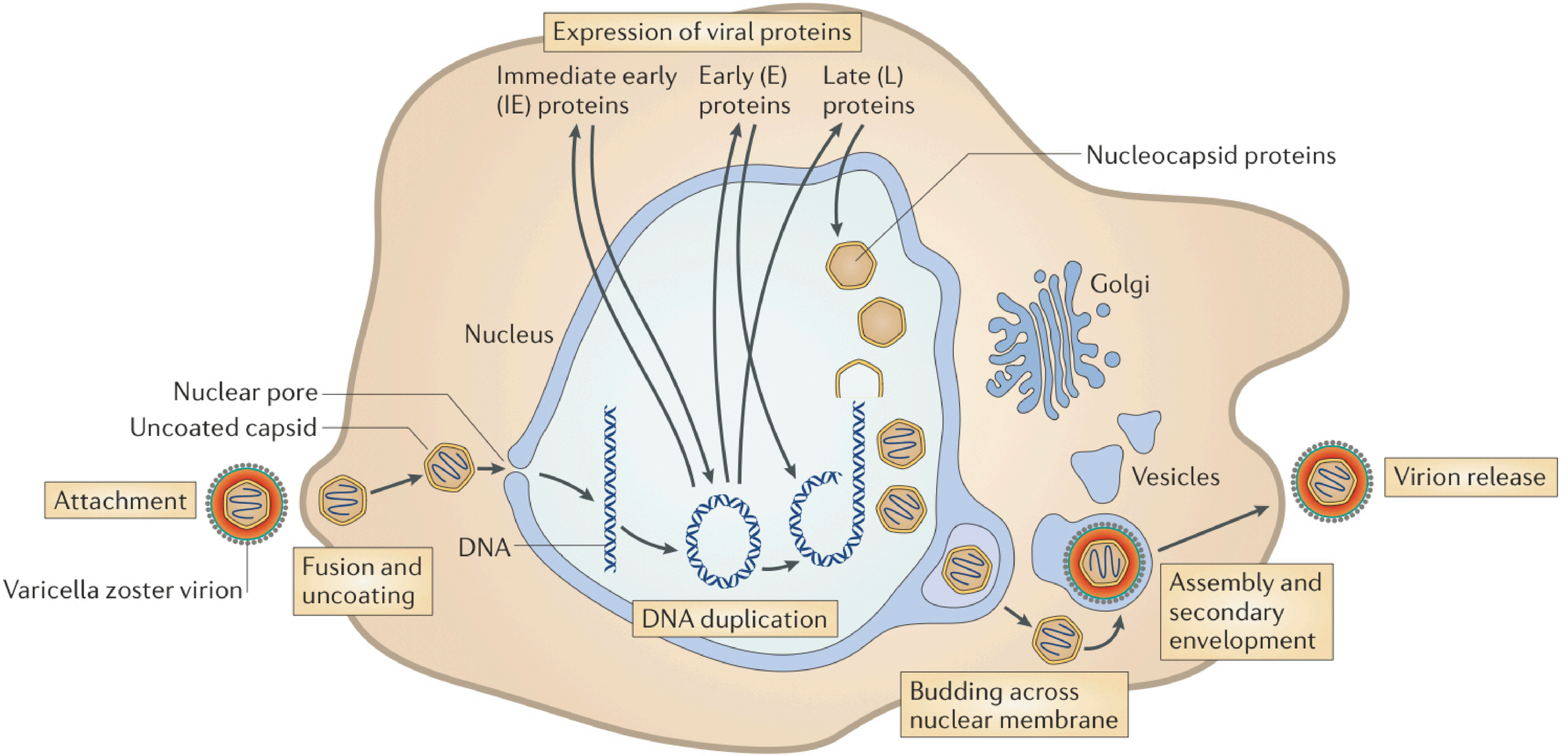


Zerboni, L., Sen, N., Oliver, S. *et al.* **Molecular mechanisms of varicella zoster virus pathogenesis**. *Nat Rev Microbiol* **12,** 197–210 (2014). https://doi.org/10.1038/nrmicro3215

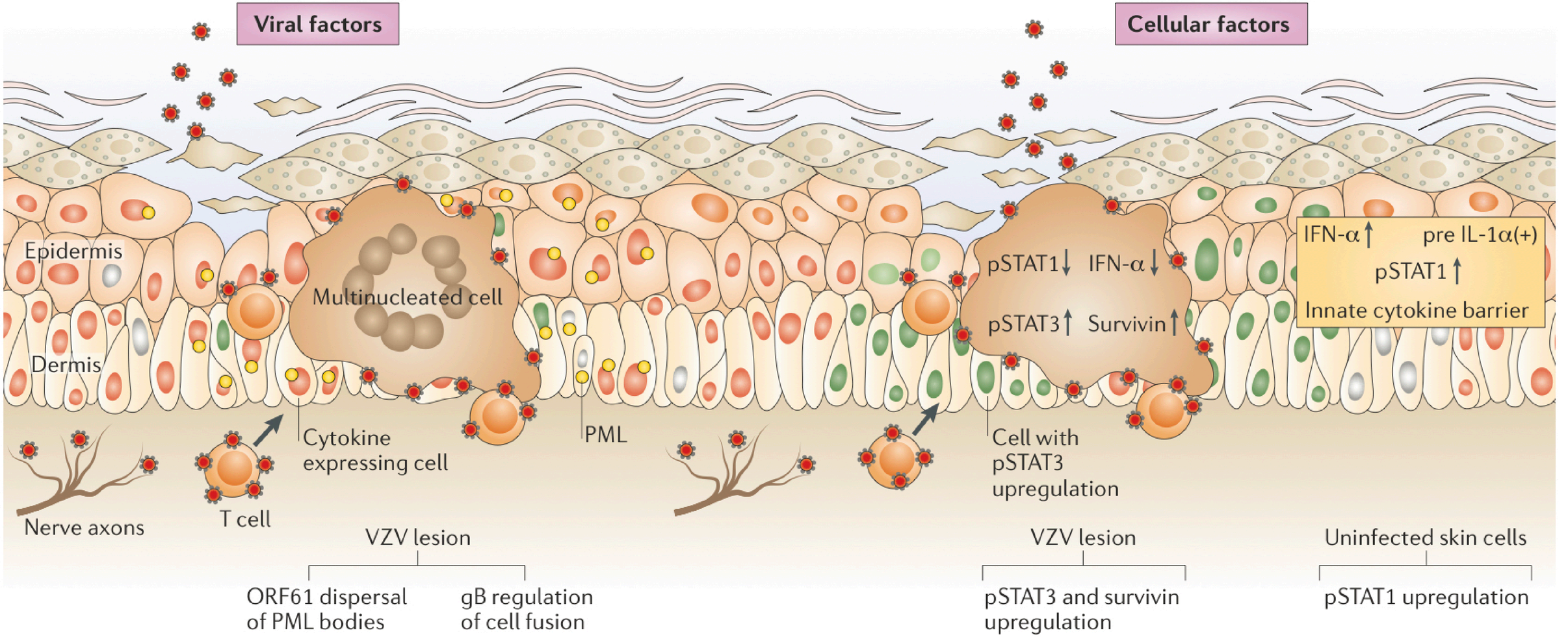
• Different phase of VZV infection



• Judy Breuer and Richard Whiteley.HERPES 14 supplement2 2007



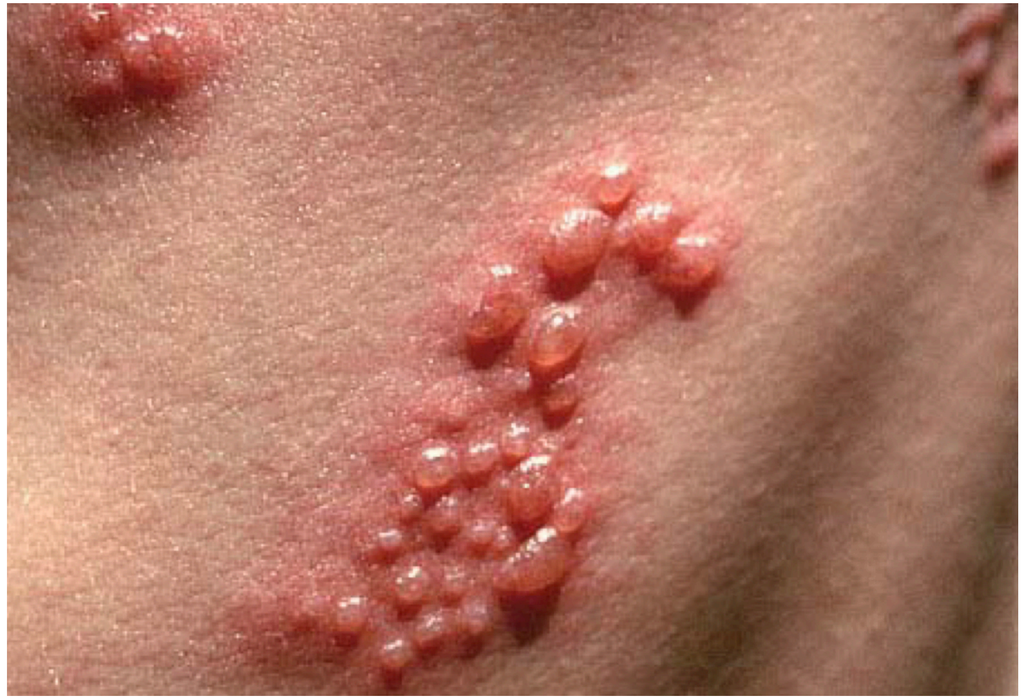
Zerboni, L., Sen, N., Oliver, S. *et al.* **Molecular mechanisms of varicella zoster virus pathogenesis**. *Nat Rev Microbiol* **12,** 197–210 (2014). https://doi.org/10.1038/nrmicro3215



Zerboni, L., Sen, N., Oliver, S. *et al.* **Molecular mechanisms of varicella zoster virus pathogenesis**. *Nat Rev Microbiol* **12,** 197–210 (2014). https://doi.org/10.1038/nrmicro3215

• Herpes Zoster

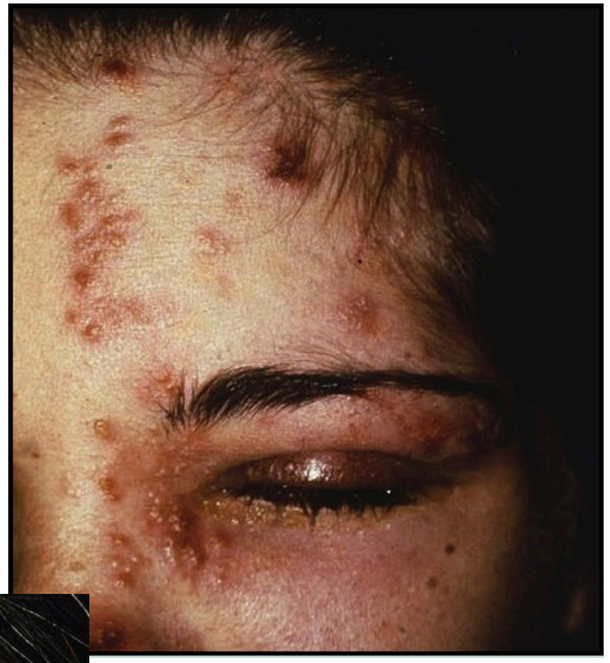
- Sharp, lancinating pain and decrease sensation preceding vesicular eruption on erythematous base in dermatome of nervous system
- Most zoster lesions are in the **same** stage of development and does not cross the midline
- 10-50% of patients with cutaneous dissemination have visceral dissemination

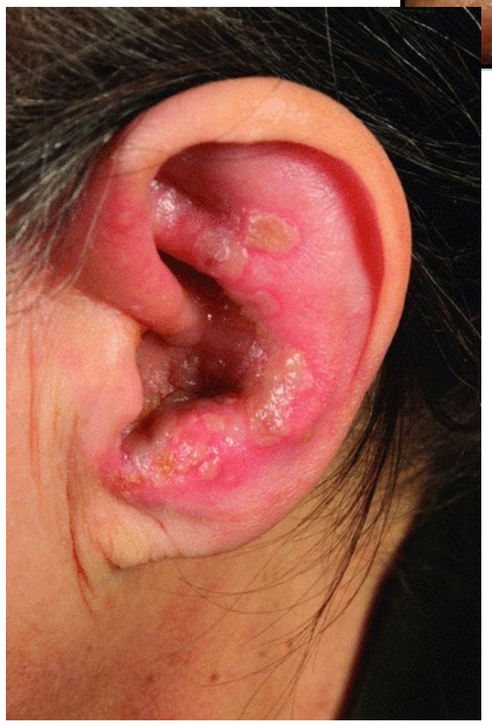


- Neurologic manifestation of varicella and herpes zoster Infectiouns of CNS (3rd edition,2004)

• Herpes Zoster

- V1 distribution of trigeminal nerve > HZ opthalmicus
  - Can lead to orbital complication : CN III,IV,VI neuropathies, Retinal necrosis, Retinal detachment, Keratitis, Uveitis, Iritis, Scleritis/Episcleritis
- Geniculate ganglion > Ramsay Hunt Syndrome/ Zoster oticus
  - Rash involving external ear, Ipsilateral tongue or palate
  - CN VII neuropathy, with hearing lass and vestibular symptom
  - C2 or C3 dermatomal zoster > Radiculitis and Peripheral nerve palsies





Herpes Zoster Ophthalmicus: A Review for the Internist
Vrcek, Ivan et al6

CONTINUUM (MINNEAP MINN) 2018;24(5, NEUROINFECTIOUS DISEASE):1349–1369.

• https://doi.org/10.1111/j.1610

VZV Vasculopathy

- Ischemic stroke > hemorrhagic stroke
- Risk of a subsequent adverse vascular event is increased for at least 1 year
- CSF analysis reveals a mononuclear pleocytosis (less than 100 cells/mm3)
  - May be accompanied by an increased number of red blood cells
  - Angiography confirms **focal arterial stenosis or arterial beading** ,involvement of large or small arteries [or both] is common

- **Other manifestation of VZV vasculopathy**

- Spinal cord infarction
- Intracerebral or SAH
- Cerebral aneurysm
- Arterial dissection, ectasia
- Vessel wall enhancement on postcontrast T1-weighted MRI sequences

- Gilden D, Cohrs RJ, Mahalingam R, Nagel MA. Varicella zoster virus vasculopathies: diverse clinical manifestations, laboratory features,pathogenesis, and treatment. Lancet Neurol 2009;8(8):731–740. doi:10.1016/S1474- 4422(09)701

• Varicella-Zoster Virus

High-resolution 3T MRI revealed arterial wall enhancement of the affected stenotic arteries, supporting the diagnosis of infectious vasculitis (FIGURES 5-5B, 5-5C, and 5-5D).[52] Initial transcranial Doppler ultrasound revealed critically elevated velocities of 200 cm/s in the right middle cerebral artery and mildly elevated velocities in the right internal carotid artery siphon.

Treatment was promptly initiated with IV acyclovir and IV methylprednisolone 1 g daily for 3 days for treatment of CNS vasculitis caused by VZV vasculopathy.[52]

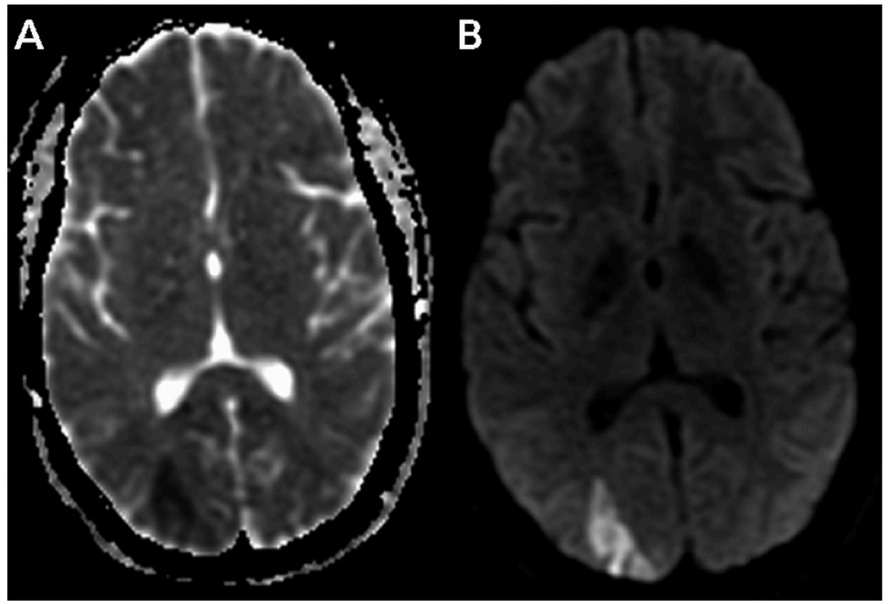


FIGURE 5-4
MRI of the patient in CASE 5-2. Apparent diffusion coefficient map (*A*) and diffusion-weighted image (*B*) show an acute ischemic stroke involving the right parietooccipital junction.

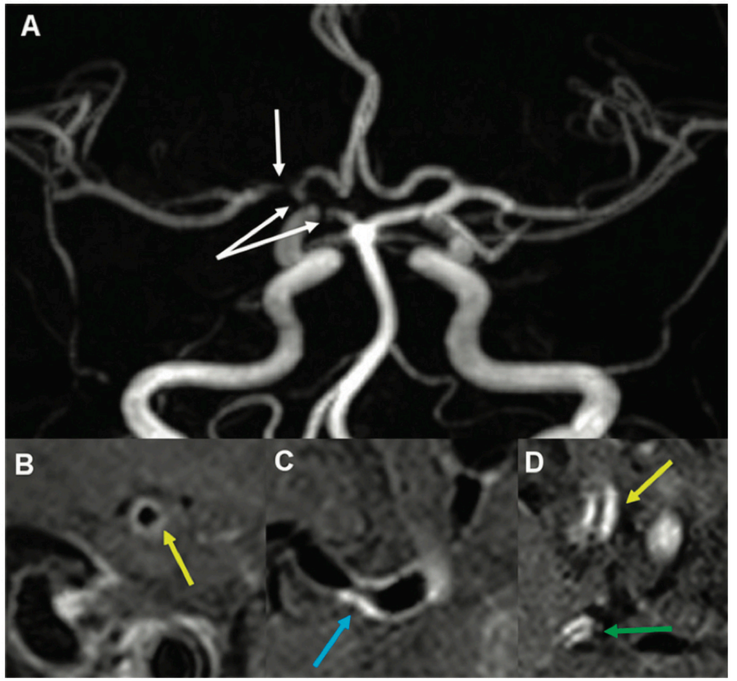


FIGURE 5-5
Imaging of the patient in CASE 5-2. Three-dimensional time-of-flight magnetic resonance angiogram (MRA) of the brain showing moderate to severe focal stenoses (*A*, *white arrows*) of the distal right internal carotid artery, proximal right middle cerebral artery, and right posterior cerebral artery. Sagittal (*B*) and axial (*C*, *D*) high-resolution 3T black blood sequence postcontrast MRI of the circle of Willis with attention to the distal right carotid region demonstrating arterial wall enhancement of the right internal carotid artery (*C*, *blue arrow*), right middle cerebral artery (*B* and *D*, *yellow arrows*), and right posterior cerebral artery (*D*, *green arrow*).

