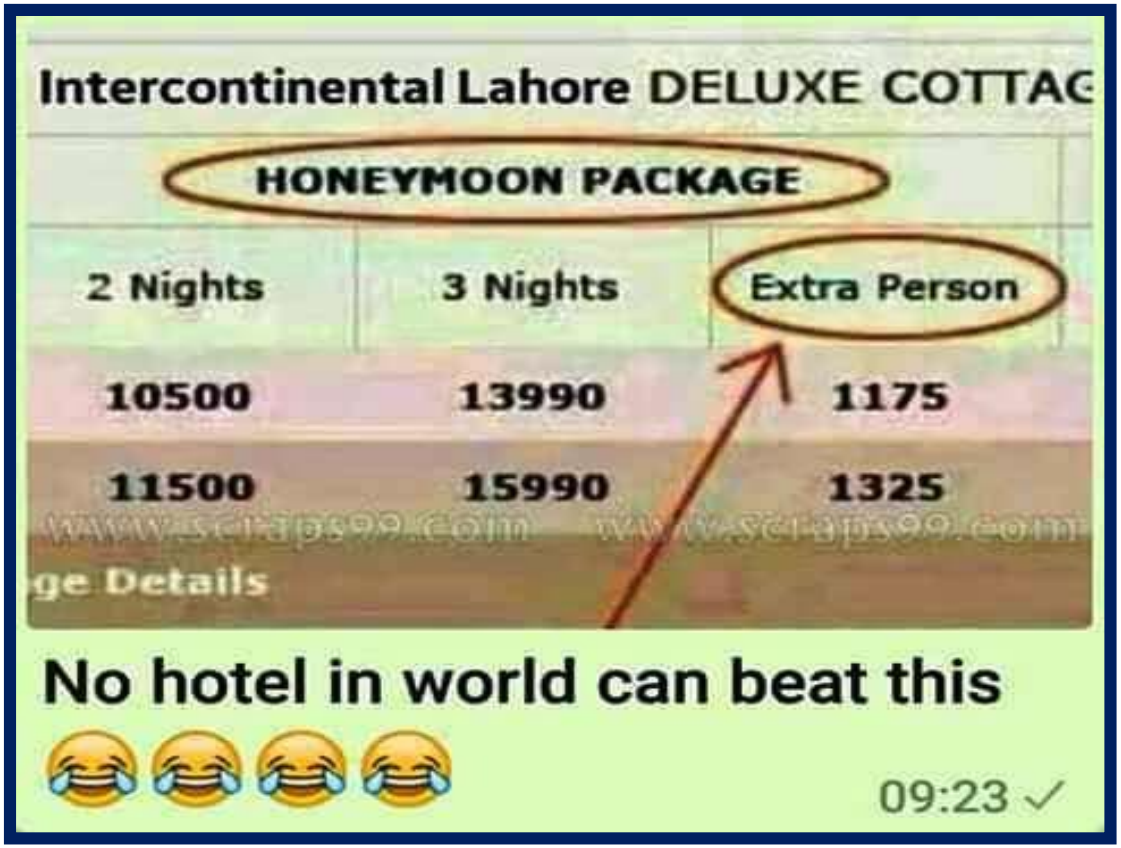
Approach to fever with altered sensorium

Dr P Senthur Nambi



Overview

- Definition of terms
- Differential diagnosis
- Points from history/epidemiology
- Investigations
- Specific management

Definitions

ENCEPHALOPATHY

- Diffuse disturbance of brain function without inflammation

ENCEPHALITIS

- Dysfunction of brain associated with inflammation

FEBRILE ENCEPHALOPATHY

- a/c onset of fever (<1wk) + alteration of consciousness >12 hrs

Acute Encephalitis Syndrome

Defined as a person of age > 1 month, at any time of year with

- acute onset of fever
- **change in mental status (confusion, disorientation, coma)**

AND/OR

- new onset of seizures (excluding simple febrile seizures)

which lasts for >24 hours with no other identifiable cause

Encephalitis = inflammation of the brain

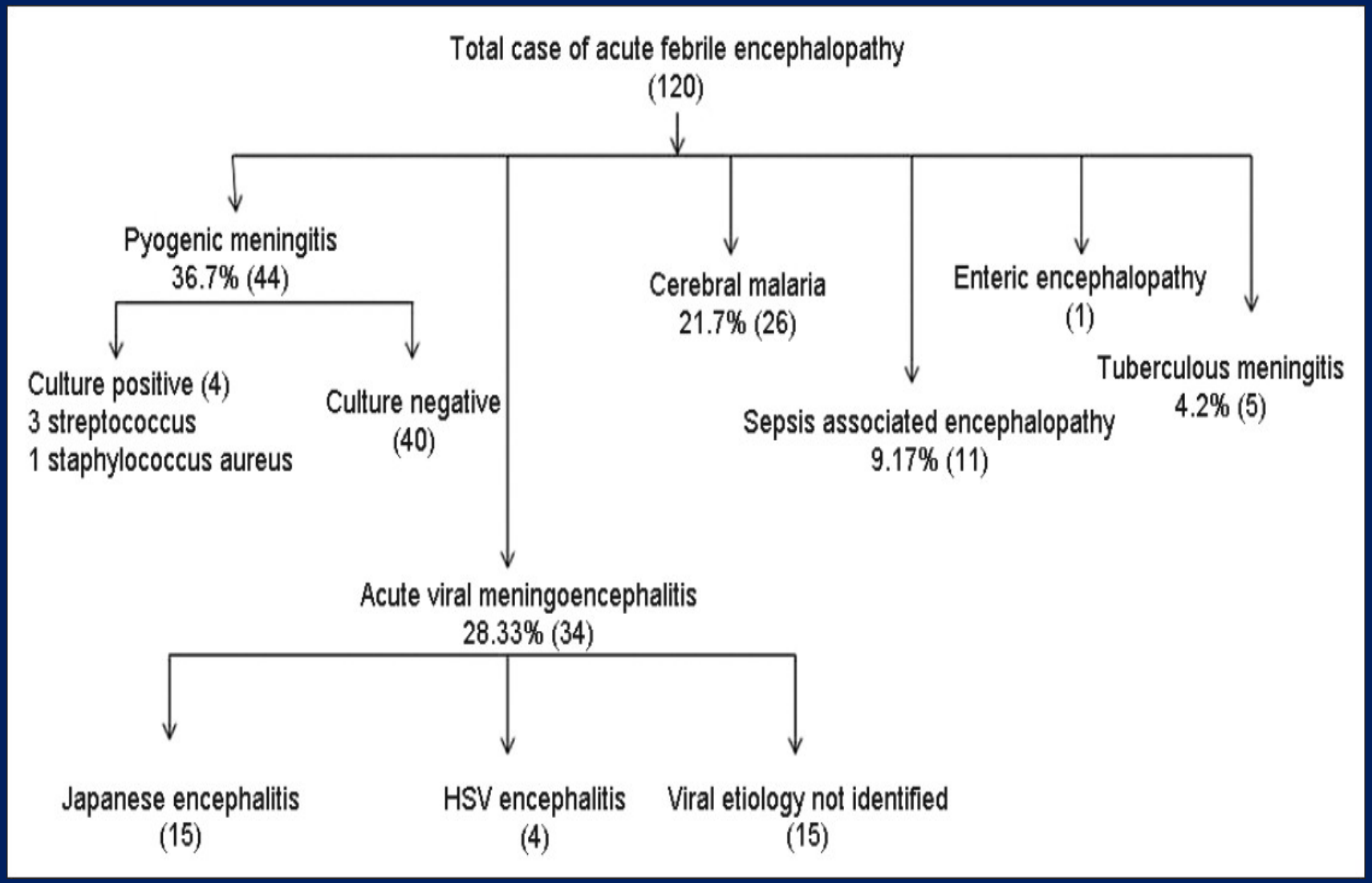
Encephalitis + meningitis : meningoencephalitis

Infectious causes

- Viral
- Bacterial
- Fungal
- Parasitic

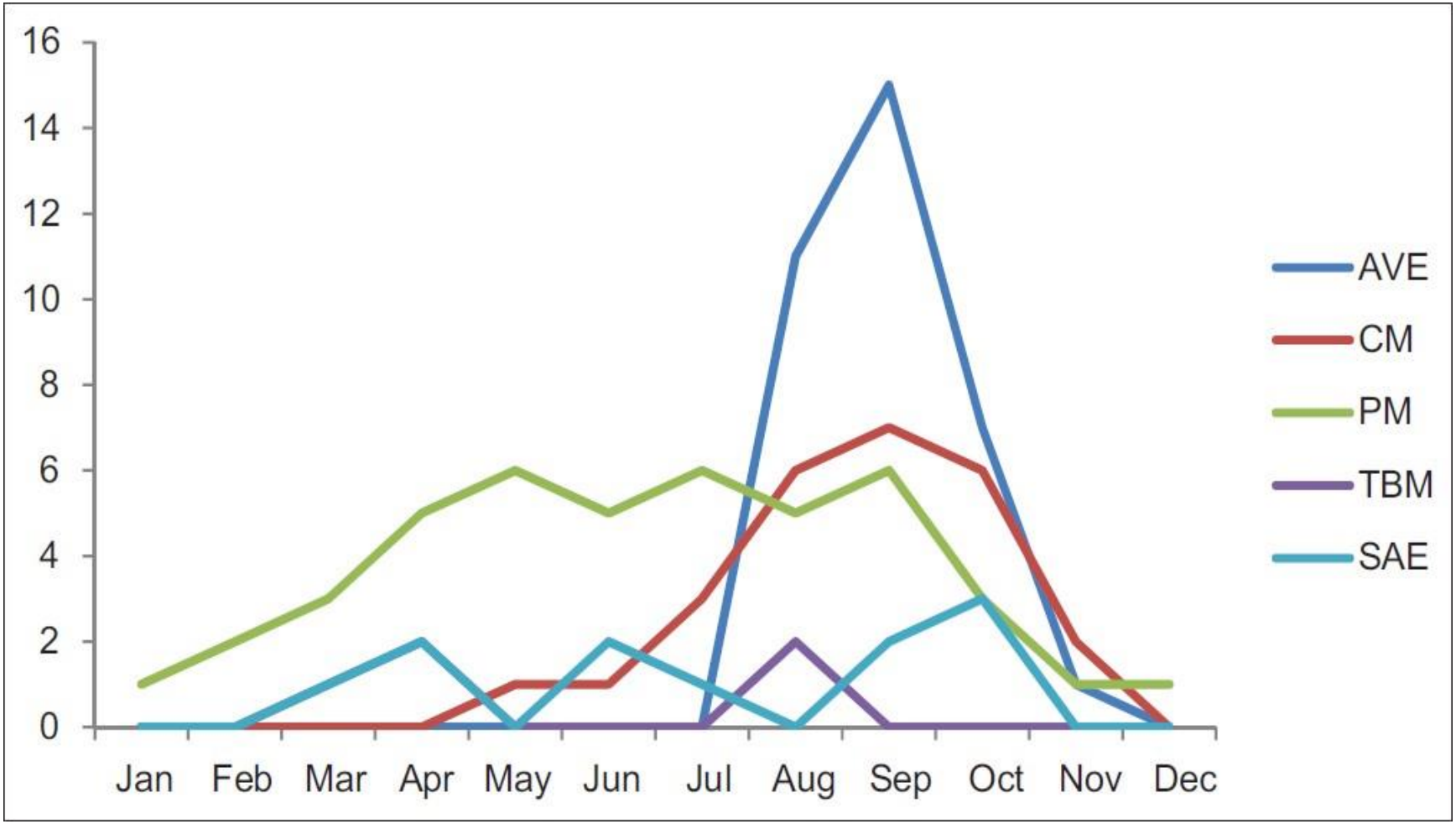
Non infectious cause

- ADEM
- Auto-immune encephalitis
- Other eg multiple sclerosis



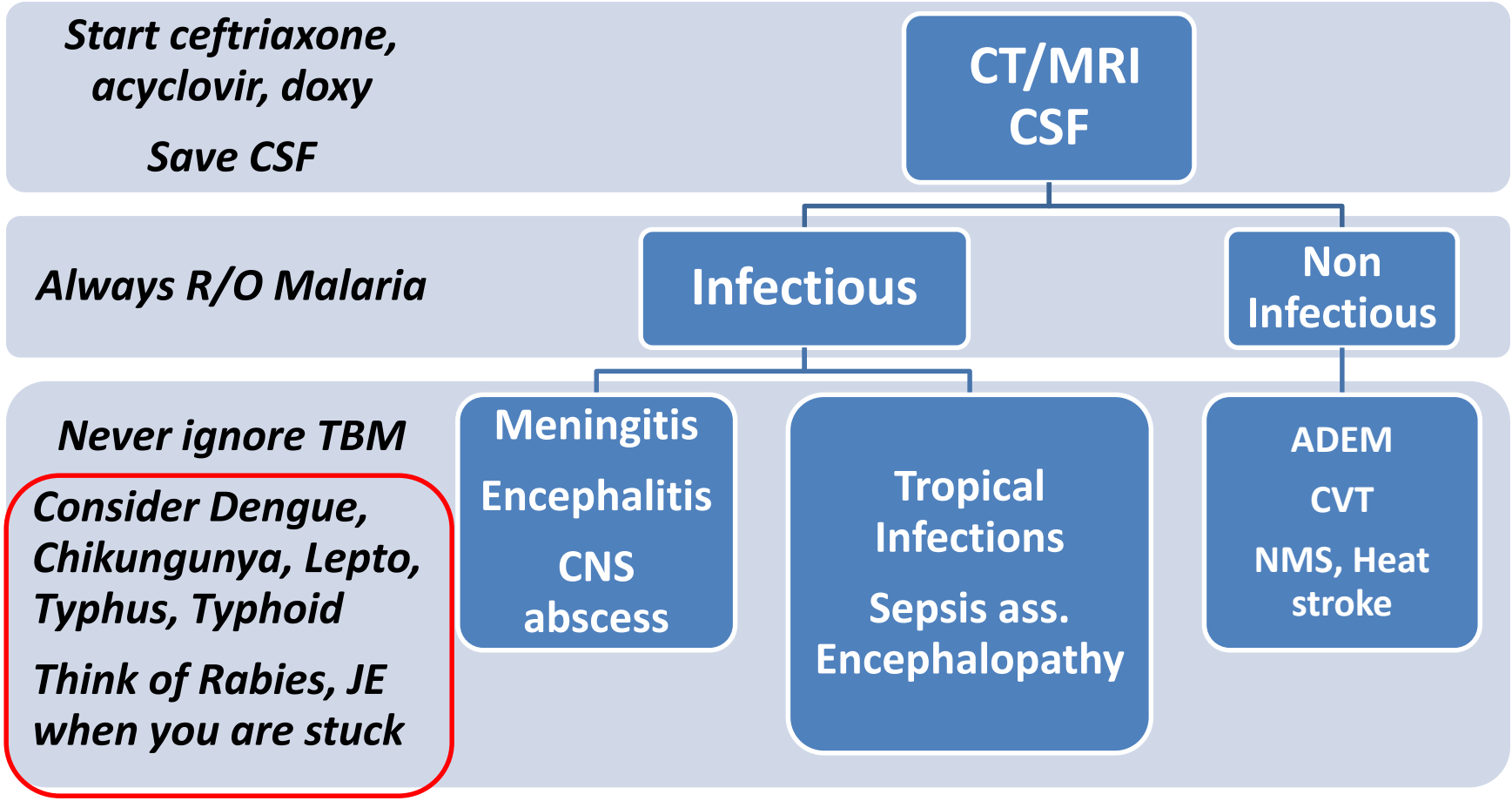
Modi A, Atam V, Jain N, Gutch M, Verma R. The etiological diagnosis and outcome in patients of acute febrile encephalopathy: A prospective observational study at tertiary care center. Neurol India 2012;60:168-73

Post monsoon effect..



Neurology India, April 2012

Fever with altered sensorium



History

Fever with rash	• Maculopapular • Vesicles • Herpes labialis • Petechiae/purpura • Eschar
Respiratory symptoms	• Influenza, Mycoplasma
Diarrhoea, vomiting	• Enteroviruses • Polio
Myalgia, arthralgia	• Dengue • Leptospirosis
Parotitis	• Mumps • EB virus • HIV

History

Season	Post monsoon - JE, Dengue
Travel	JE, Nipah
Family illness	Entero virus, TB
Exposure	Dog bite - Rabies Vaccine - ADEM Mosquito - JE, dengue
Immunocompromised	Cryptococcus, TB
Unpasteurised dairy product	Brucella

Clinical pointers

Skin rash	Dengue, Measles
Herpangina	Coxsackie
Purpura	Dengue, Chikungunya, Sepsis
Jaundice	Dengue, Malaria, Lepto, Sepsis
Hypotension	Dengue, Sepsis
Others	Neck stiffness, LN, Fundus

Non-infectious causes of fever

Over production of heat

- Neuroleptic malignant syndrome
- Malignant hyperthermia
- Drugs- cocaine, salicylate
- Thyrotoxic encephalopathy
- Convulsive status epilepticus
- Catatonic schizophrenia