- In case of Cerebral vasculitis
- CSF PCR for VZV DNA is only 30% sensitive
- Addition of VZV IgG in CSF , Sensitivity 93%

• Viral Meningitis : Diagnosis and Investigation

Table 22.2 CSF findings in acute bacterial meningitis and other CNS infectious conditions

Type of infection	Macroscopic appearance	Cells	Protein (mg/dL)	Glucose (mg/dL)	Other tests
Normal	Clear	<5 lymphocytes/mm^3	15–45	50–75	Negative test results
Bacterial meningitis (*S. pneumoniae*; *N. meningitides*; *L. monocytogenes*)	Cloudy or turbid	*Increased* (*commonly* > *200*) *Typically >90 % PMNs* Can be normal in meningococcemia	>100	Reduced (<40)	Gram stain, bacterial culture, and antigen tests may be positive
Viral meningitis (enteroviruses; herpes simplex; arboviral encephalitis)	Clear or rarely opalescent	Increased May have PMN predominance early in the course of infection; converts to lymphocytic predominance within 12–24 h	Usually <100	Normal	Gram stain, bacterial culture, and antigen tests negative PCR for HSV, VZV, arboviruses, and enteroviruses may be positive
Fungal meningitis (cryptococcus; histoplasmosis; coccidioidomycosis)	Cloudy or turbid	>100 (<50 %) Usual range 100–400 usually lymphocytic predominance May be normal in cryptococcal meningitis	100–900	< 40	Cryptococcus can be diagnosed from India ink preps, antigen tests, or culture; PCR
Tuberculous meningitis	Cloudy or turbid	Increased Typically >100 Usual range 100–400 PMN early but converts to lymphocytic predominance	100–900	<40	Acid-fast bacilli occasionally seen on CSF smear stained with Kinyoun or Ziehl-Neelsen stains

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

- **Varicella-Zoster Virus**

$$\text{CSF VZV antibody index} = \frac{\text{CSF VZV IgG} \div \text{serum VZV IgG}}{\text{CSF total IgG or albumin} \div \text{serum total IgG or albumin}}$$

The CSF antibody index is considered to be elevated for values of 1.5 or higher and is used to prevent the possibility of false-positive detection of CSF anti-VZV IgG antibody due to serum contamination.[50,51] **CASE 5-2** demonstrates a classic

• Varicella-Zoster Virus

•Treatment

- Chickenpox > Self-limited infection in healthy children , no specific treatment
  - Avoid Aspirin (Reye syndrome)
  - Adult (Ongoing infection / Reactivation) Rx Systemic antiviral x -10 days
    - Shortening duration for rash
    - Age > 50 years
    - Immunocompromise
    - HZ ophthalmicus/Oticus

• Continuum (Minnaeap Minn) 2018;24(5): 1349-69.

• Varicella-Zoster Virus

•Treatment

- **CNS infection** : Vasculopathy or Disseminated
  - IV acyclovir x 14 days
  - Symptomatic : Pain
    - Anticonvulsant : Gabapentin, Pregabalin, Oxcarbazepine, Levetiracetam
    - TCA : Amitriptyline, Nortriptyline
    - Opioid : Tramadol , MO

• Continuum (Minnaeap Minn) 2018;24(5): 1349-69.

• Varicella-Zoster Virus

•Vaccine

- Zostavax (SC) single dose (Live attenuated)
  - Decrease zoster about 51.3%
  - Decrease PHN about 67%
  - Indication: age ≥ 50 years
  - Contraindication: immunocompromised : on steroid, chemotherapy, malignancy, severe allergic to gelatin or neomycin

• Continuum (Minnaeap Minn) 2018;24(5): 1349-69.

Viral Pathogen	Clinical Syndrome	Medication	Adult Dose
Herpes simplex virus type 1/ herpes simplex virus type 2	Encephalitis	Acyclovir[a]	10 mg/kg IV every 8 hours
	Meningitis	Acyclovir[a]	10 mg/kg IV every 8 hours
Varicella-zoster virus (VZV)	Shingles, herpes zoster ophthalmicus, zoster oticus	Valacyclovir[b]	1000 mg orally 3 times a day
		Famciclovir[a]	500 mg orally 3 times a day
		Acyclovir[a]	800 mg orally 5 times a day; 5–10 mg/kg IV every 8 hours for immunocompromised
	Disseminated zoster, encephalitis, cerebellitis, myelitis, zoster sine herpete	Acyclovir[a]	10 mg/kg IV every 8 hours
	Vasculopathy	Acyclovir[a]	10–15 mg/kg IV every 8 hours
		Prednisone	1 mg/kg orally daily

- Continuum (Minnaeap Minn) 2018;24(5): 1349-69.

- Arbovirus

• Arboviruses

•Arthropod-borne viruses

- Carried by mosquito or tick vectors
- Can cause meningitis, encephalitis
  - JE encephalitis (mosquito-borne flavivirus)
  - Mosquito-borne arboviruses : dengue, chikungunya, Zika virus
  - Tick-borne encephalitis virus
  - West Nile virus

• Clinical

- Neurotrophic Arboviruses may cause meningitis/encephalitis
- Incubation period few days - few weeks
- Progressive neurologic dysfunction
  - Headache
  - Meningismus
  - Seizures

• Japanese Encephalitis

•Enveloped Virus , 50 nm in diameter

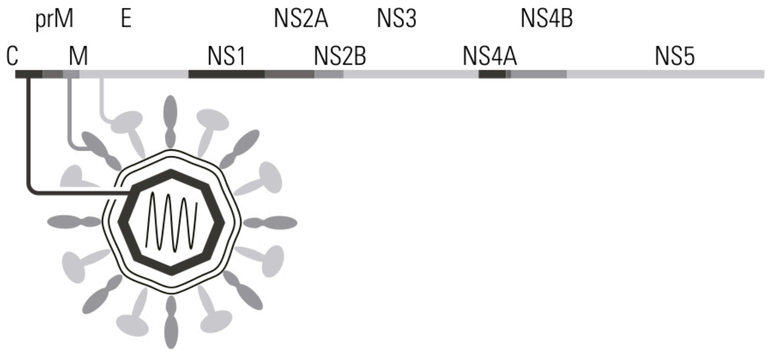


Fig. 1
Schematic representation of the genome and structure of a Japanese encephalitis virus particle
The lines connect specific parts of the genome with the specific virus protein structures which they encode

- Following ingress of the virus through a mosquito bite
- JEV replicates in the skin and local lymph nodes, leading to a transient low viremia in humans
- During the **incubation** period, JEV replicates primarily in **monocytes/macrophages and dendritic cells (DCs)**
- The infected cells then transmigrate from the periphery to the CNS, leading to inflammation in the brain
- “Several Escaping Mechanism” : MHC and Interferon pathway

- Banerjee A, Tripathi A. Recent advances in understanding Japanese encephalitis. *F1000Res*. 2019;8:F1000 Faculty Rev-1915. Published 2019 Nov 13. doi:10.12688/f1000research.19693.1
- Morita K, Nabeshima T, Buerano CC. Japanese encephalitis. Rev Sci Tech. 2015 Aug;34(2):441-52. doi: 10.20506/rst.34.2.2370. PMID: 26601447.

• Japanese Encephalitis

•Countries in which Japanese encephalitis virus has been identified

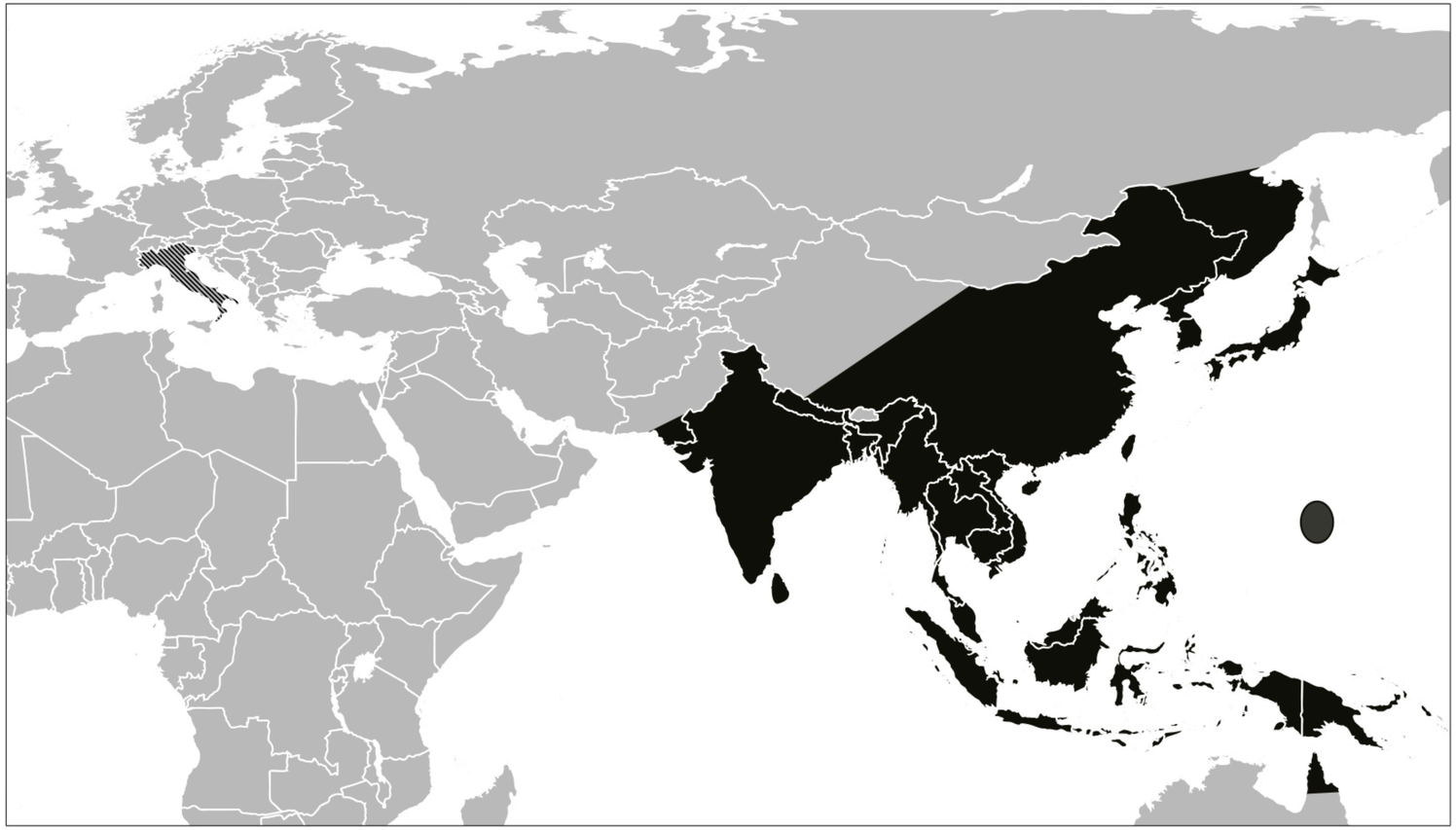


Fig. 2

Distribution of Japanese encephalitis virus (JEV) around the world

Areas in which JEV has been detected are in black. The area marked with black and grey stripes is Italy, where JEV RNA showing 99–100% similarity to NS5 or E protein-coding regions of JEV genotype 3 has been detected (in dead birds in 1997 and 2000, and in mosquitoes in 2010 [38, 39])

• Morita K, Nabeshima T, Buerano CC. Japanese encephalitis. Rev Sci Tech. 2015 Aug;34(2):441-52. doi: 10.20506/rst.34.2.2370. PMID: 26601447.

• Japanese Encephalitis

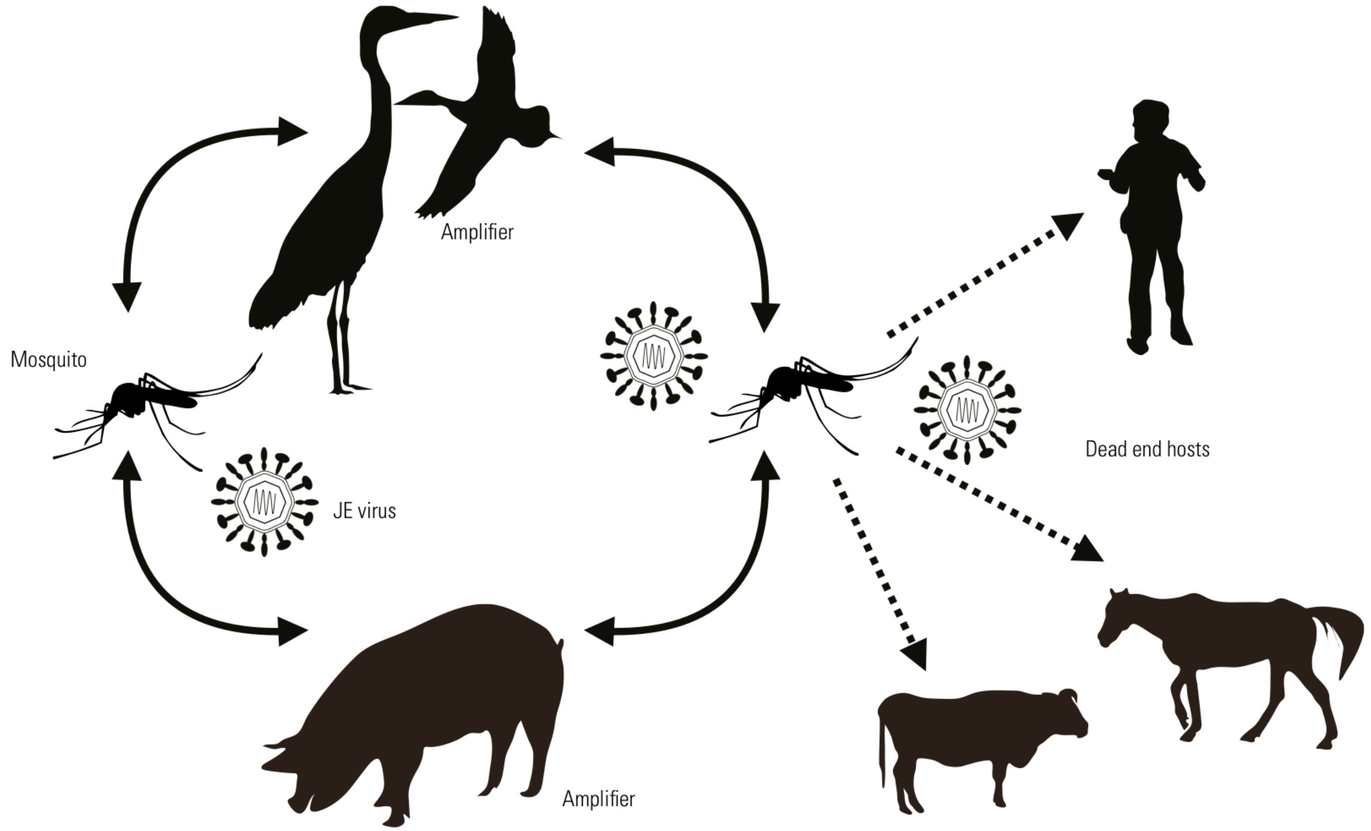


Fig. 3
Transmission cycle of Japanese encephalitis virus between amplifiers (pigs and wild birds) and mosquito vectors (especially *Culex tritaeniorhynchus*), including the infection of dead-end hosts (humans, horses, cattle)

• Morita K, Nabeshima T, Buerano CC. Japanese encephalitis. Rev Sci Tech. 2015 Aug;34(2):441-52. doi: 10.20506/rst.34.2.2370. PMID: 26601447.

• Japanese Encephalitis

•Clinical Sign

- Incubation period: 5 -15 days
- Most infections of humans are asymptomatic or cause a non-specific flu-like illness
- JEV Encephalitis
  - 85% convulsions
  - 30% EPS
  - other symptoms: neck stiffness, motor paralysis
- Prodromic fever
- Headache
- Arthralgia then altered mental status, seizure up to 85%
- Prominent extrapyramidal sign : masked face, parkinsonism, tremor, hypertonia > choreoathetosis, dystonia
- Can involve anterior horn cell (anterior myelitis)

• CONTINUUM (MINNEAP MINN) 2018;24(5, NEUROINFECTIOUS DISEASE):1512 –1534.

Japanese Encephalitis

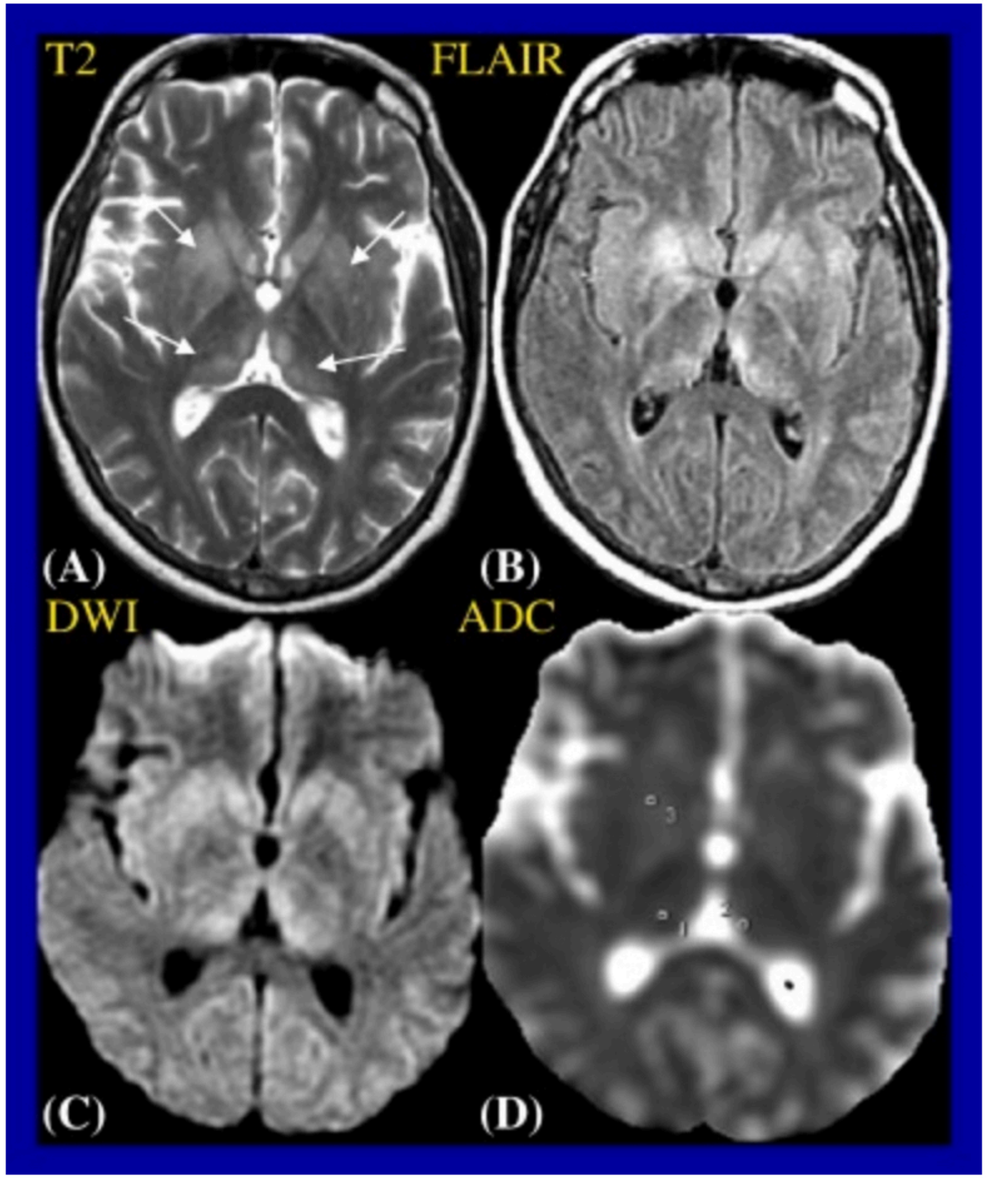


Fig. 2 Japanese encephalitis. Axial T2WI (A). FLAIR (B), DWI (C) and ADC map (D) in a JE patient 4 days after clinical presentation shows involvement of bilateral thalami (arrows) and basal ganglia (arrows). ADC values were computed from cursor locations and later averaged (average ADC 678×10^{-6} mm^2/s).