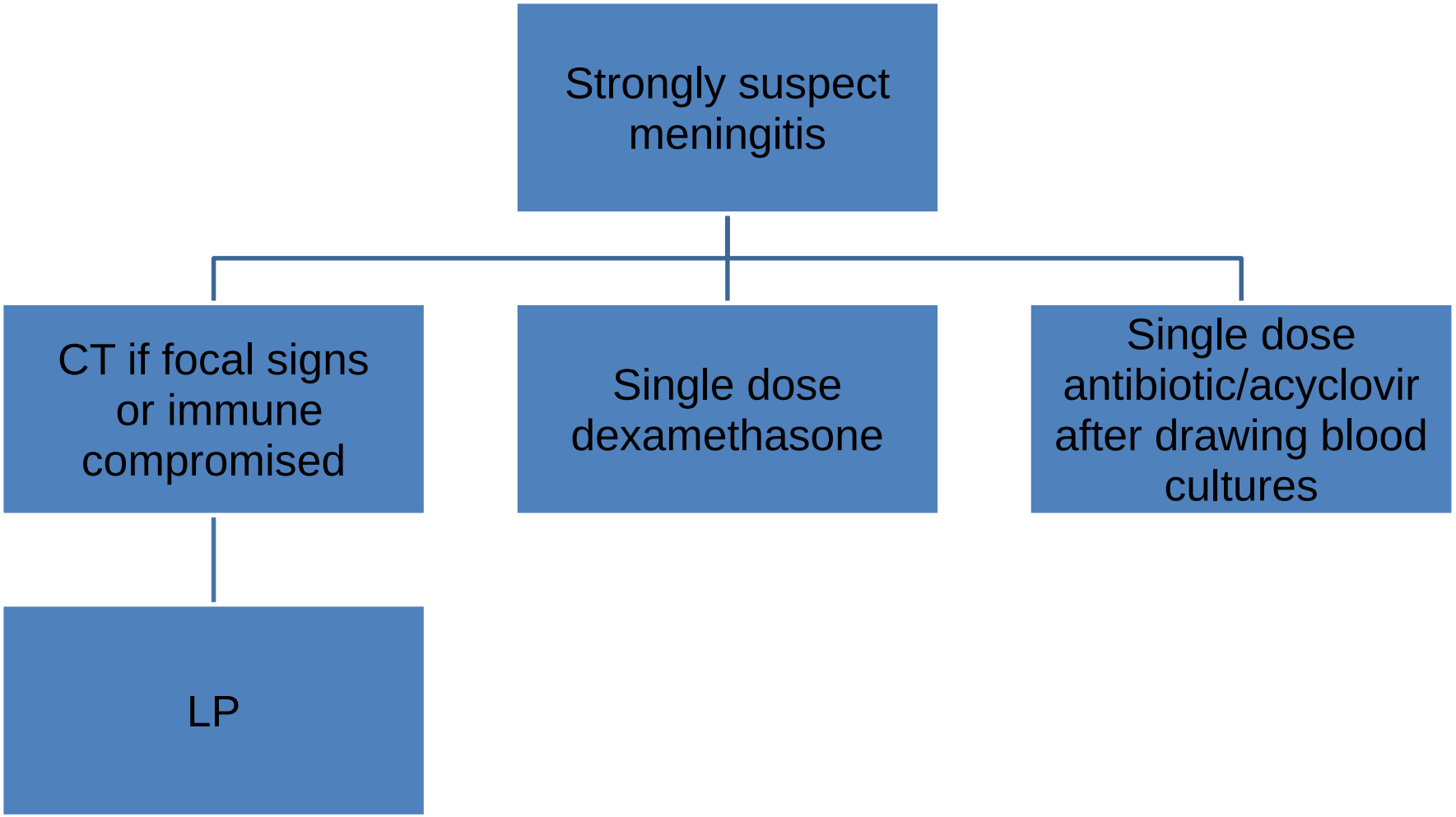
Impaired heat dissipation

- Anticholinergic toxicity e.g. amitryptiline
- Heat stroke

Investigations

- BLOOD INVESTIGATIONS
  - Complete blood count and peripheral smear
    - Relative lymphocytosis in viral meningitis
    - Leucopenia & thrombocytopenia – in rickettsial inf & viral haemorrhagic fevers
    - Malaria
  - Blood culture
  - Blood biochemistry, sugar

Initial approach to fever with altered sensorium



Recommended criteria for adult patients with suspected bacterial meningitis who should undergo CT prior to lumbar puncture

Criterion	Comment
Immunocompromised state	HIV infection or AIDS, receiving immunosuppressive therapy, or after transplantation
History of CNS disease	Mass lesion, stroke, or focal infection
New onset seizure	Within 1 week of presentation; some authorities would not perform a lumbar puncture on patients with prolonged seizures or would delay lumbar puncture for 30 min in patients with short, convulsive seizures
Papilledema	Presence of venous pulsations suggests absence of increased intracranial pressure
Abnormal level of consciousness	...
Focal neurologic deficit	Including dilated nonreactive pupil, abnormalities of ocular motility, abnormal visual fields, gaze palsy, arm or leg drift

Allan R. Tunkel et al. Clin Infect Dis. 2004;39:1267-1284

Lumbar Puncture

Tube Number	Volume Required
1 (biochemistry)	0.5ml (10 drops)
2 (cytology)	1 ml (20 drops) (6 ml for flow cytometry)
3 (microbiology)	10ml (full tube)

- Gram stain & culture
- AFB stain & culture, Gene Xpert MTB-rif
- Special staining
- Viral PCR- HSV, VZV
- Save sample!

CSF analysis

- False positive elevations of CSF WBC: traumatic lumbar puncture, intracerebral or subarachnoid hemorrhage
- Seizures: CSF pleocytosis (neutrophilic), < 80/mm
- Traumatic lumbar puncture: CSF protein concentration determined by subtracting 1 mg/dL of protein for every 1000 RBC
- CSF may be stored at +4°C if delays in processing for virus culture or viral PCR will be less than 24 hrs
- If greater delays are likely, CSF should be frozen at -80°C

BACTERIAL MENINGITIS	• PMN • High protein, low sugar, gram stain
ASEPTIC MENINGITIS	• Few lymphocytes • Normal protein • Normal sugar
VIRAL ENCEPHALITIS	• lymphocytic • Normal sugar, normal to slightly raised protein
TUBERCULOUS MENINGITIS	• Lymphocytic • High protein, low sugar