Diffusion-weighted imaging and apparent diffusion coefficient evaluation of herpes simplex encephalitis and Japanese encephalitis
Sawlani, Vijay Journal of the Neurological Sciences, Volume 287, Issue 1, 221 - 226

• Japanese Encephalitis

•Diagnosis

- Serum or CSF **JEV IgM**
- 20-30% of JE case are fatal
- 30-50% of survivors have significant neurologic sequelae
- JE vaccine is recommended for travelers who plan spend 1 month or more in endemic area during JE virus transmission season

- WWW.CDC.GOV

• Dengue Encephalitis

- Virus serotypes DENV-1 to DENV-4
- Dengue virus is transmitted by *Aedes aegypti* and *Aedes albopictus* mosquitoes
- **DENV-2 and DENV-3** are most commonly associated with neurologic manifestations
- Neurologic involvement during dengue infection is typically attributed to systemic complications, including electrolyte imbalance, microcapillary hemorrhage, and multiorgan failure

• MarziaPuccioni-Sohleret al. **Advances and new insights in the Neuropathogenesis of dengue infection**

• Dengue Encephalitis

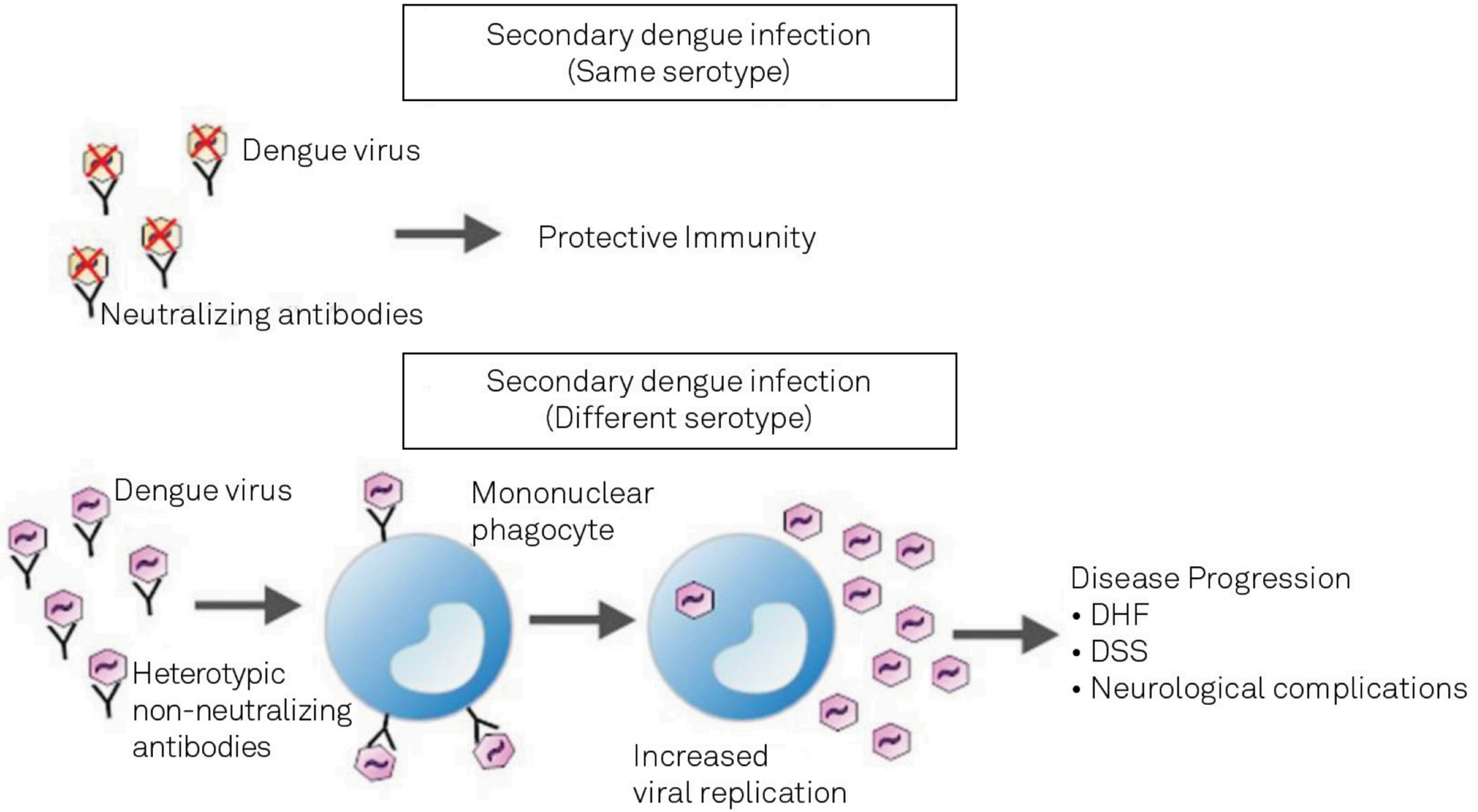
- **Neurological complications** of dengue can be found in **1-21 %** of patients with classic dengue infection
- Prevalence of DENV among viral infection in **CNS 20% in Thailand**
- Seizure 22-88%
- Headache 55-100%
- Fever and confusion 40-100%
- Abnormal movement 9-13%
  - Meningitis, acute disseminated encephalomyelitis (ADEM), ischemic and hemorrhagic stroke, Guillain-Barre´syndrome,myelitis, myositis, hypokalemic paralysis, and neuropathy have also been reported

- MarziaPuccioni-Sohleret al. **Advances and new insights in the Neuropathogenesis of dengue infection**

• Dengue Encephalitis

- **Neurotropic effect of the dengue virus**
- **Complications from the systemic infection of the virus;** encephalopathy, stroke, HIBI, retinal vasculopathy, hepatic failure, and myositis
- **Result of autoimmune reactions; acute disseminated;** ADEM, post-infectio us cerebellitis, GBS, transverse myelitis, and brachial plexitis

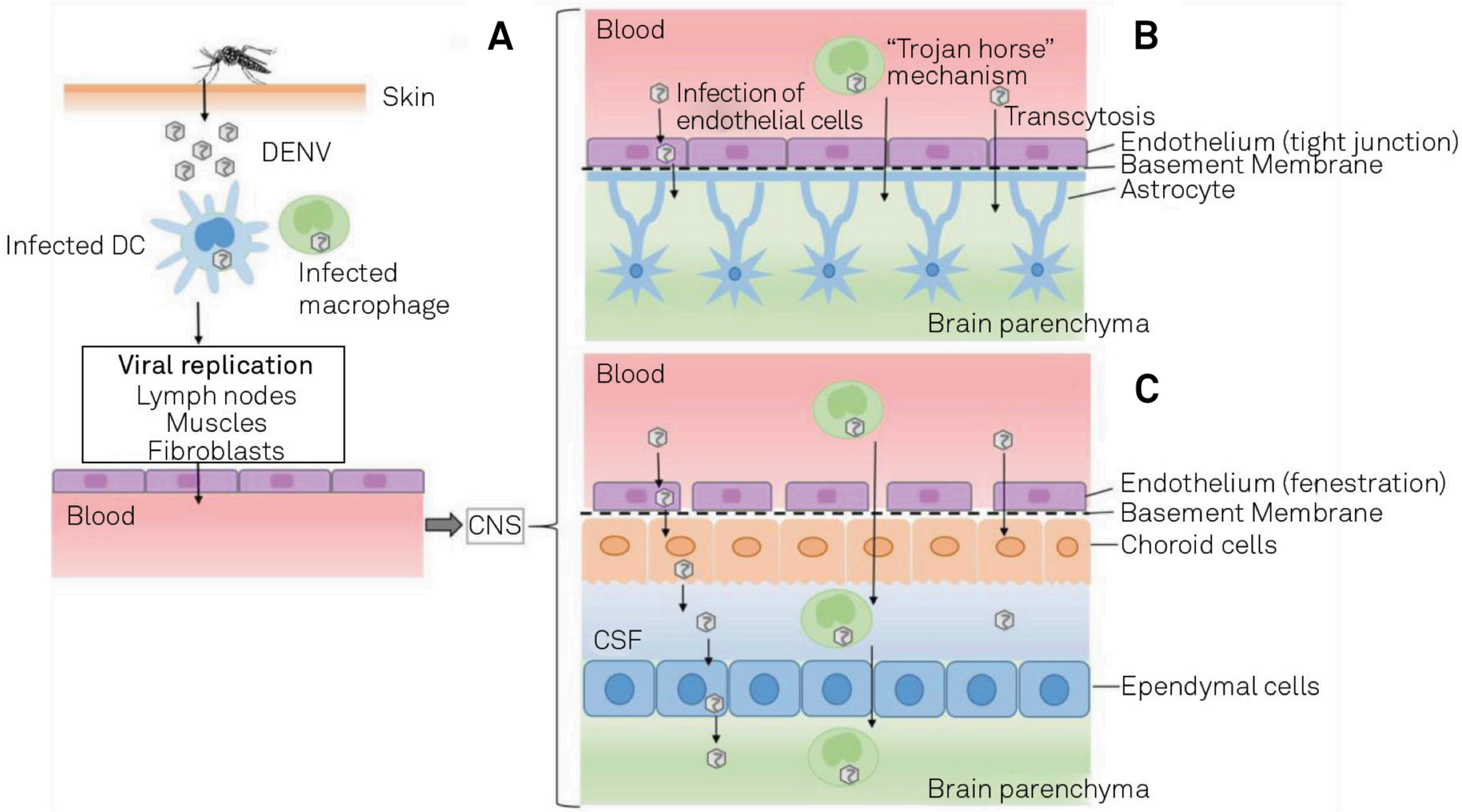
- Carod-ArtalFJ et.al, Lancet Neurol. 2013;12(9):906-19.
- SolbrigMV et al. CurrNeurolNeurosci www.thelancet.com Rep. 2015;15(6):29.



DENV: dengue virus; DHF: dengue severe hemorrhagic syndrome; DSS: dengue severe shock syndrome.

Figure 1. Antibody-dependent enhancement (ADE) in dengue virus infection.

- MarziaPuccioni-Sohleret al. **Advances and new insights in the Neuropathogenesis of dengue infection**

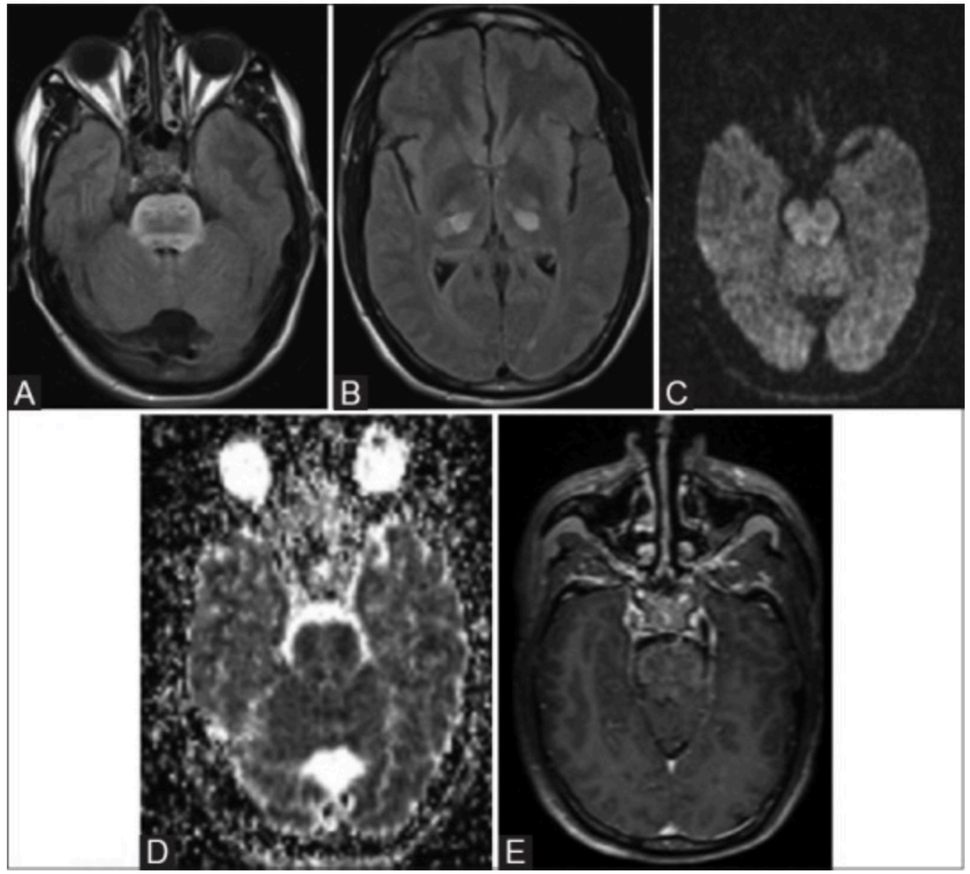


DENV: dengue virus; CNS: central nervous system; CSF: cerebrospinal fluid.

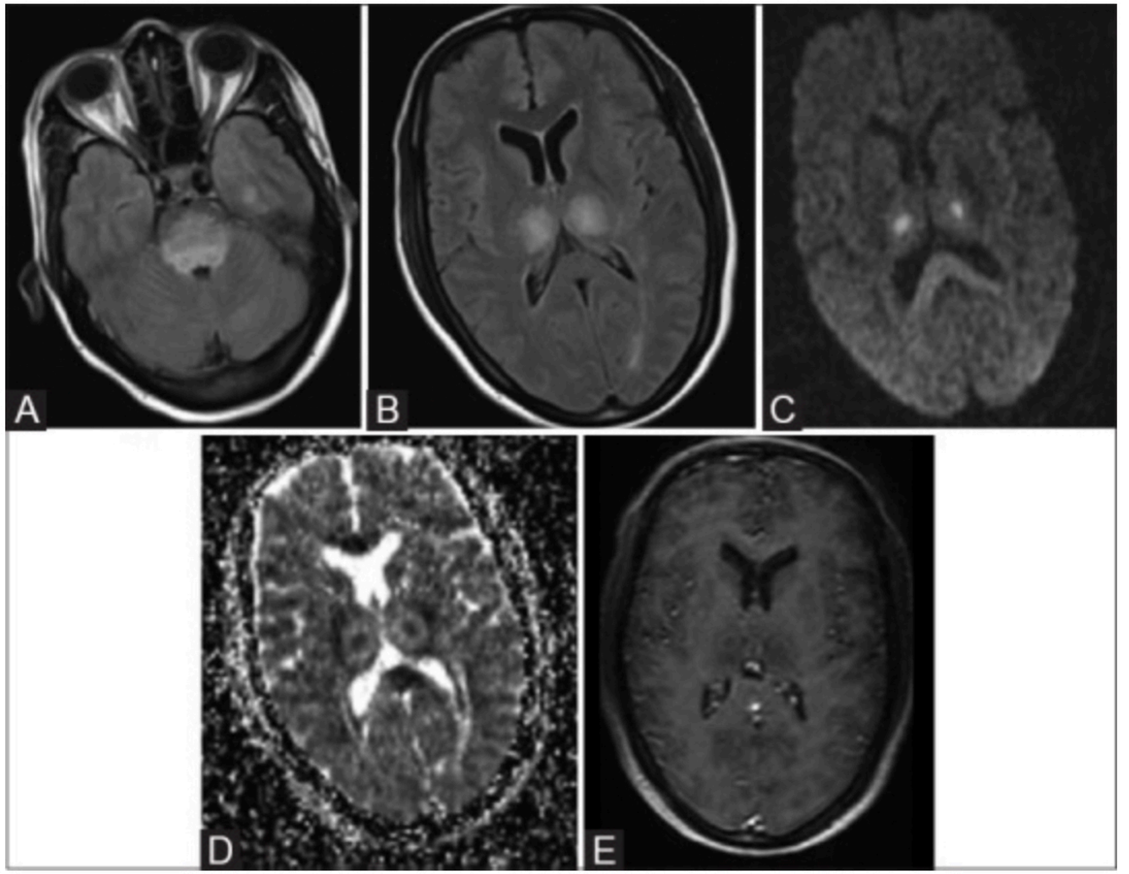
Figure 2. Neuroinvasivess of DENV in central nervous system. **A.** Viral invasion cross the skin after mosquito bite. It is followed by viral replication in lymph nodes, muscles and fibroblasts. The free particles or especially the infected monocyte disseminate the virus from the blood (viremia) to the visceral organ, inclusive the nervous system. **B.** Blood-brain barrier invasion. **C.** Blood-CSF barrier invasion.