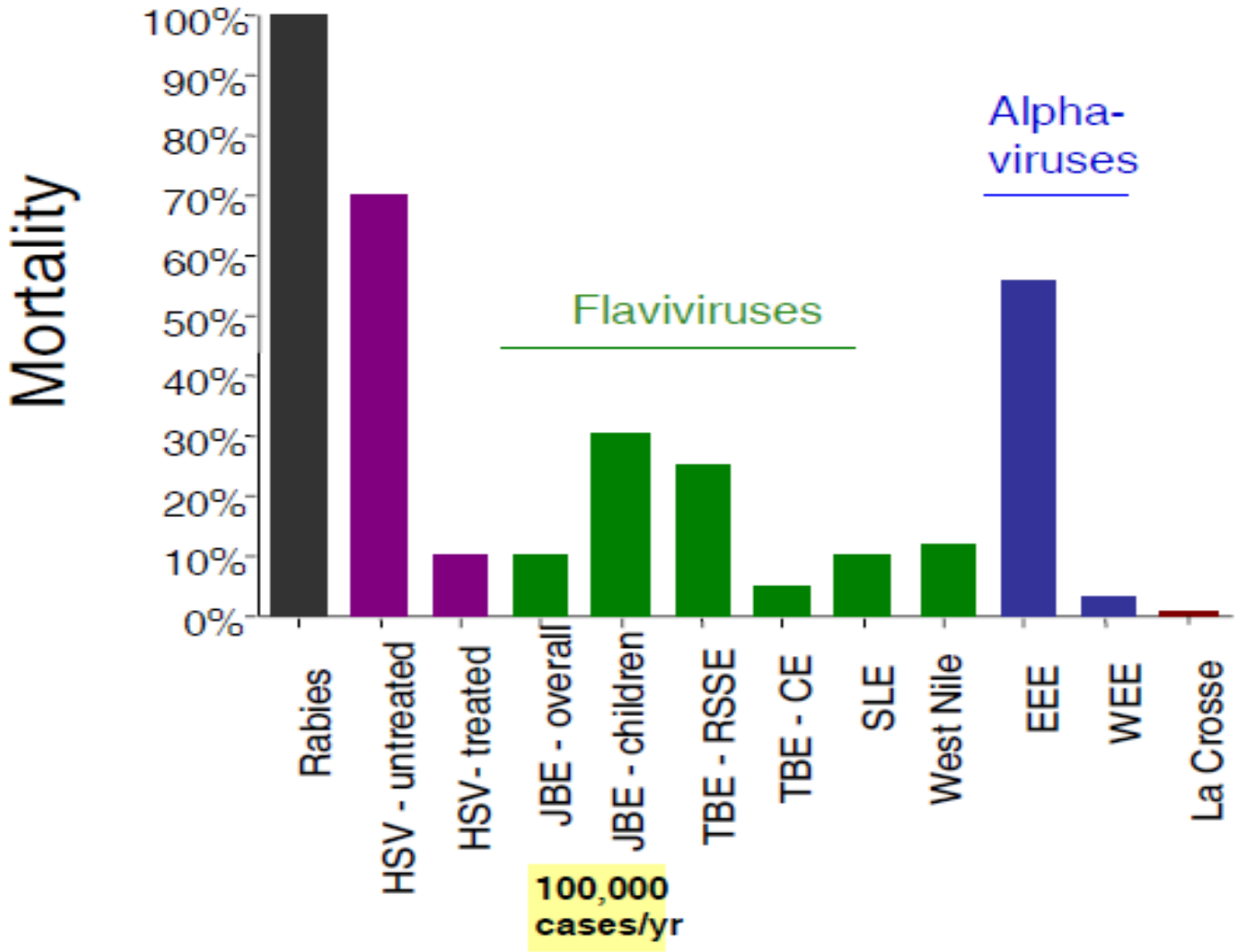
Encephalitis (Viral)

- Arbo viruses (50% in epidemics)
- HSV

- Entero virus
- VZV

- EBV
- CMV
- Rabies

Encephalitis mortality



Arbovirus encephalitis in India

Flaviviridae

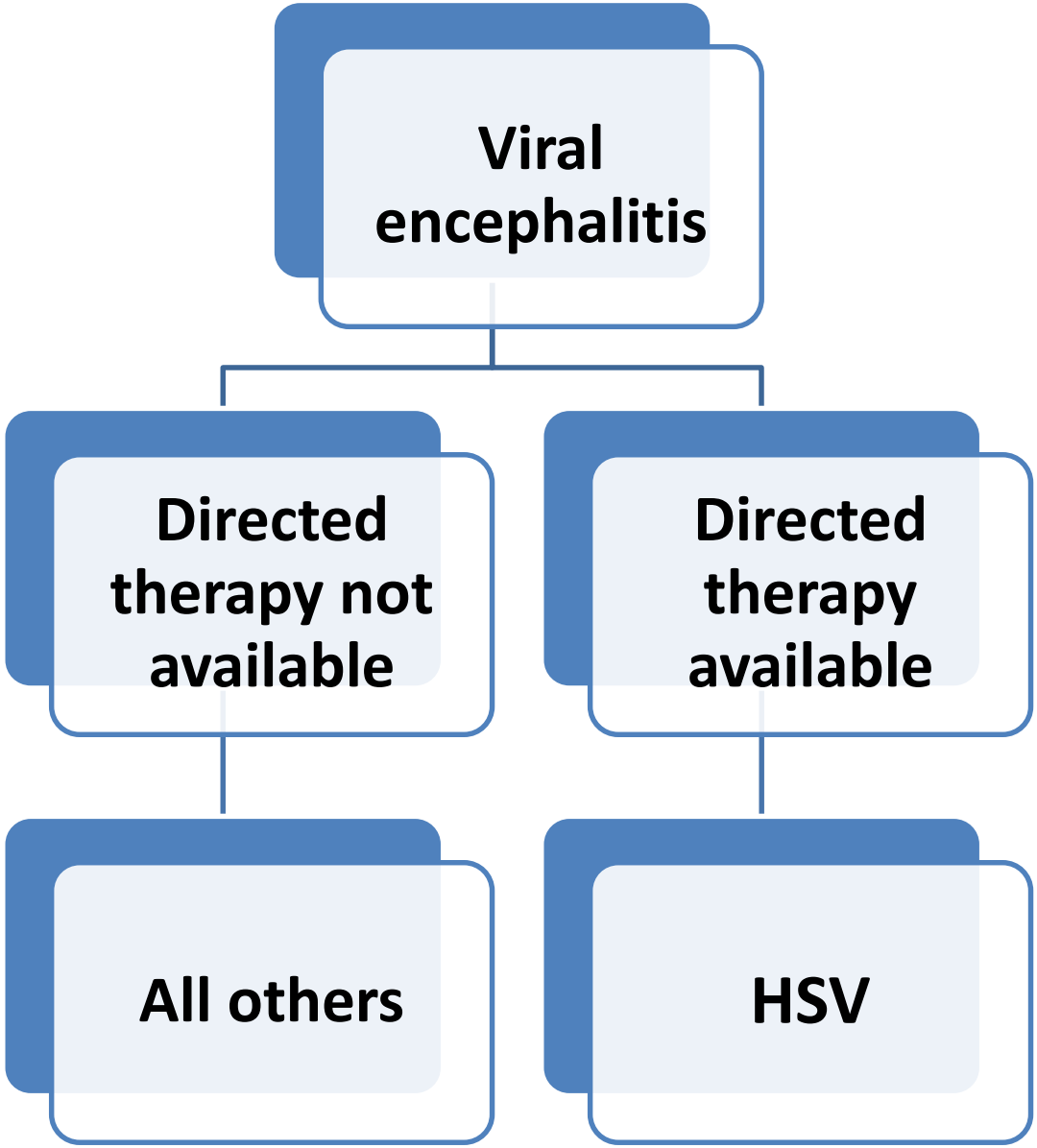
- Japanese Encephalitis virus
- West Nile virus
- Dengue