- MarziaPuccioni-Sohleret al. **Advances and new insights in the Neuropathogenesis of dengue infection**

• Dengue Encephalitis



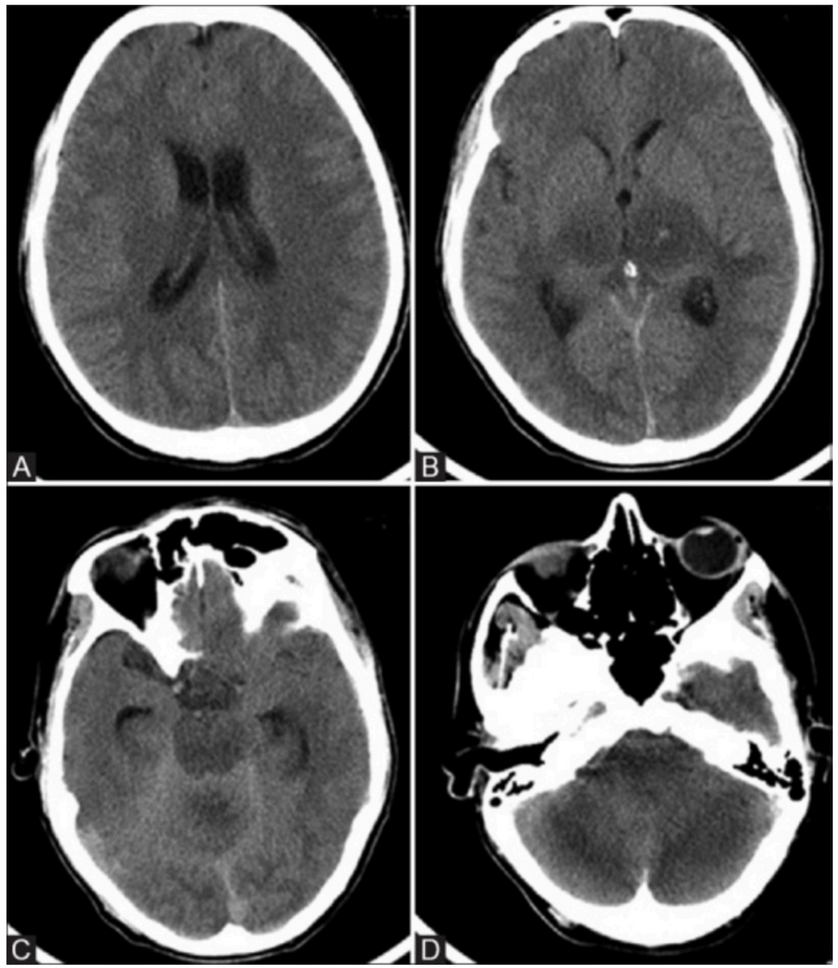
Axial FLAIR images show bilateral symmetrical hyperintensities in thalami and pons (A and B). DWI and ADC images shows restriction on diffusion in pons (C and D). Post contrast image show meningeal enhancement along the surface of pons (E)



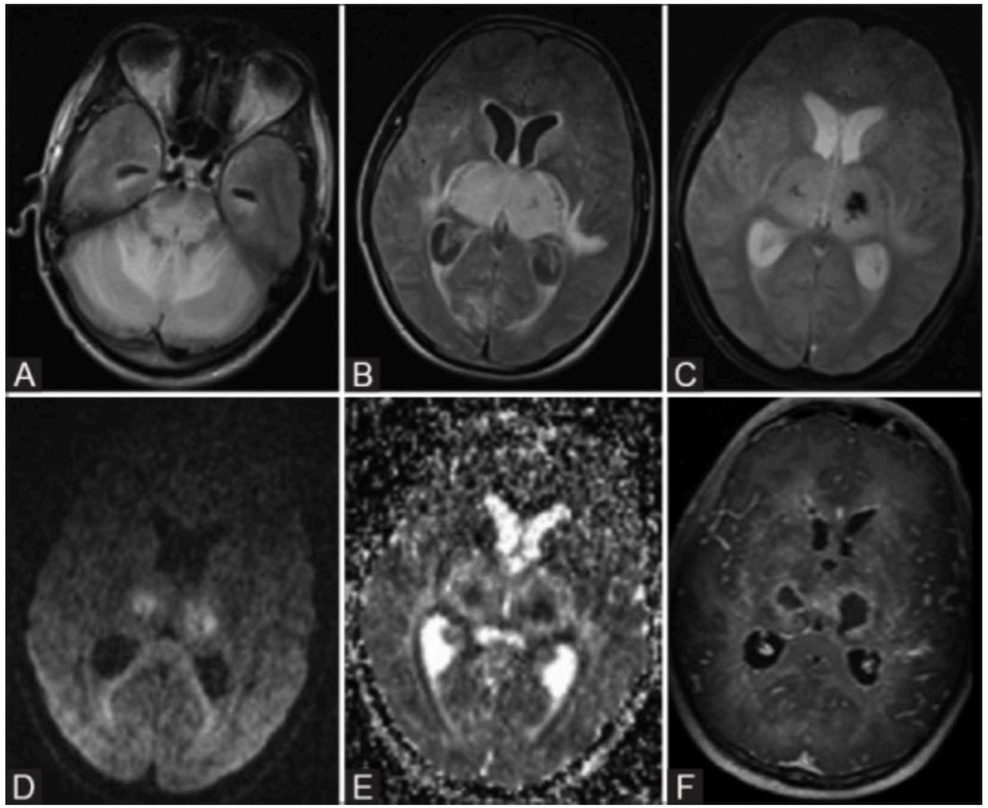
Axial FLAIR images show bilateral symmetrical hyperintensities in thalami, Pons and left temporal lobe (A and B). DWI and ADC images shows restriction on diffusion (C and D). Post contrast image show peripheral enhancement in bilateral thalami (E)

- Soni BK, Das DSR, George RA, Aggarwal R, Sivasankar R. **MRI features in dengue encephalitis: A case series in South Indian tertiary care hospital.** *Indian J Radiol Imaging*. 2017;27(2):125-128.

• Dengue Encephalitis



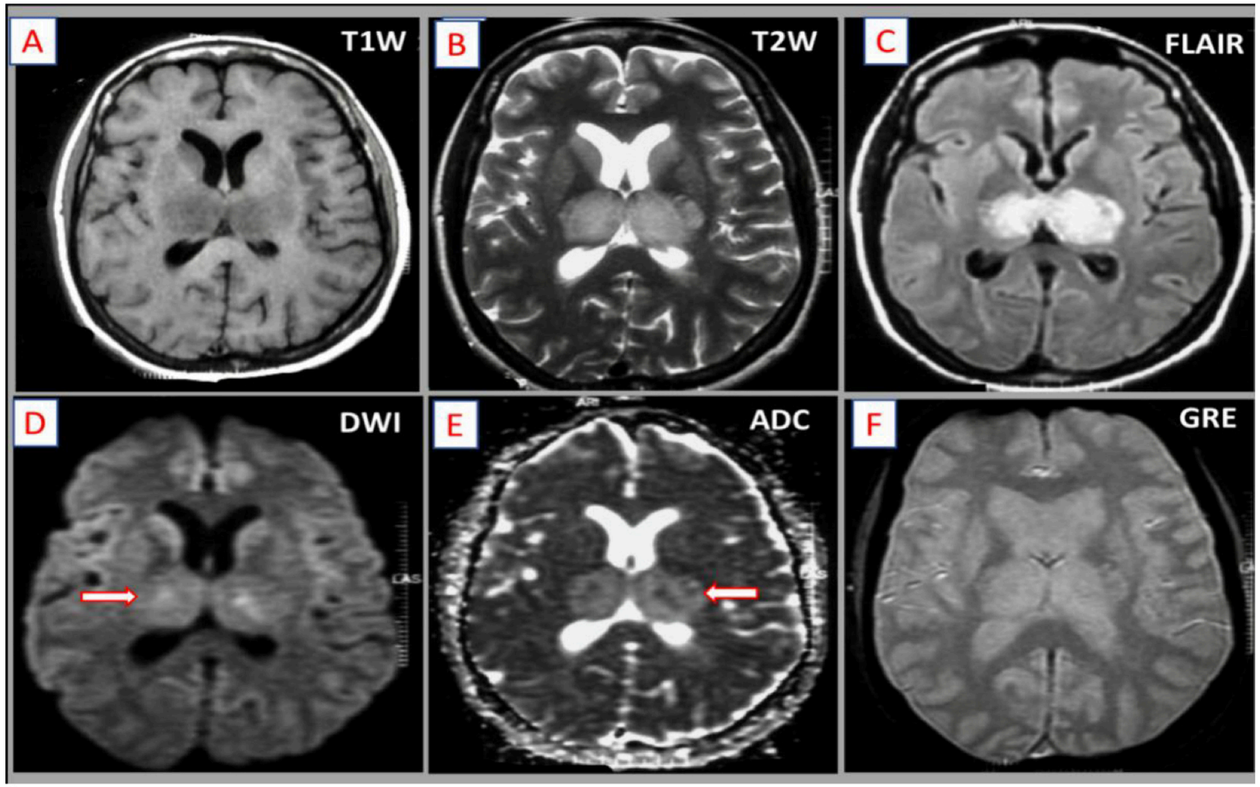
NCCT head demonstrating diffuse cerebral oedema (A). Bilateral symmetrical hypodensity in thalami with focal hyperdensity in left thalamus (B). Hypodensity in bilateral temporal lobe, mid brain, cerebellum and tonsillar herniation (C and D)

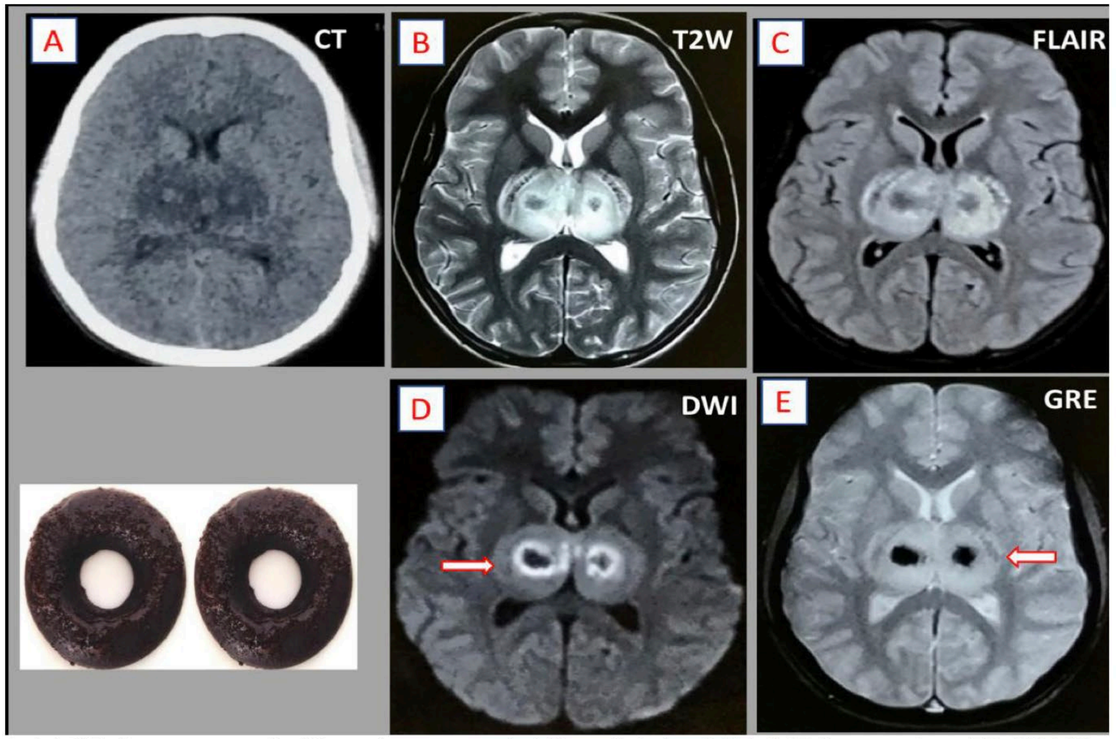


Axial FLAIR images show bilateral symmetrical hyperintensities in thalami, pons, bilateral temporal lobe and cerebellum (A and B). GRE image show loss of signal in bilateral thalamus (C). DWI and ADC images shows restriction on diffusion in bilateral thalamus (D and E). Post contrast image show peripheral enhancement in bilateral thalami (F)

- Soni BK, Das DSR, George RA, Aggarwal R, Sivasankar R. **MRI features in dengue encephalitis: A case series in South Indian tertiary care hospital.** *Indian J Radiol Imaging*. 2017;27(2):125-128.

• Dengue Encephalitis





Axial CT show symmetrical hypodense areas in bilateral thalami (A). MR images show T2, FLAIR symmetric
ities in bilateral thalami (B & C). GRE images (E) show central area of blooming in bilateral thalami giving the
appearance of "DOUBLE DOUGHNUT"

- MRI of the brain showed symmetrical T2 and FLAIR hyperintensities involving bilateral thalami and cerebellum. The corresponding areas in both thalami showed areas of centraldiffusion restriction giving the appearance of "DOUBLE DOUGHNUT". (Figure 1)

- Shah N, Nair AV, Ahamed S, Manoj KS. **Dengue doughnut: A diagnostic magnetic resonance imaging finding in dengue encephalitis.** *J Postgrad Med.*

• Dengue Encephalitis

•Diagnostics

- NS1 Antigen sensitivity 52-66%, Specific 90-100%
- The **specificity of RT-PCR is 100%** with 70% sensitivity when performed within 5 days of onset of illness
- Viral isolation by culture, the current gold standard, takes 1 to 2 weeks,

• Continuum (Minneap Minn) 2015;21(6):1639–1661

TABLE 1 | Main central neurological system complications associated with dengue infection.

Complications	Main symptoms and signs	CSF parameters	CT/MRI
Encephalitis	Acute signs of cerebral involvement	Normal cell count/Pleocytosis, normal/High level of protein	Normal/Signal changes in involved regions
Encephalopathy	Cognitive disorders, convulsions, mood/personality/behavior disorders	Normal in most cases	Suggestive of extensive involvement of the bilateral cerebellar region, brainstem, and thalami along with peculiar rim enhancement (MRI)
Meningitis	Acute onset of fever and symptoms such as headache, vomiting, and/or nuchal rigidity; absence of parenchymal involvement	CSF cell count greater than 5 cells/mm^3, and negative tests for bacteriological and fungal infections	Cranial CT was normal

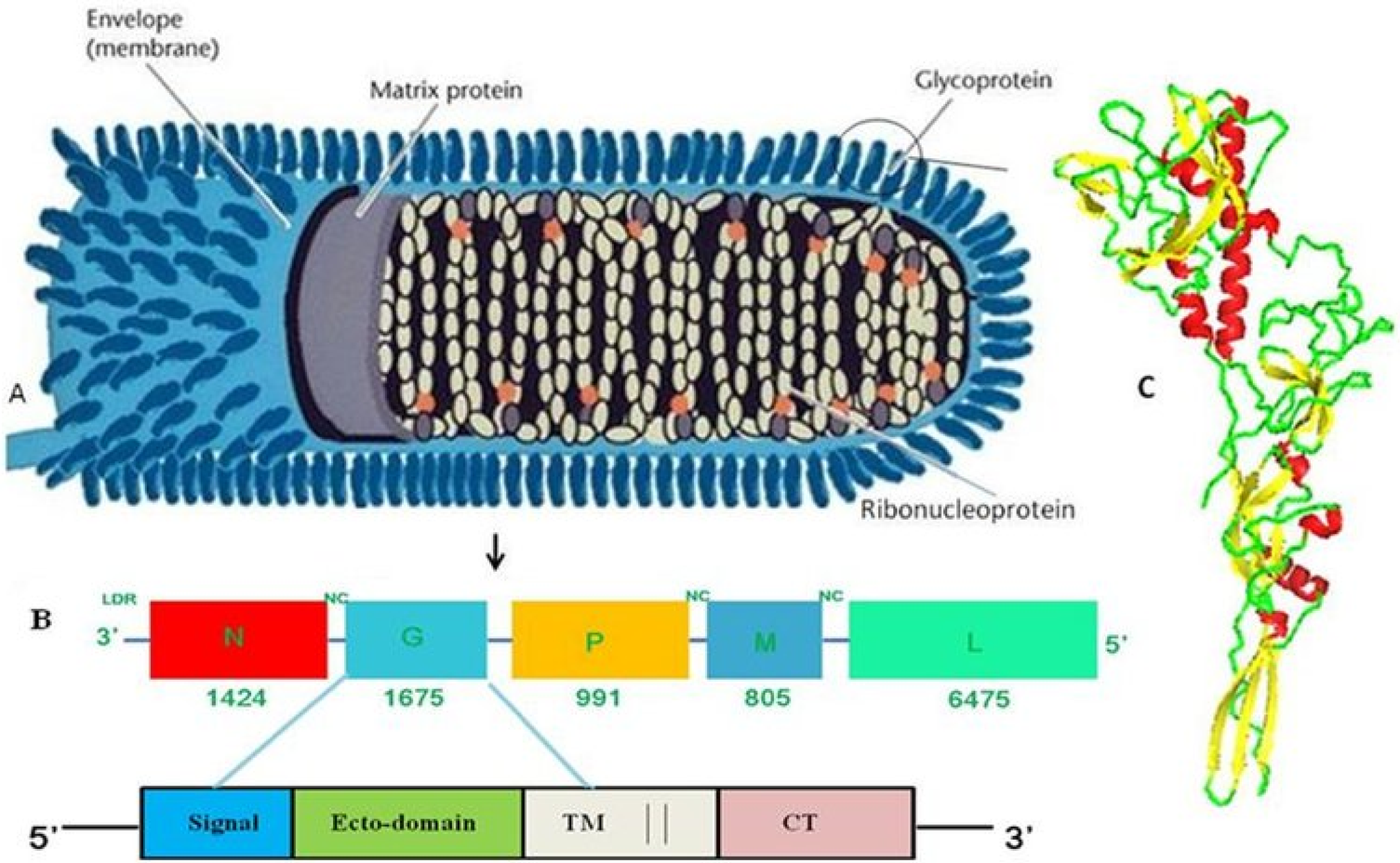
• Li G-H, Ning Z-J, Liu Y-M and Li X-H (2017) **Neurological Manifestations of Dengue Infection.**Front. Cell. Infect. Microbiol. 7:449.doi: 10.3389/fcimb.2017.00449

Complications	Main symptoms and signs	CSF parameters	CT/MRI
Ischemic stroke	Focal neurological signs such as hemiparesis, dysarthria, and so on	15 cells (all lymphocytes) with normal protein and sugar levels	Hypodensity on cranial CT
Hemorrhage stroke	Headache, vertigo, vomiting, somnolence, hemiparesis, and dysarthria	Normal/Hemorrhagic CSF if blood escapes into the ventricular system	Hyperdensity on cranial CT
Cerebellar syndrome	Bilateral vertical and horizontal nystagmus, dysarthria, bilateral limb, and gait ataxia	Normal	Normal/Cerebellar T2 hyperintense lesions (MRI)
Transverse myelitis/Longitudinally extensive transverse myelitis	Relatively abrupt onset of motor, sensory, and sphincter disturbances due to an inflammatory demyelinating lesion/spinal lesion extending over at least three vertebral segments	Signs of inflammation in the CSF in most patients	Hyperintensity in T2-weighted images in spinal MRI
Acute disseminated encephalomyelitis	Acute inflammatory demyelinating disorder of the central nervous system, monophasic course, and multifocal white matter involvement that occur during or after dengue virus infection	Normal/ Inflammatory CSF	Extensive involvement of the white matter of the frontal, parietal, or temporal lobes; and lesions of basal ganglia, brainstem, cerebellum, corpus callosum, and periventricular regions

• Li G-H, Ning Z-J, Liu Y-M and Li X-H (2017) **Neurological Manifestations of Dengue Infection.**Front. Cell. Infect. Microbiol. 7:449.doi: 10.3389/fcimb.2017.00449

• Rabies Encephalitis

- **Single-stranded RNA** virus, Most common in Africa and Asia
- Rabies replicates in local peripheral nerves within cytoplasmic inclusions (Negri bodies) and travel from peripheral nerves to cortex



- Abraham, Sunil & Ravindran, Jayaishrei & Abishaw, Nishawlini & Sandam, Nathaniel & Thimmareddy, Prashanth & Govindaraju, Goutham. (2017).
- **Review on Rabies and Vaccines.** ICJMAS. 6. 2064-2085. 10.20546/ijcmas.2017.612.237.