Togaviridae (Alphavirus)

- Chikungunya

Rhabdoviridae

- Chandhipura virus


Viral encephalitis
Directed therapy not available
Directed therapy available
All others
HSV

Neuroimaging

- CT is less sensitive than MRI & is normal in upto 33% of patients

- Characteristic neuroimaging changes:
  - ✓ Fronto temporal changes in HSV
  - ✓ Thalamic & midbrain changes in Japanese encephalitis
  - ✓ Basal exudates after contrast in TB Meningitis
  - ✓ Basal ganglia ring enhancing lesion in Toxoplasmosis
  - ✓ Multiple ring enhancing lesions in tuberculoma

Lab diagnosis of viral encephalitis

- CSF cultures in encephalitis: disappointing

  Negative in >95% of cases of HSV-1 encephalitis

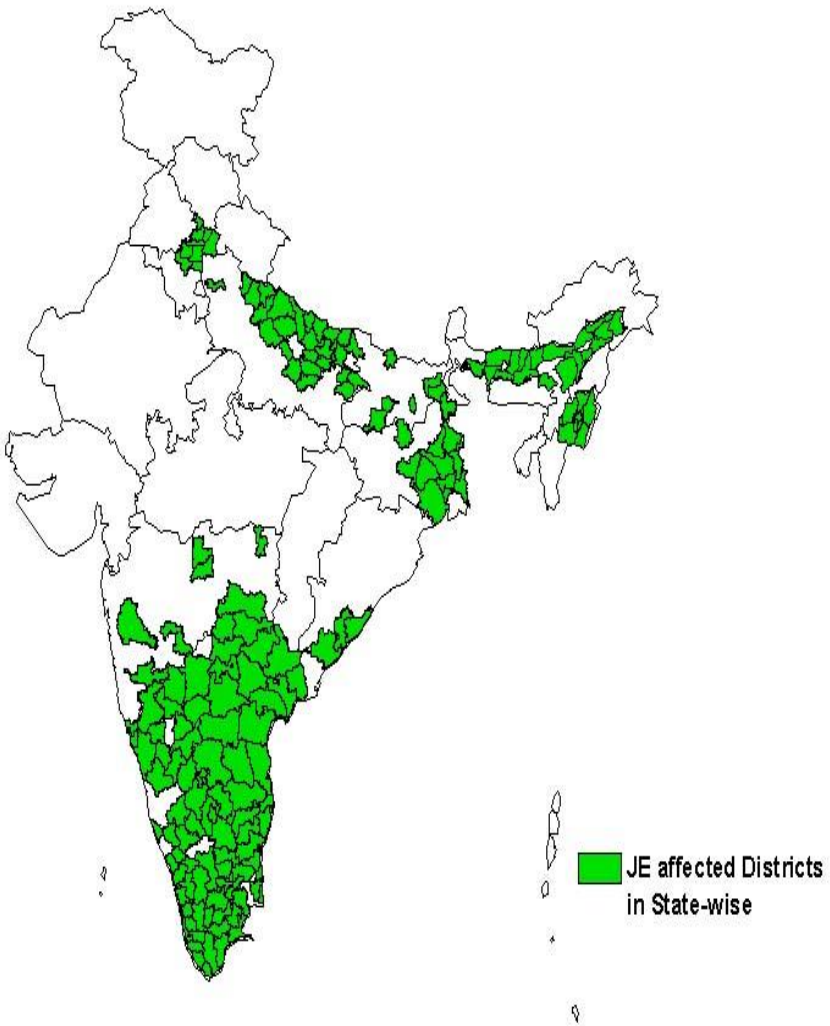
- Serum antibody determination is less useful for viruses with high seroprevalence rates (HSV, VZV, CMV, EBV)