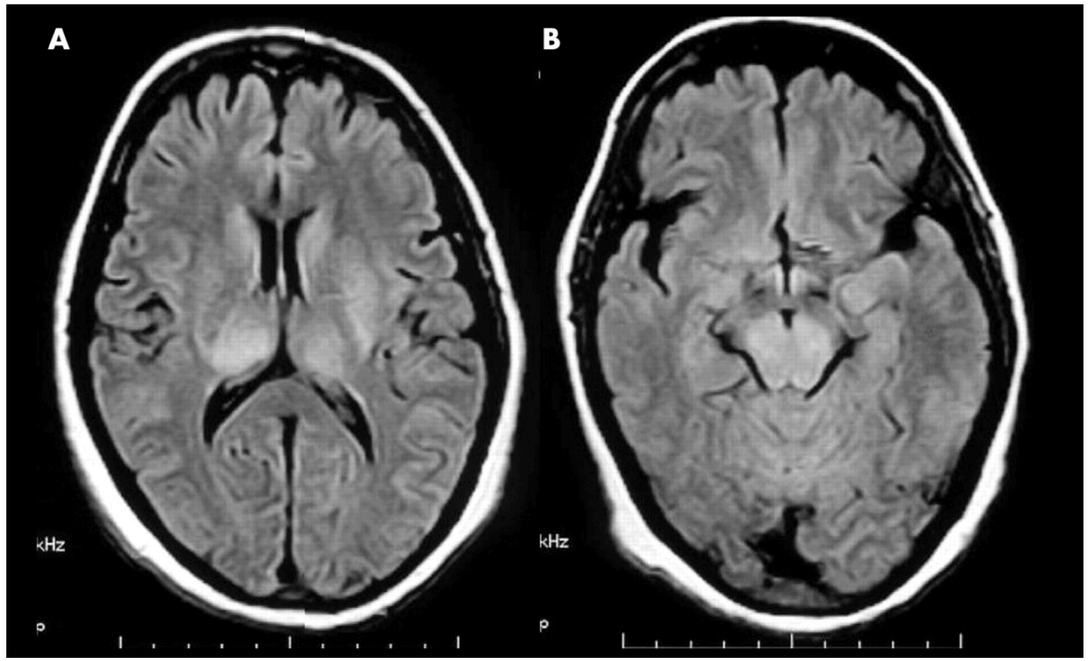
• Rabies Encephalitis

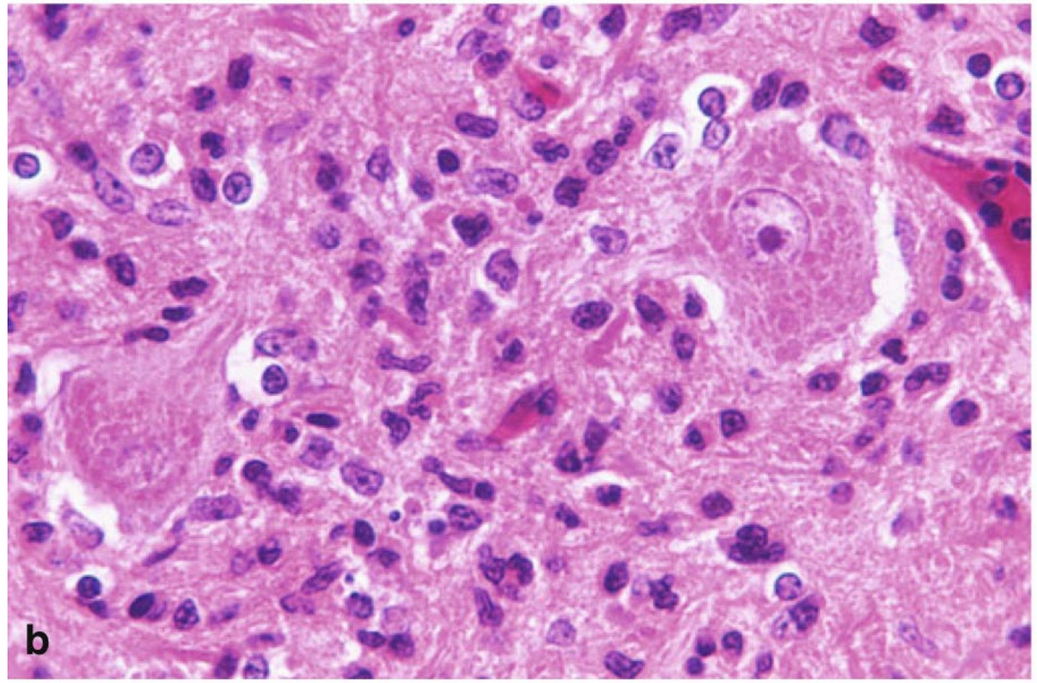
- Incubation period is variable , usually a few weeks to months (has been reported as longer than 8 years)
- Initial symptoms: Fever, pain/paresthesia at inoculation site
- Finally: diffuse, severe, fatal encephalitis
- 2 Form
  - Furious: Hydrophobia, aerophobia, agitated, ANS instability, inspiratory (laryngeal) photic spasm
  - Paralytic: slower, paralysis of bitten limbthen progressive ascending paralysis, then coma

- Lancet Neurol 2013; 12:498-513.
- Continuum (Minnaeap Minn)2018;24(5): 1284-97.

• Rabies Encephalitis

•Investigation





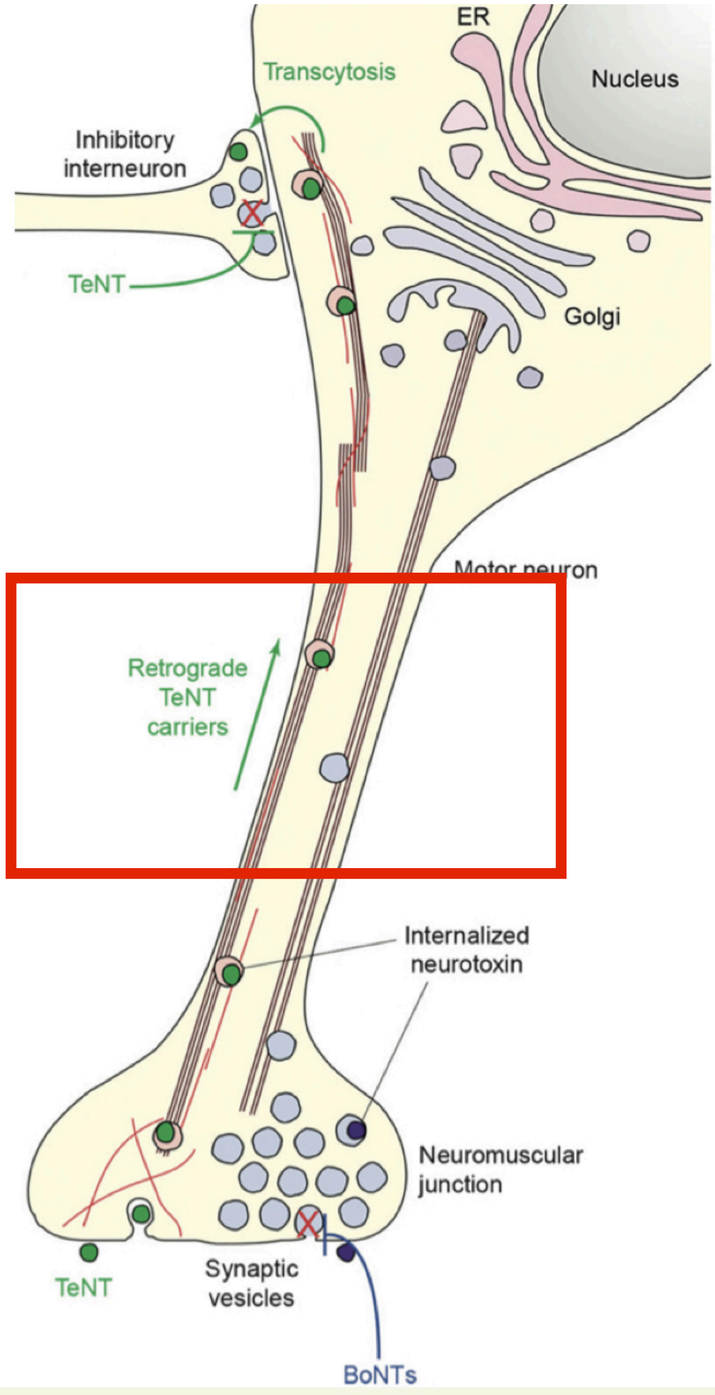
cytes). Figure (**b**) is a photomicrograph of H&E stained brain tissue from a rabies encephalitis patient displaying the pathognomonic finding of Negri bodies within the neuronal cytoplasm (Both: Courtesy of the Centers for Disease Control and Prevention)

- PCR from CSF, saliva, urine, hair follicles from back of neck
- MRI : exclusive involvement of the grey matter including the basal ganglia, thalami, pontine and midbrain nuclei

- Postgraduate Medical Journal, 2003; 79:352-4
- Lancet Neurol 2013; 12:498-513.
- Continuum (Minnaeap Minn)2018;24(5): 1284-97.

- Bacterial Toxin

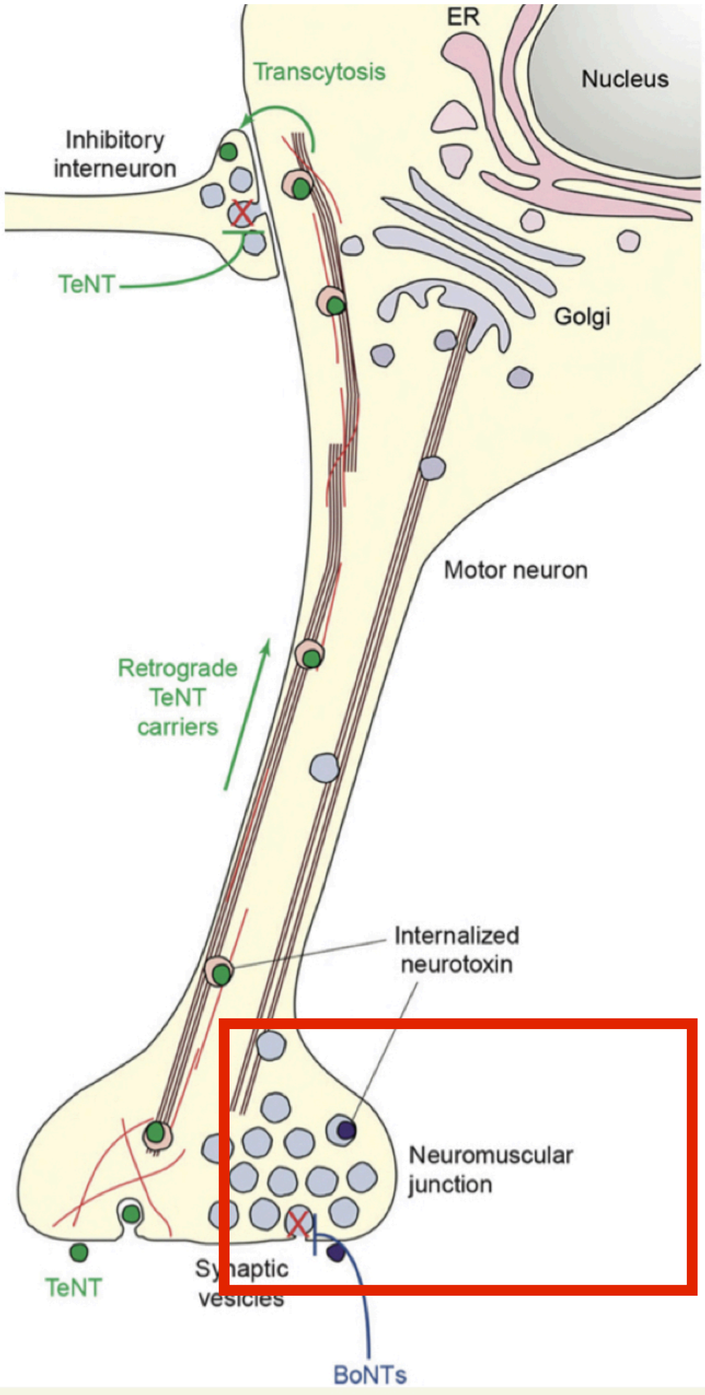
	Tetanus	Botulism
Bacterium	*Clostridium tetani*	*Clostridium botulinum*
Toxin	Tetanospasmin	Botulinum toxin (types A–G)
Location of toxin action	Inhibitory interneurons in spinal cord and brainstem	Presynaptic terminals of neuromuscular junction
Mode of acquisition	Wound; operation; injection; unhygienic birth, abortion, or umbilical cord practices	Home-canned food, inadequately refrigerated or cooked food, injection drug use (wound botulism), honey (infant botulism), iatrogenic, adult intestinal colonization
Major clinical features	Muscular rigidity, painful spasms, trismus, risus sardonicus, opisthotonos, autonomic instability	Classic pentad: dry mouth, nausea/vomiting, dysphagia, diplopia, fixed dilated pupils; followed rapidly by extremity weakness
Diagnosis	Clinical	Serum or stool culture, toxin identification by mouse-based assay or enzyme-linked immunosorbent assay (ELISA), EMG



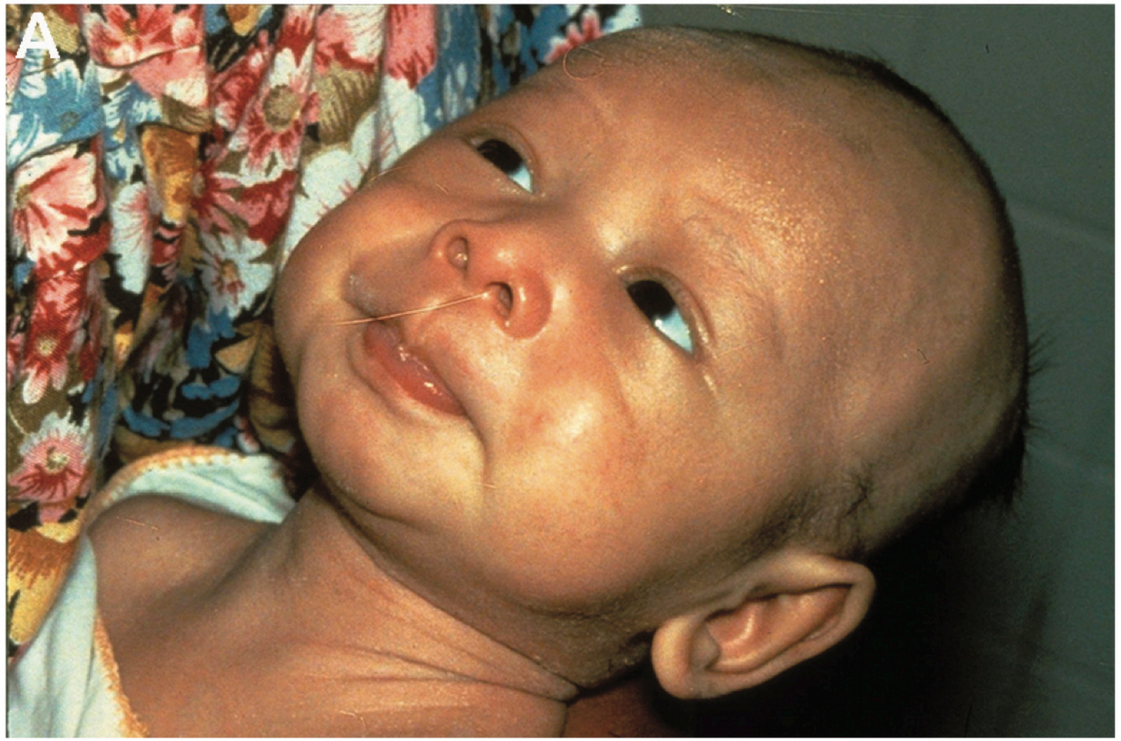
	Tetanus	Botulism	Diphtheric Neuropathy
Nerve conduction study and EMG findings	Continuous involuntary spontaneous motor activity, increased F-wave amplitude, absence of silent period following peripheral stimulation	Decreased compound muscle action potential (CMAP) amplitudes, decremental response to low-frequency repetitive stimulation, incremental response (facilitation) to high-frequency repetitive stimulation, persistence of post-tetanic facilitation, short-duration low-amplitude motor unit potentials, increased jitter on single fiber EMG, normal velocities/latencies	Demyelinating polyneuropathy: slowed conduction velocities, prolonged distal latencies, conduction block, prolonged F waves, preserved sensory and motor amplitudes
Treatment	Antibiotics (metronidazole preferred), tetanus antitoxin, toxoid vaccination, diazepam or other benzodiazepine for spasms (neuromuscular blockade if inadequate), wound debridement, supportive care	Antitoxin (infant: human-derived botulism immunoglobulin [BIG-IV]; adult: heptavalent botulinum antitoxin), antibiotics for wound botulism only, supportive care	Antibiotics, antitoxin
Prevention	Vaccination and boosters, wound prophylaxis (refer to TABLE 10-2)	Proper food preparation and canning techniques, avoidance of honey for infants	Vaccination and boosters

EMG = electromyography.

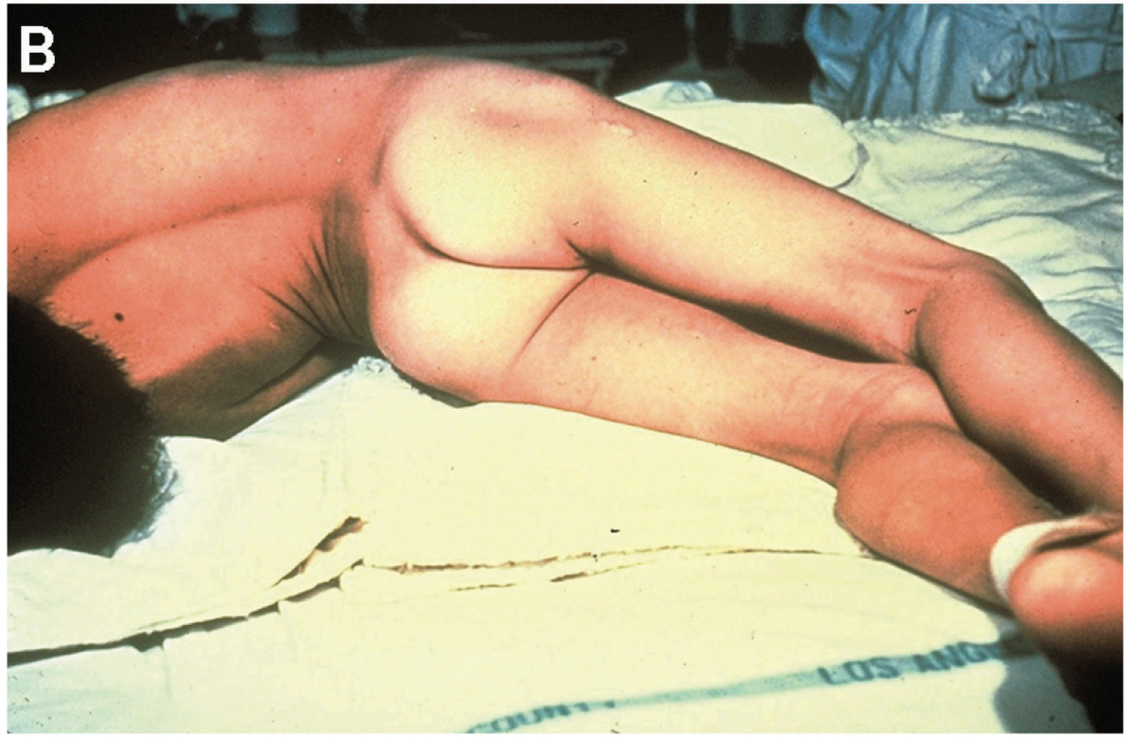
	Tetanus	Botulism
Bacterium	*Clostridium tetani*	*Clostridium botulinum*
Toxin	Tetanospasmin	Botulinum toxin (types A–G)
Location of toxin action	Inhibitory interneurons in spinal cord and brainstem	Presynaptic terminals of neuromuscular junction
Mode of acquisition	Wound; operation; injection; unhygienic birth, abortion, or umbilical cord practices	Home-canned food, inadequately refrigerated or cooked food, injection drug use (wound botulism), honey (infant botulism), iatrogenic, adult intestinal colonization
Major clinical features	Muscular rigidity, painful spasms, trismus, risus sardonicus, opisthotonos, autonomic instability	Classic pentad: dry mouth, nausea/vomiting, dysphagia, diplopia, fixed dilated pupils; followed rapidly by extremity weakness
Diagnosis	Clinical	Serum or stool culture, toxin identification by mouse-based assay or enzyme-linked immunosorbent assay (ELISA), EMG



• TETANUS



• A, Risus sardonicus



• B, opisthotonos

• CONTINUUM (MINNEAP MINN) 2018;24(5, NEUROINFECTIOUS DISEASE):1459–1488

Brain Abscess

- **Clinical Features and Presentation**
  - Triad : Fever, Headache, Focal Neurological deficit
  - Fever, may be absent > 1/2 of cases
  - Headache, most frequent symptom at presentation

- **Source of infection**
  - Local site (Otitis media, Mastioditis, Sinusitis)
    - 50% Polymicrobial
    - Streptococci app. > Anaerobes > Enterobacteriaceae
  - Hematogenous seeding from distant source > Multiple at gray-white junction and borderzone
  - Penetrating trauma
  - Neurosurgery

- Predisposing factors
- Congenital Heart Disease
- DM
- Alcohol use
- Cortocosteroid use
- Immunocompromised states

- Continuum 2018; 24 (5, Neuroinfectious disease) : 1327-1348

• Brain Abscess

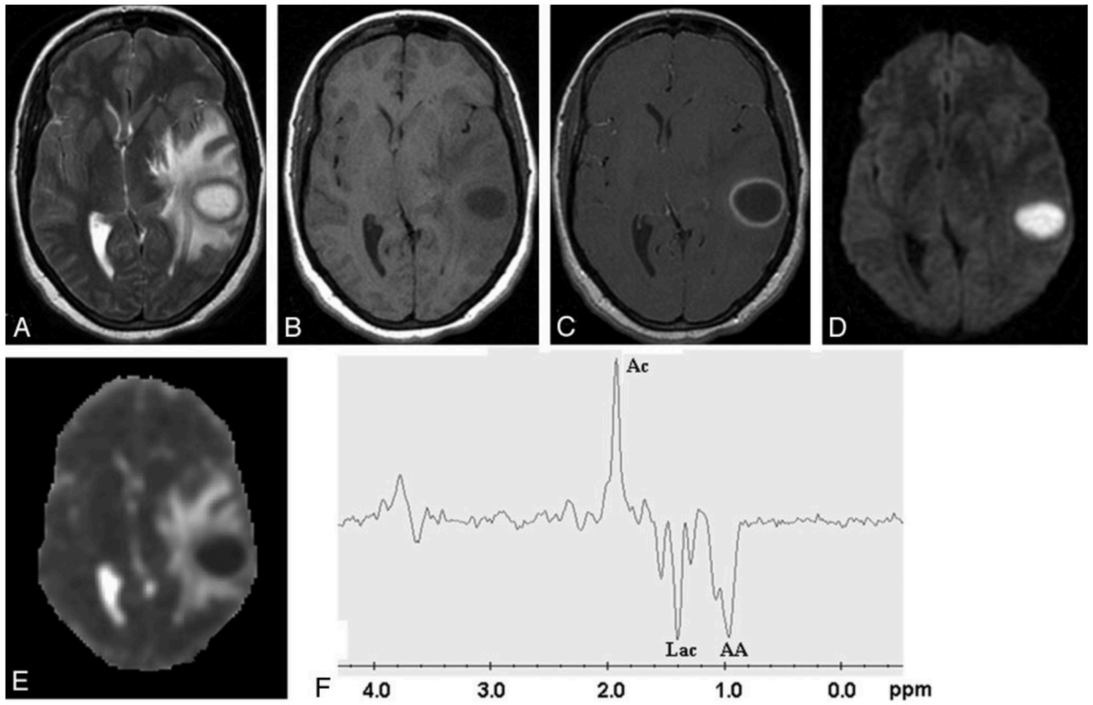


Fig 1. Pyogenic abscess in the left temporal lobe of a 31-year-old woman.

Axial T2-weighted image (*A*) shows a well-defined hyperintense lesion with hypointense wall that appears hypointense on axial T1-weighted image (*B*) with isointense wall. On postcontrast T1-weighted image (*C*), it shows ring enhancement. Diffusion-weighted image shows homogeneous hyperintensity in the cavity (*D*) with low ADC (0.63×10^{-3} mm^2/s) (*E*). PMRS from the center of the lesion with a voxel size of 2.4 mL shows amino acids (*AA, 0.9 ppm*), lactate (*Lac, 1.3 ppm*), and acetate (*Ac, 1.9 ppm*) (*F*). Culture from pus grew *Bacteroides* species.

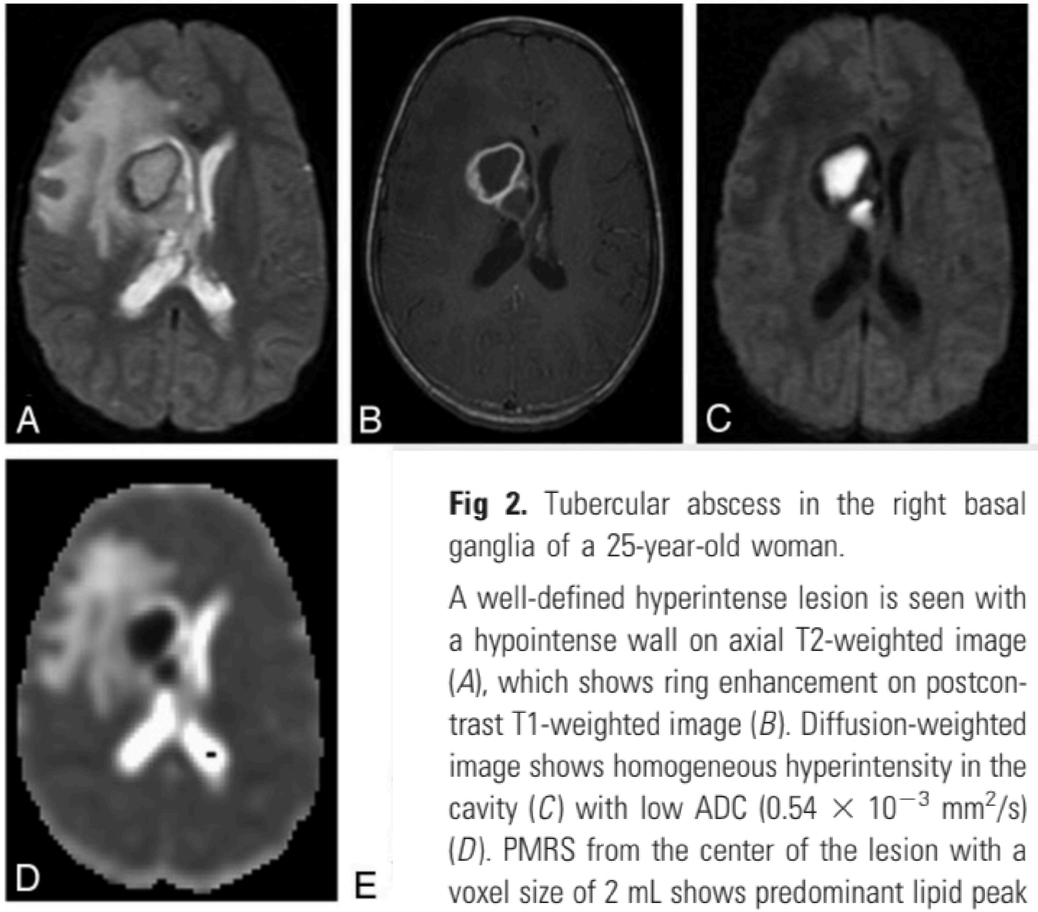


Fig 2. Tubercular abscess in the right basal ganglia of a 25-year-old woman.

A well-defined hyperintense lesion is seen with a hypointense wall on axial T2-weighted image (*A*), which shows ring enhancement on postcontrast T1-weighted image (*B*). Diffusion-weighted image shows homogeneous hyperintensity in the cavity (*C*) with low ADC (0.54×10^{-3} mm^2/s) (*D*). PMRS from the center of the lesion with a voxel size of 2 mL shows predominant lipid peak (*Lip, 1.3 ppm*) (*E*). Culture from pus shows the presence of *Mycobacterium tuberculosis*.

- AJNR Am J Neuroradiol 28:1332–38 ,Aug 2007

Brain Abscess

- Role of Lumbar Puncture
- With an encapsulated abscess, the diagnostic yield of lumbar puncture (LP) for CSF analysis is **low**
  - except in situations of abscess rupture, into the ventricular system or concomitant meningitis
  - The CSF of patients with brain abscess can be bland, and no organism may be identified in more than 80% of those who undergo LP

- Continuum 2018; 24 (5, Neuroinfectious disease) : 1327-1348

• Brain Abscess

•SURGICAL APPROACH AND CONSIDERATIONS

- Posterior fossa
- Multiloculated
- Near ventricles
- Mass effect with increased ICP
- Superficial solitary abscess, well circumscribed
  - esp. fungus, MTB, Actinomyces, Nocardia spp.

• Stereotactic Aspiration

- Unknown pathogens: unresponsive to empirical ATBs
- Size > 2.5 cm
- Brainstem abscess

- N Engl J Med 2014; 371: 447-56

• Treatment

- Ceftriaxone 2 g IV q 12 hr + Metronidazole 500 mg IV q 6-8 hr
- Otitis Media: ceftazidime/cefipime + Metronidazole to cover Pseudomon

TABLE 4-1 **Common Causative Pathogens of Pyogenic Brain Abscess and Empiric Antimicrobial Regimens by Source of Infection[a]**

Source of Infection	Common Pathogens	Suggested Empiric Antimicrobial Regimens
Odontogenic and sinus	*Streptococcus* species, *Haemophilus* species, anaerobes (eg, *Fusobacterium, Actinomyces* species), *Staphylococcus aureus*	Ceftriaxone or cefotaxime and metronidazole; add vancomycin if high risk for *Staphylococcus aureus*, including chronic sinusitis, recent sinus surgery; alternative option for odontogenic infections is penicillin G and metronidazole
Otogenic	*Streptococcus* species, Enterobacteriaceae, *Pseudomonas aeruginosa*, anaerobes (eg, *Bacteroides* species)	Ceftriaxone or cefotaxime and metronidazole; can consider ceftazidime or cefepime in place of third-generation cephalosporin for pseudomonal coverage
Postneurosurgical or post–penetrating trauma	*Staphylococcus* species, *Streptococcus* species, Enterobacteriaceae, *Pseudomonas aeruginosa*, anaerobes (eg, *Clostridium* species)	Postneurosurgical: vancomycin and ceftazidime or cefepime or meropenem Post-penetrating trauma: vancomycin and ceftriaxone or cefotaxime, with or without metronidazole

- Duration : at least 4-8 weeks (IV drug at least 2 weeks)
- Nocardia > 6-12 months
- Follow up brain imaging 1-2 weeks if no clinical response then q 2 wks up to 3 months until clinical recovery
- For symptomatic seizure, AEDs for at least 6-month seizure free period

- Post-Sx: Vancomycin + ceftazidime/cefipime/meropenem

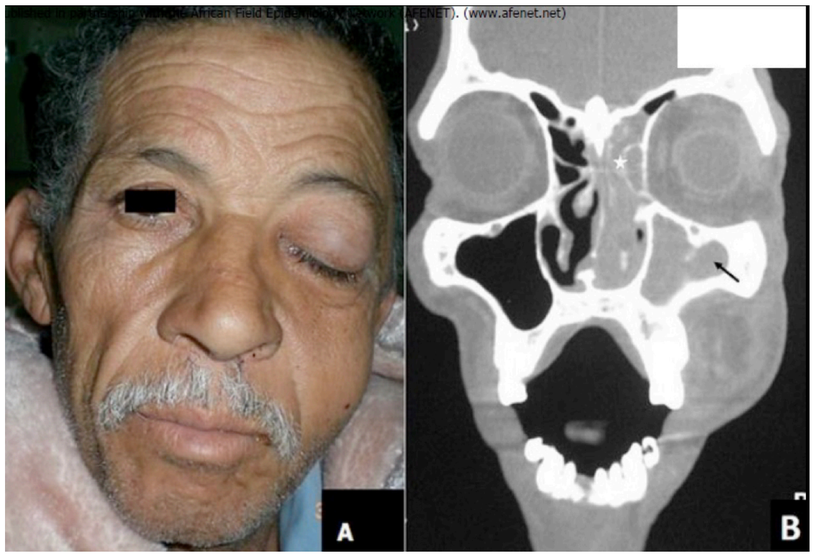
- Continuum 2018; 24 (5, Neuroinfectious disease) : 1327-1348

• Brain Abscess : Fungus

•Rhinocerebral mucormycosis

- Host : Hematologic malignancy, Organ transplantation, uncontrolled DM
- Spreading via direct extension with angioinvasion
- Clinical : headache, facial & orbital pain, ptosis, proptosis, blindness, cavernous sinus thrombosis

- Treatment of the condition is based on three main principles
  - Rapid reversal of underlying predisposing factors
  - Antifungal therapy with amphotericin B 1 mg/kg/day
  - Surgical intervention



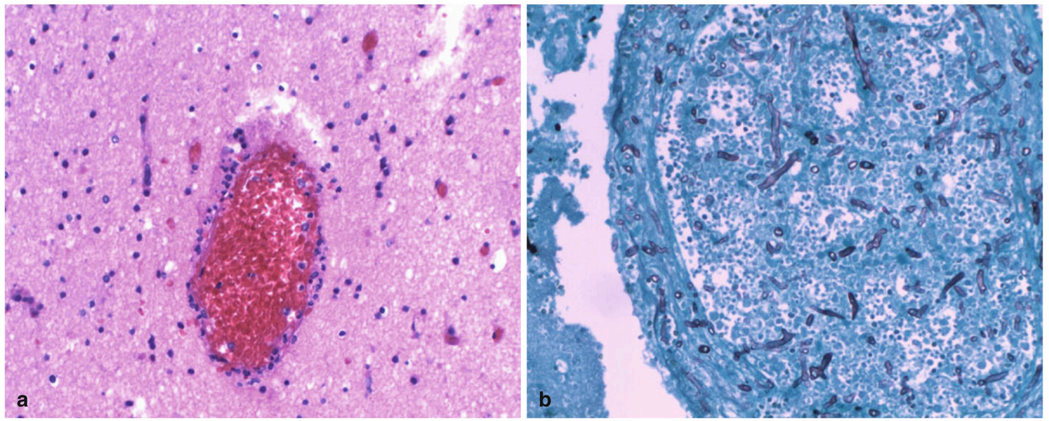


Fig. 22.24 (**a**) A 63-year-old male with disseminated mucor infection. Shows CNS vasculitis with neutrophils invading CNS parenchymal vessels with early vessel wall destruction (H&E, 20×). (**b**) Same patient. Features a Gomori methenamine silver (GMS)-stained specimen demonstrating angioinvasion 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)

- Left eye ptosis and left cheek edema, CT: soft tissue opacification of left maxillary and ethmoid sinuses
  - Imaging: fulminant sinusitis, intracranial extension (cerebritis)

- Continuum 2018; 24 (5, Neuroinfectious disease) : 1327-1348
- A.J. Layon et al. (eds.), Central Nervous System Infection Textbook of Neurointensive Care, DOI 10.1007/978-1-4471-5226-2_22,

• Spinal Epidural Abscess

•Symptoms

- Back pain (Most Common)
- Fever , only 50%
- Neurological deficit
  - Triad only 2-33%

- Common : posterior epidural of Thoracolumbar spine
- Via Hamatogenous spreading from local infection
- Usually 1-2 vertebral levels
- Organism : S.aureus > Streptococci spp.,
- Coagulase-negative Staphylococci > Gram negative

• Continuum (Minnaeap Minn) 2018;24(5):1327-48.

• Spinal Epidural Abscess

- **Investigation**
  - MRI
  - HC = Sensitivity 60%
  - Contraindication to LP

• Continuum (Minnaeap Minn) 2018;24(5):1327-48.