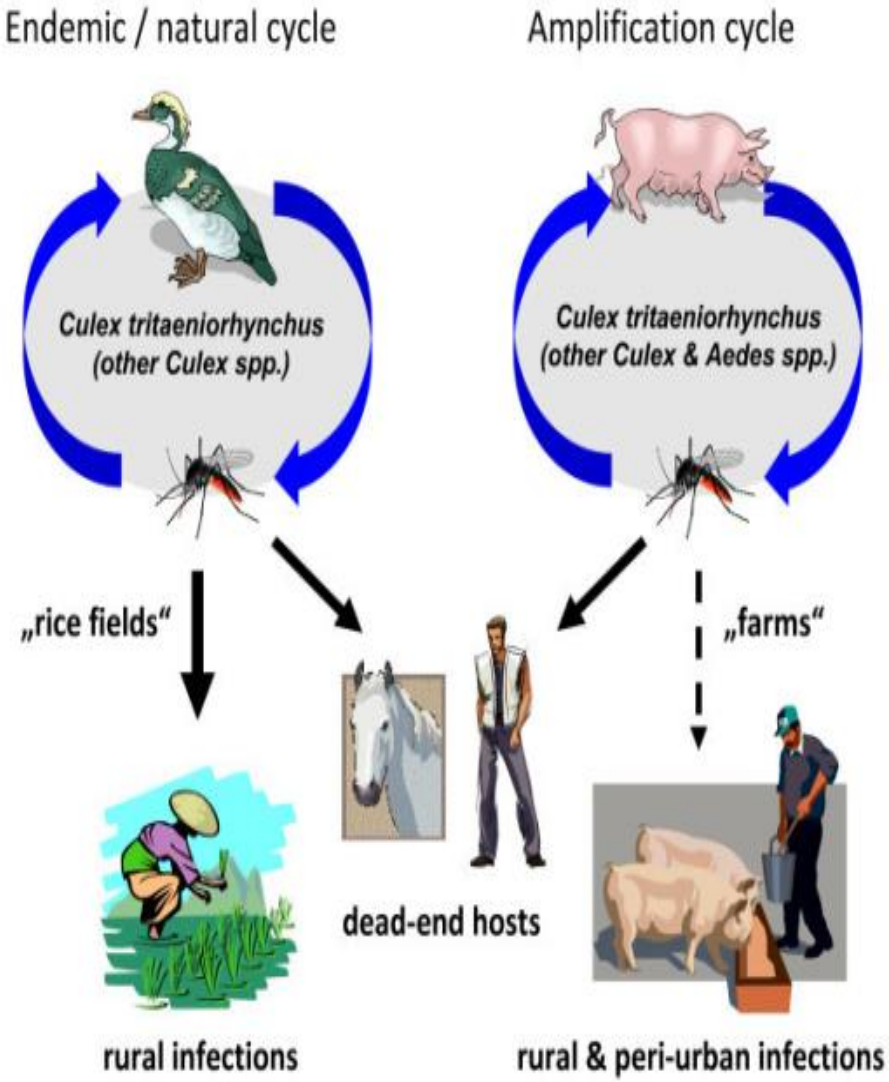
- CSF serology is more useful than serum serology alone

- JE - CSF IgM ELISA
- WNV IgM antibodies is diagnostic of WNV encephalitis
- Dengue - Serum/CSF IgM ELISA

  Highest positivity in 2nd week
- HSV - CSF PCR initial stage (96% sensitivity & 99% specificity)

JE in India


JE affected Districts
in State-wise


Endemic / natural cycle
Amplification cycle
Culex tritaeniorhynchus
(other Culex spp.)
Culex tritaeniorhynchus
(other Culex & Aedes spp.)
„rice fields“
„farms“
dead-end hosts
rural infections
rural & peri-urban infections

WNV in India!!

- Antibodies against WNV - first detected in humans in Bombay in 1952

- Virus activity has been reported in southern, central, and western India

- WNV has been isolated from

  Culex vishnui - Andhra Pradesh, Tamil Nadu

  Culex quinquefasciatus - Maharashtra

- WNV isolated from humans in Karnataka State

J Med Sci. 1952;6:733–46; IndianJ Med Res. 2003;118:101–8.; Indian J Med Res.1987;86:131–4.

West Nile Virus: Recent outbreaks

WNV in Kerala

- May - July 2011 in Kerala, India
- 208 AES cases
- 4 deaths
- 33% - children
- 67 % - adults

Genome Announc. 2013 May-Jun; 1(3)

WNV in Assam

Table. Incidence of JEV and WNV infections among patients with acute encephalitis syndrome, Assam, India*

District	No. with acute encephalitis syndrome	No. positive/no. tested	
		JEV	WNV
Dhemaji	1	0/1	0/0
Dibrugarh	29	9/29	6/29
Golaghat	81	47/81	2/18
Jorhat	15	8/15	0/15
Lakhimpur	6	5/6	0/6
Sivasagar	30	9/30	2/30
Tinsukia	5	2/5	2/5
Total	167	80/167	12/103†

*JEV, Japanese encephalitis virus; WNV, West Nile virus.
†One person was not included because the address could not be verified.

Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 17, No. 5, May 2011

Therapy in acute bacterial meningitis

- S. pneumoniae
- Neisseriae meningitidis
- Haemophilus influenzae

- Listeria if age>65 , pregnancy immunocompromised

- Initial empiric therapy
  - Ceftriaxone
  - Ampicillin if immune compromised or >65
  - Acyclovir if HSV suspected

- After cell count & Gram stain
  - Stop acyclovir

- After culture
  - As per sensitivities
  - Ask for MIC if pneumococcus grown

Other treatment

- Doxycycline 100mg BD
- Dexamethasone
  - 0.15 mg/kg q6h for 2–4 days with the first dose administered
  - 10–20 min before, or at least concomitant with the first dose of antibiotic
  - adults with suspected or proven pneumococcal meningitis

CSF Penetration of antibiotics

Excellent

- Metronidazole
- Rifampicin
- Chloramphenicol
- Fluoroquinolone
- Cotrimoxazole
- Linezolid