• Spinal Epidural Abscess

•Gadolinium-enhanced MRI

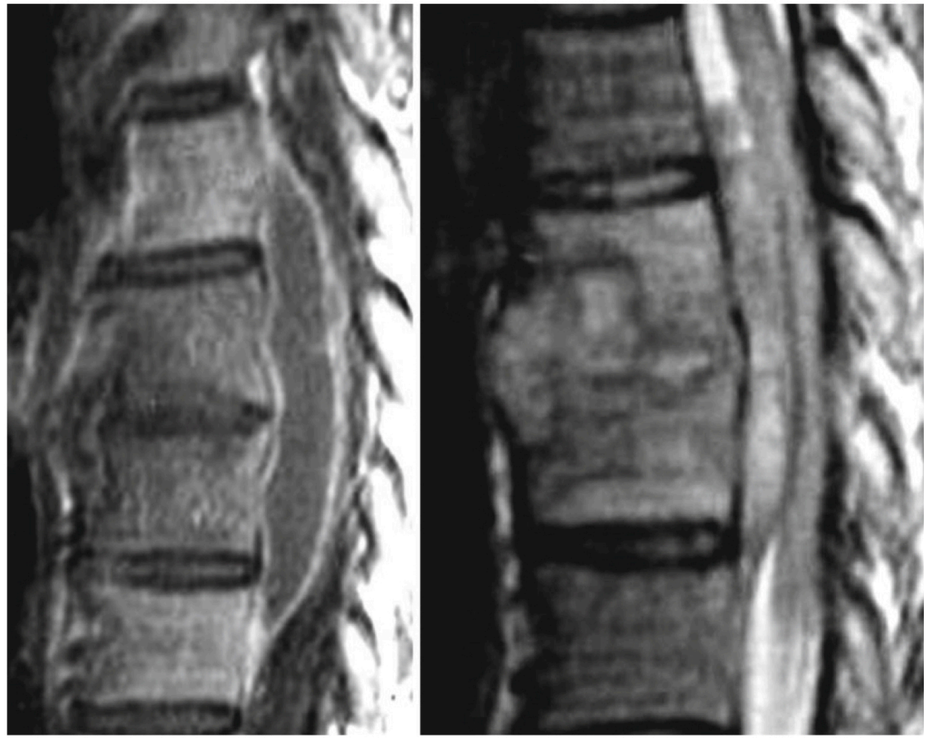


Fig. 22.17 Acute discitis with secondary osteomyelitis and anterior epidural empyema; images include post-contrast T1-w (on *left*) and T2-w (on *right*) sequences. In this instance there is a central disc infection with adjacent osteomyelitis in vertebral bodies above and below the disc infection. This is the pattern usually associated with primary disc infection with secondary bone involvement and is usually of pyogenic causative agent. Additionally, there is an anterior epidural abscess that bridges the infected motion segment

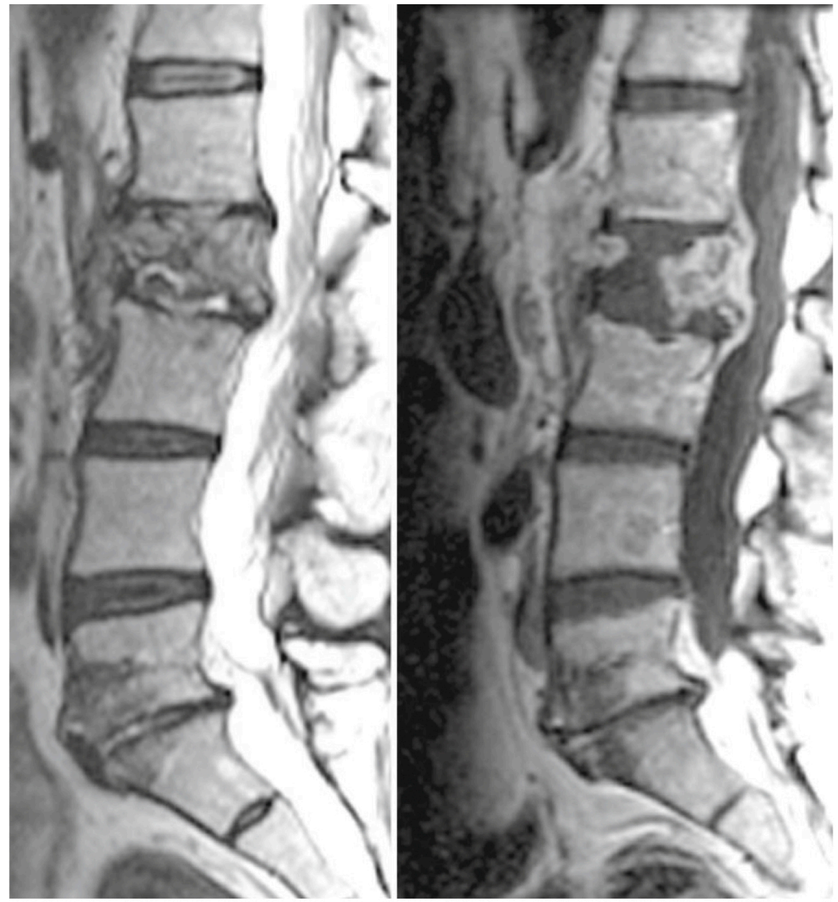


Fig. 22.18 Spinal vertebral osteomyelitis with relative sparing of the disc space; images include T2-w sagittal image (*left*) and a post-contrast T1-w image (*right*). In this instance the spinal infection has virtually destroyed the L1 vertebral body. There is prominent residual contrast enhancement in the affected vertebral body. There is only minimal edema in the L1–2 disc space and relatively little enhancement. This complex would be consistent with hematogenous seeding the vascularized vertebral body rather than a primary disc infection with secondary osteomyelitis

- Urgent surgical drainage (Best at first 36 hours),decompression
  - Empiric ceftriaxone and vancomycin
  - Duration ATB at least 4-8 weeks

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

- COVID-19

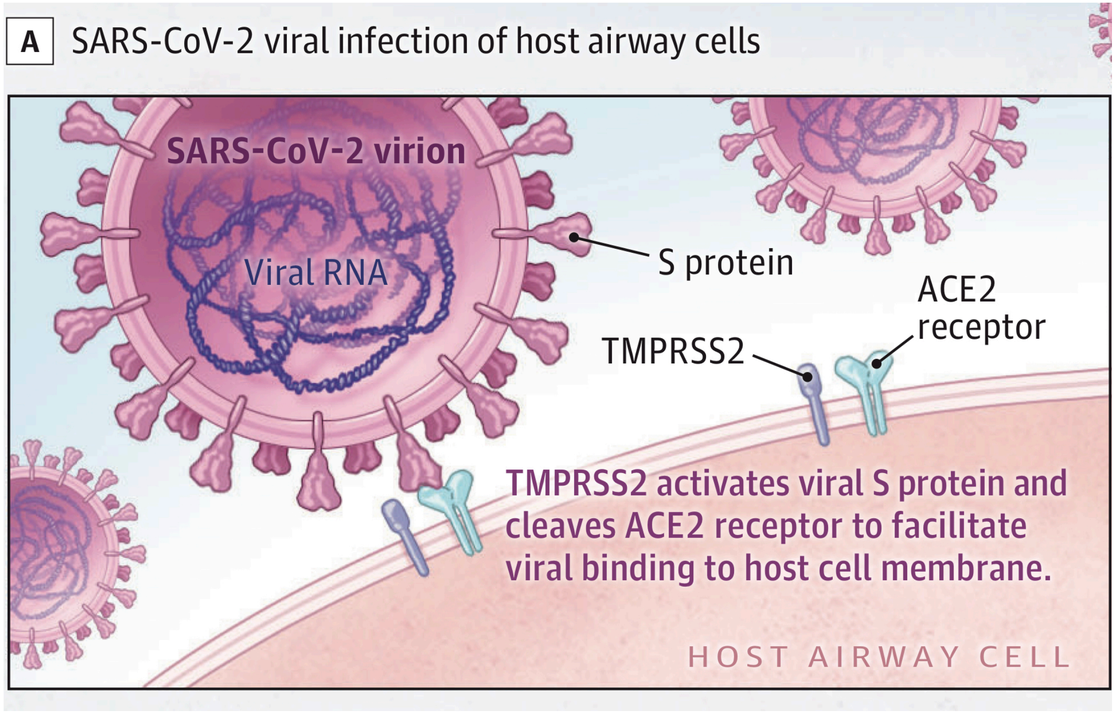
• SARS-CoV-2

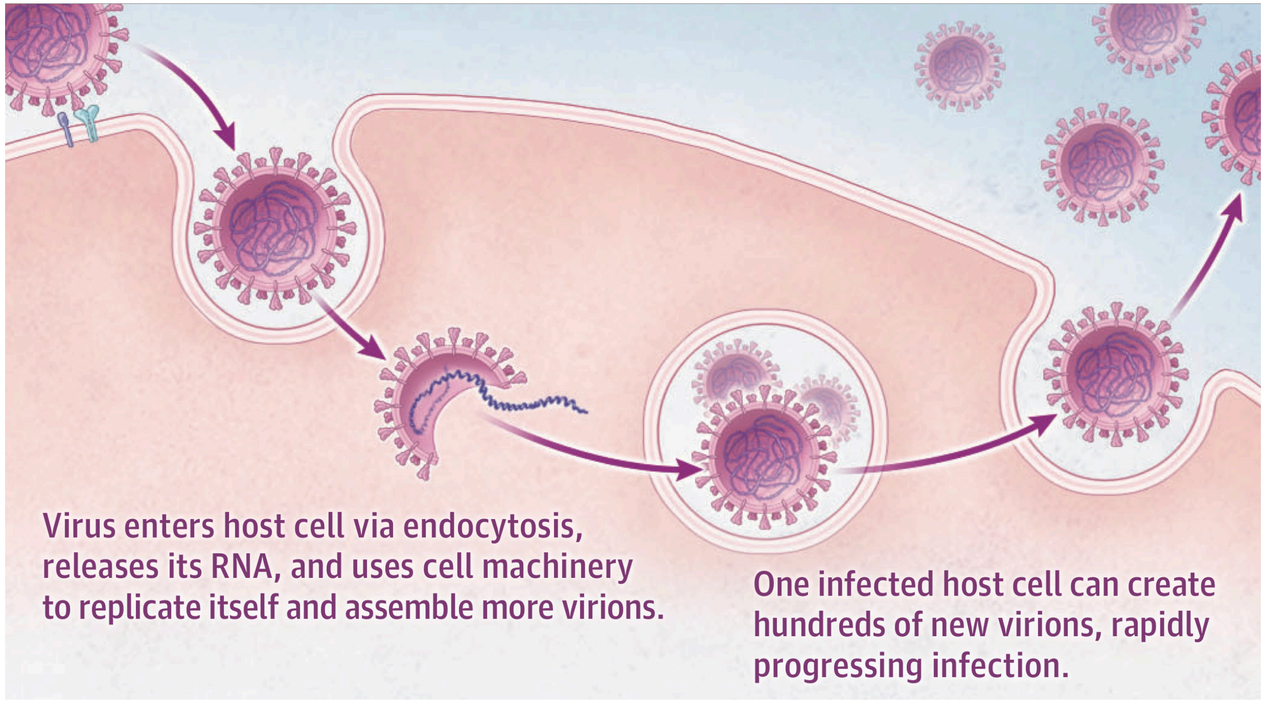
•3 HCoV : Infect Neurons

•HCoV-229E

•HCoV-OC43

•SARS-CoV-1

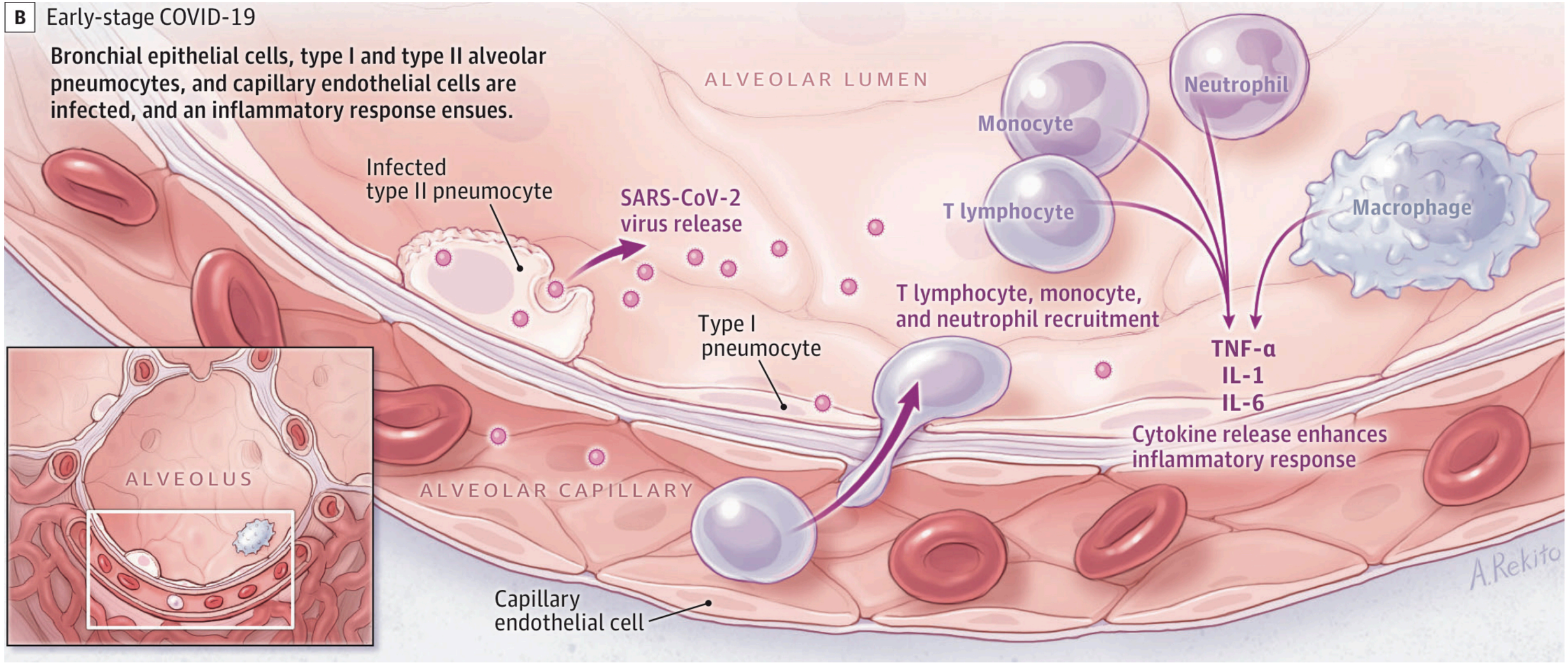




•Large, enveloped SS-DNA

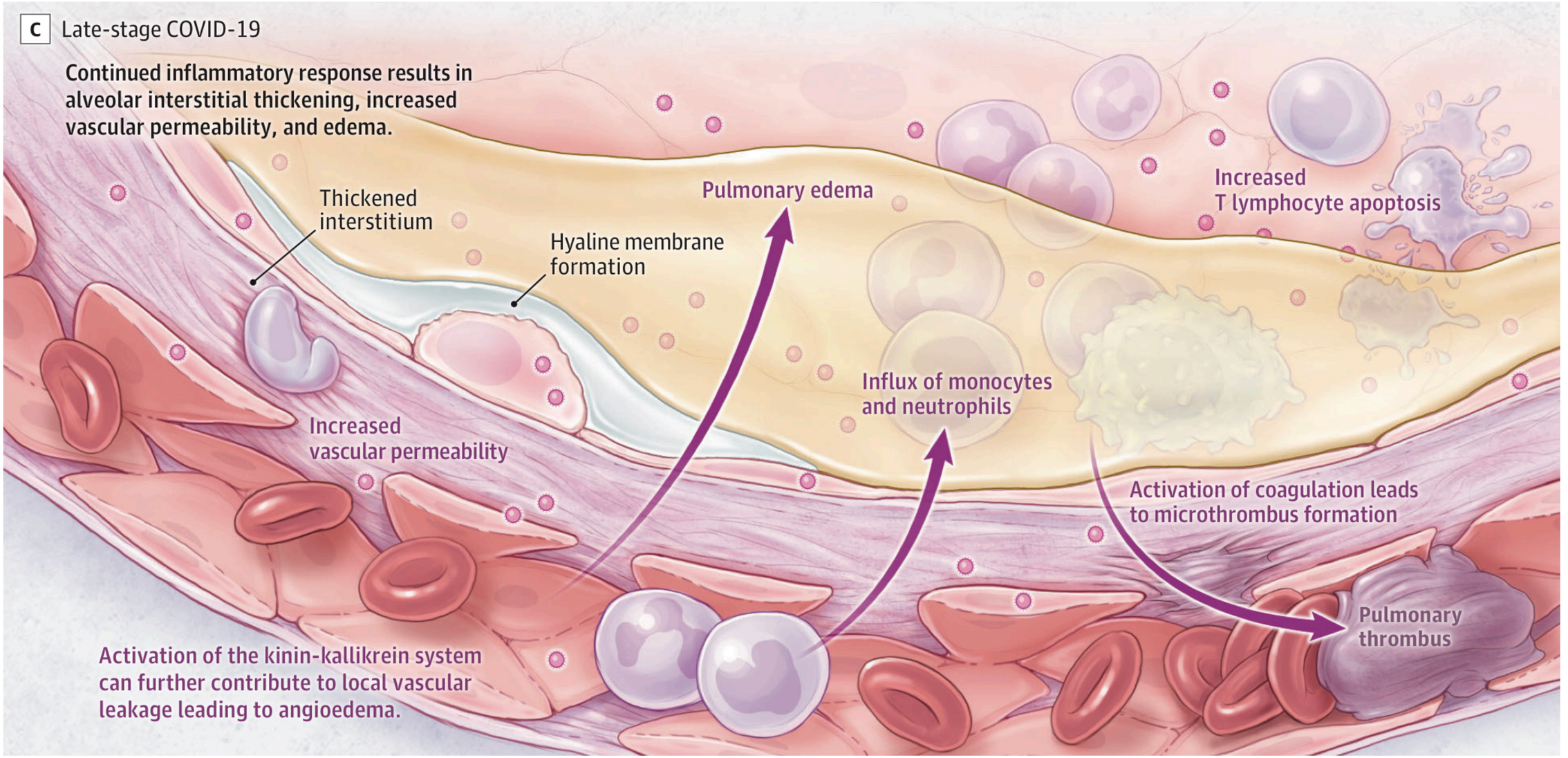
• JAMA. 2020;324(8):782-793. doi:10.1001/jama.2020.12839

• SARS-CoV-2



• JAMA. 2020;324(8):782-793. doi:10.1001/jama.2020.12839

- # SARS-CoV-2

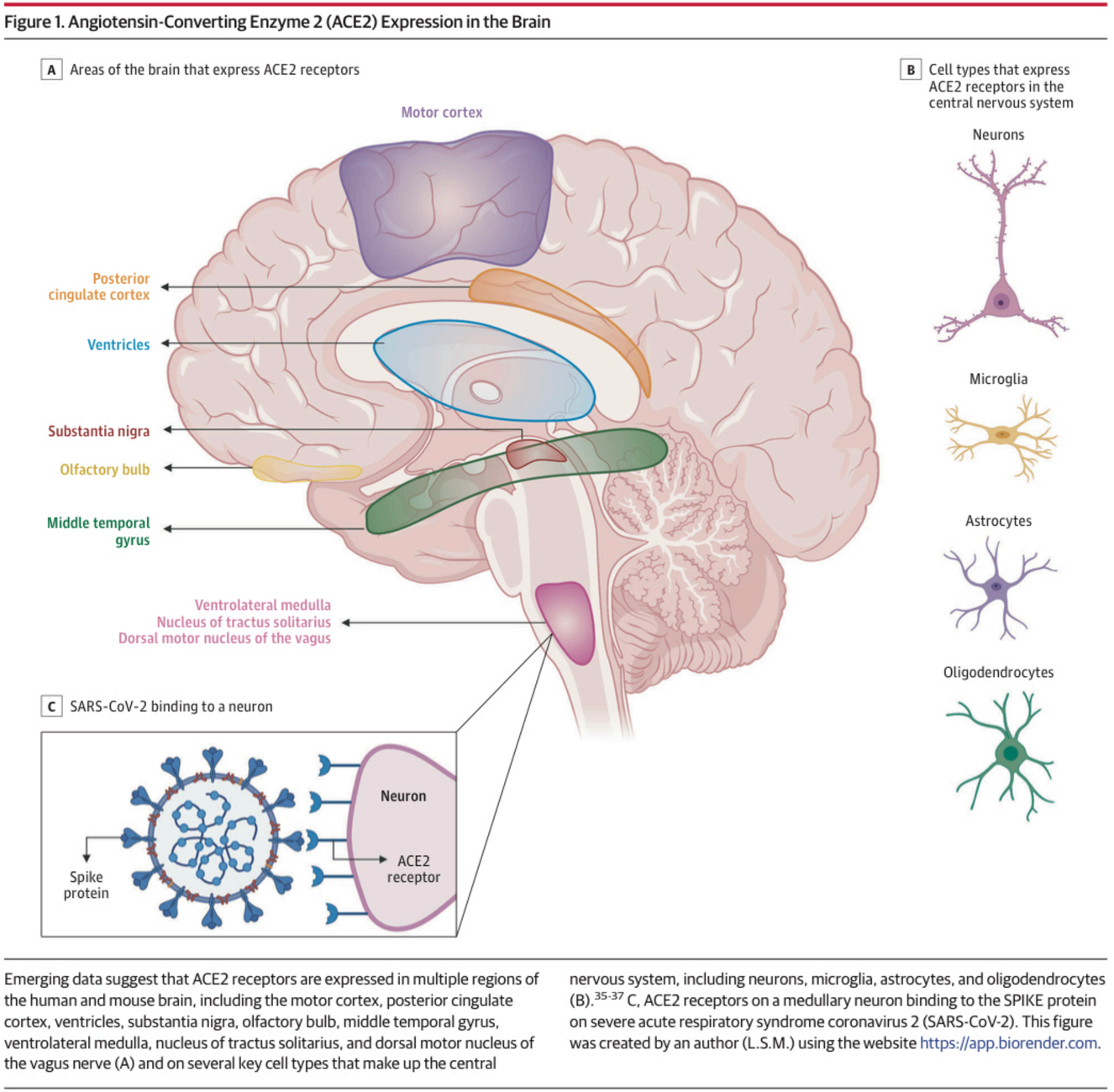


- JAMA. 2020;324(8):782-793. doi:10.1001/jama.2020.12839

• SARS-CoV-2

•Pathophysiology

- SARS-COV-2 may enter the CNS through the hematogenous or retrograde neuronal route.
- Supported by the fact that some patients in this study had smell impairment.

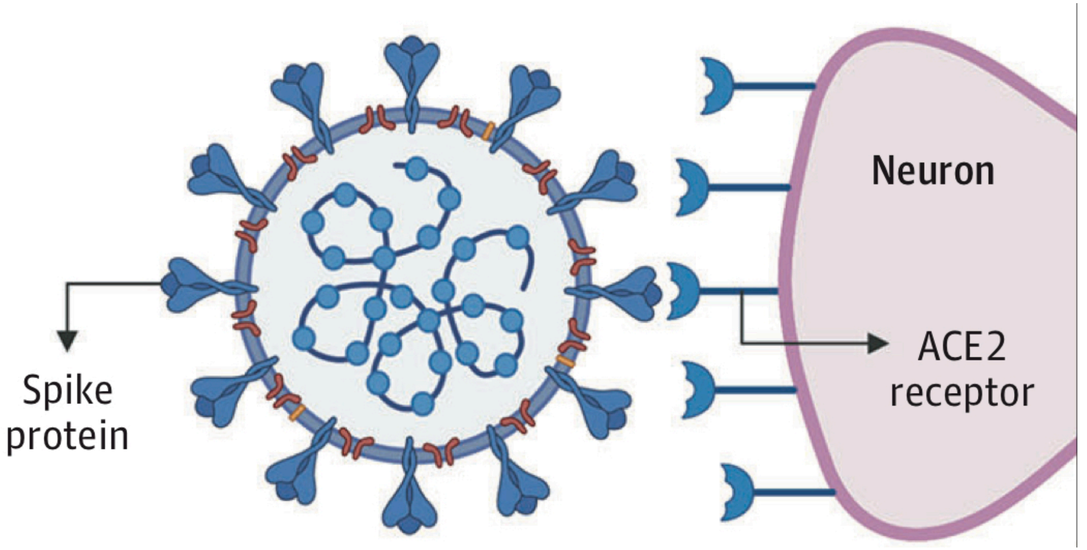


• JAMA Neurol. 2020;77(8):1018-1027. doi:10.1001/jamaneurol.2020.2065

• SARS-CoV-2

•Mechanism of Neuroinvasion

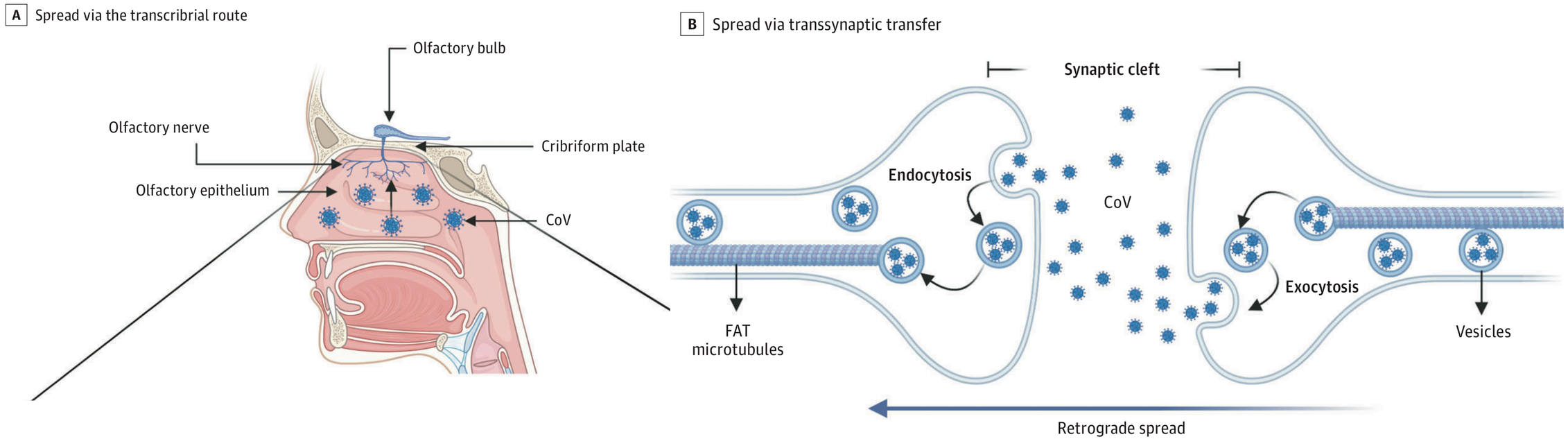
- Direct Invasion : Entry via olfactory nerve
- Transsynaptic Spread : Peripheral nerve terminals, Spread retrograde along nerve synapses and gain access to CNS
- Infection of vascular endothelium
- Leukocyte migration across the BBB



• JAMA Neurol. 2020;77(8):1018-1027. doi:10.1001/jamaneurol.2020.2065

• SARS-CoV-2

•Mechanism of Neuroinvasion

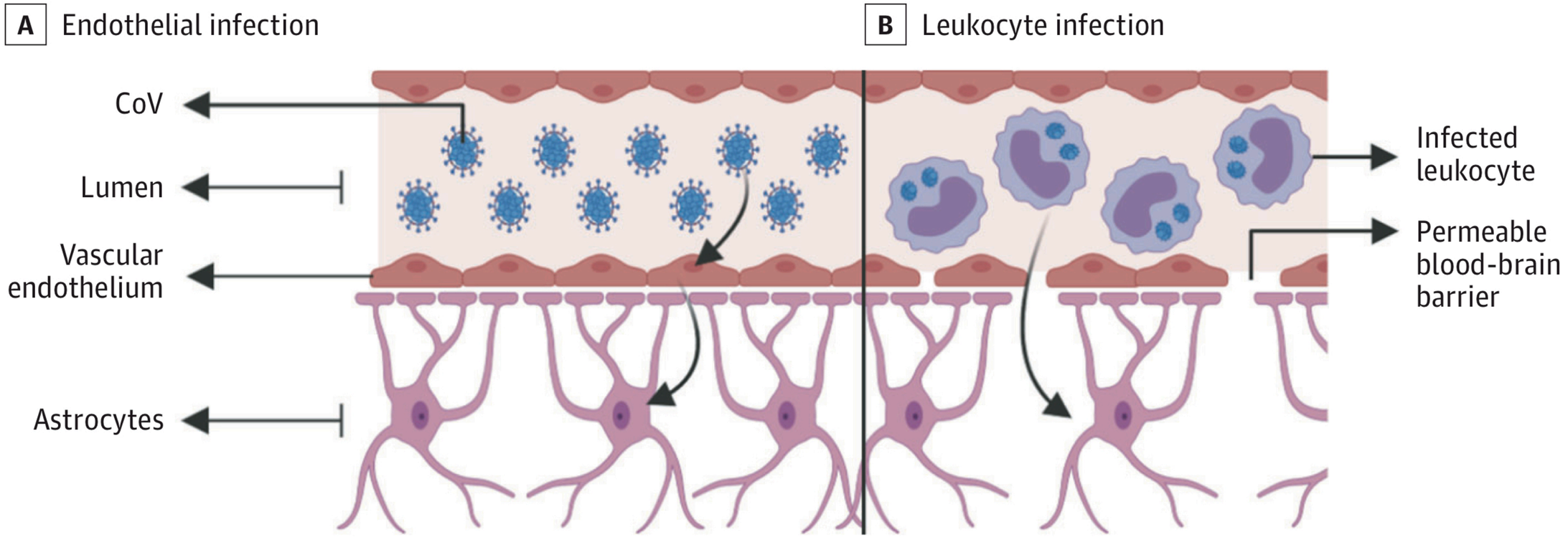


• JAMA Neurol. 2020;77(8):1018-1027. doi:10.1001/jamaneurol.2020.2065

• SARS-CoV-2

•Mechanism of Neuroinvasion

Figure 3. Mechanisms of Spread Across the Blood-Brain Barrier



• JAMA Neurol. 2020;77(8):1018-1027. doi:10.1001/jamaneurol.2020.2065

• SARS-CoV-2

•Pathophysiology

- Toxic-Metabolic encephalopathy : Severe infection , Cytokines Storm
- Hypoxic Brain Injury
- Direct viral invasion
- Post-Infectious process
  - Molecular mimicry
  - Autoreactive T cell > Autoimmune Encephalitis

• JAMA Neurol. 2020;77(8):1018-1027. doi:10.1001/jamaneurol.2020.2065

COVID-19 Meningitis and Encephalitis

- Viral meningitis/Encephalitis
- Acute necrotizing hemorrhagic encephalopathy
- Post infectious acute disseminated encephalomyelitis
- Post infectious brainstem encephalitis

Table 1. Clinical Characteristics of Patients With COVID-19

Characteristic	No. (%)			*P* value[a]
	Total (N = 214)	Severe (n = 88)	Nonsevere (n = 126)	
Onset of symptoms to hospital admission, median (range), d				
CNS				
Dizziness	1 (1-30)	1 (1-30)	1 (1-14)	NA
Headache	1 (1-14)	1 (1-3)	3 (1-14)	NA
Impaired consciousness	8 (1-25)	10 (1-25)	1 (1-3)	NA
Acute cerebrovascular disease	9 (1-18)	10 (1-18)	1 (1)	NA
Ataxia	2 (2)	2 (2)	NA	NA
Seizure	2 (2)	2 (2)	NA	NA
PNS				
Impairment				
Taste	2 (1-5)	3 (1-3)	2 (1-5)	NA
Smell	2 (1-5)	1 (1-4)	2 (1-5)	NA
Vision	2 (1-3)	3 (2-3)	1 (1)	NA
Nerve pain	1 (1-1)	1 (1-1)	1 (1)	NA
Skeletal muscle injury	1 (1-11)	1 (1-11)	1 (1-6)	NA

Table 1. Clinical Characteristics of Patients With COVID-19

Characteristic	No. (%) Total (N = 214)	Severe (n = 88)	Nonsevere (n = 126)	*P* value[a]
Age, mean (SD), y	52.7 (15.5)	58.2 (15.0)	48.9 (14.7)	
Age, y				
<50	90 (42.1)	24 (27.3)	66 (52.4)	<.001
≥50	124 (57.9)	64 (72.7)	60 (47.6)	
Sex				
Female	127 (59.3)	44 (50.0)	83 (65.9)	.02
Male	87 (40.7)	44 (50.0)	43 (34.1)	
Comorbidities				
Any	83 (38.8)	42 (47.7)	41 (32.5)	.03
Hypertension	51 (23.8)	32 (36.4)	19 (15.1)	<.001
Diabetes	30 (14.0)	15 (17.0)	15 (11.9)	.29
Cardiac or cerebrovascular disease	15 (7.0)	7 (8.0)	8 (6.3)	.65
Malignancy	13 (6.1)	5 (5.7)	8 (6.3)	.84
Chronic kidney disease	6 (2.8)	2 (2.3)	4 (3.2)	.69
Typical symptoms				
Fever	132 (61.7)	40 (45.5)	92 (73.0)	<.001
Cough	107 (50.0)	30 (34.1)	77 (61.1)	<.001
Anorexia	68 (31.8)	21 (23.9)	47 (37.3)	.04
Diarrhea	41 (19.2)	13 (14.8)	28 (22.2)	.17
Throat pain	31 (14.5)	10 (11.4)	21 (16.7)	.28
Abdominal pain	10 (4.7)	6 (6.8)	4 (3.2)	.21

- JAMA Neurol. 2020;77(6):683-690. doi:10.1001/jamaneurol.2020.1127

Table 1. Clinical Characteristics of Patients With COVID-19

Characteristic	No. (%) Total (N = 214)	Severe (n = 88)	Nonsevere (n = 126)	*P* value[a]
Nervous system symptoms				
Any	78 (36.4)	40 (45.5)	38 (30.2)	.02
CNS	53 (24.8)	27 (30.7)	26 (20.6)	.09
Dizziness	36 (16.8)	17 (19.3)	19 (15.1)	.42
Headache	28 (13.1)	15 (17.0)	13 (10.3)	.15
Impaired consciousness	16 (7.5)	13 (14.8)	3 (2.4)	<.001
Acute cerebrovascular disease	6 (2.8)	5 (5.7)	1 (0.8)	.03
Ataxia	1 (0.5)	1 (1.1)	0	NA
Seizure	1 (0.5)	1 (1.1)	0	NA
PNS	19 (8.9)	7 (8.0)	12 (9.5)	.69
Impairment				
Taste	12 (5.6)	3 (3.4)	9 (7.1)	.24
Smell	11 (5.1)	3 (3.4)	8 (6.3)	.34
Vision	3 (1.4)	2 (2.3)	1 (0.8)	.37
Nerve pain	5 (2.3)	4 (4.5)	1 (0.8)	.07

- JAMA Neurol. 2020;77(6):683-690. doi:10.1001/jamaneurol.2020.1127

Case Report

A first case of meningitis/encephalitis associated with SARS-Coronavirus-2

Takeshi Moriguchi[a,*], Norikazu Harii[b], Junko Goto[a], Daiki Harada[a], Hisanori Sugawara[a], Junichi Takamino[a], Masateru Ueno[a], Hiroki Sakata[a], Kengo Kondo[a], Natsuhiko Myose[a], Atsuhito Nakao[c], Masayuki Takeda[d], Hirotaka Haro[e], Osamu Inoue[f], Katsue Suzuki-Inoue[g], Kayo Kubokawa[h], Shinji Ogihara[i], Tomoyuki Sasaki[g],

- A-24-year-old man
- Headache, generalized fatigue and fever (D1)
- Laninamivir and antipyretic agents under the diagnosis of influenza (D2)
- Three days later (D5), he visited another clinic because of the worsening of his previous symptoms, headache, and sore throat.
- Day 9, he was found lying on the floor with consciousness disturbance.

- At hospital, he had a Glasgow coma scale (GCS) of 6 (E4 V1 M1) with hemodynamically stability.
- He had obvious neck stiffness.
- Blood investigation showed an increased white cell, neutrophil dominant, relatively decreased lymphocytes, increased C-reactive protein.
- CT demonstrating no evidence of brain edema.
- Chest CT : showed that there was small ground glass opacity on the right superior lobe and both sides of the inferior lobe.

• International Journal of Infectious Disease 94(2020) 55-58

• Meningitis/encephalitis

•associated with SARS-Coronavirus-2

- Lumbar puncture examination, clear and colorless
  - the initial pressure was greater than 320 mmH2O.
  - The CSF cell count 12 mononuclear , 2 PMN without red blood cells.
  - RT-PCR test
    - SARS- CoV-2 RNA was not detected in the nasopharyngeal swab
    - SARS- CoV-2 RNA was detected in CSF

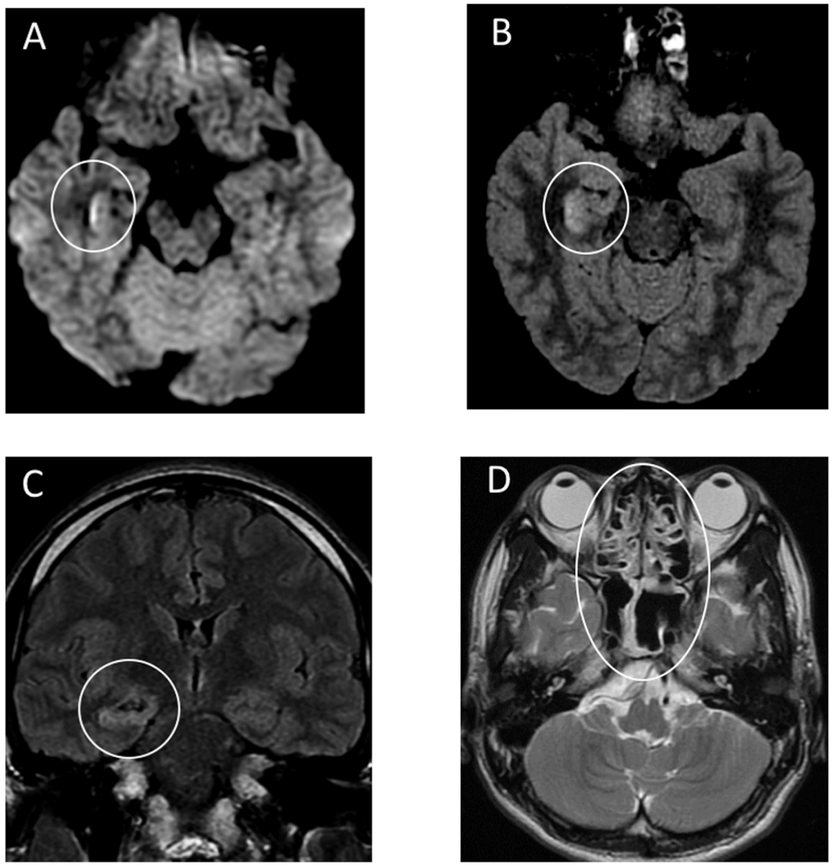


Figure 1. Brain MRI performed 20 hours after admission.
A: Diffusion weighted images (DWI) showed hyperintensity along the wall of inferior horn of right lateral ventricle.
B,C: Fluid-attenuated inversion recovery (FLAIR) images showed hyperintense signal changes in the right mesial temporal lobe and hippocampus with slight hippocampal atrophy. These findings indicated right lateral ventriculitis and encephalitis mainly on right mesial lobe and hippocampus.
D: T2-weighted image showed pan-paranasal sinusitis.

- International Journal of Infectious Disease 94(2020) 55-58

• Encephalitis

- Prodome : Myalgia, Headache, Fever, Sore throat, Cough
- Neurological : Neck stiffness, Drowsiness, Seizure
- CSF
  - Usually aseptic meningitis
  - Normal CSF glucose level
  - Mild Elevate Protein

- **MRI**
- Leptomeningeal Enhancement
- Mesial temporal encephalitis
- Ventriculitis

• International Journal of Infectious Disease 94(2020) 55-58

- Thank you