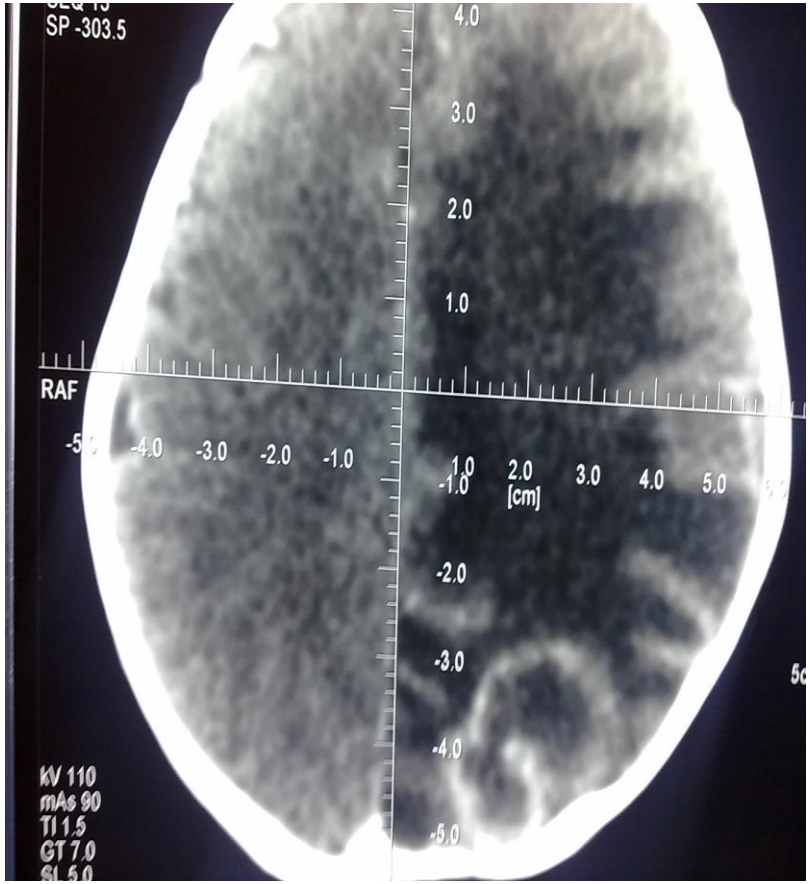
Poor

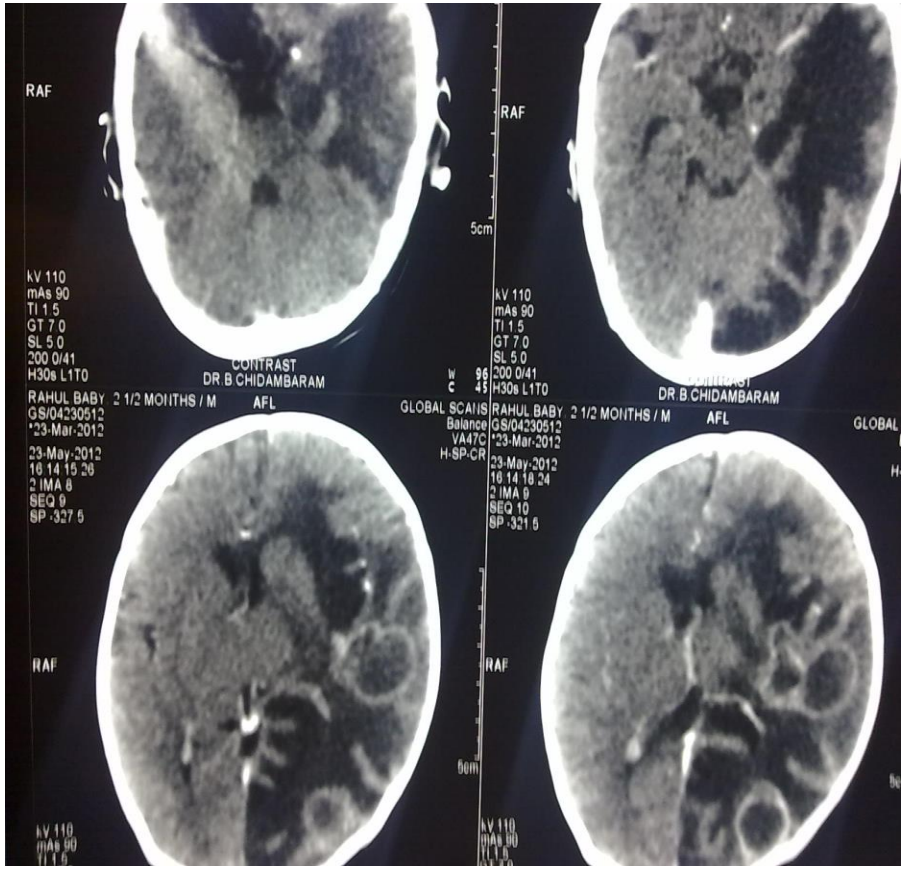
- Macrolides
- Aminoglycosides
- Clindamycin

Good with inflammed meninges

- Beta lactams
- Vancomycin

H/O fever with seizures, altered sensorium ..





Predisposing Conditions & Microbiology of Brain Abscess

Predisposing Condition	**Usual Microbial Isolates**
Otitis media or mastoiditis	Streptococci, *Bacteroides*, *Prevotella* *Enterobacteriaceae*
Sinusitis (frontoethmoid or sphenoid)	Streptococci, *Bacteroides* spp Enterobacteriaceae, *Staph. aureus, Haemophilus* spp.
Dental sepsis	*Fusobacterium, Prevotella* and *Bacteroides* spp., streptococci
Penetrating trauma or postneurosurgical	*S. aureus,* streptococci, Enterobacteriaceae, *Clostridium* spp.

TABLE 88-3 Empirical Antimicrobial Therapy for Bacterial Brain Abscess

Predisposing Condition	*Antimicrobial Regimen*
Otitis media or mastoiditis	Metronidazole + third-generation cephalosporin*
Sinusitis (frontoethmoid or sphenoid)	Metronidazole + third-generation cephalosporin*†
Dental infection	Penicillin + metronidazole
Penetrating trauma or postneurosurgical	Vancomycin + third-generation cephalosporin*‡
Lung abscess, empyema, bronchiectasis	Penicillin + metronidazole + sulfonamide§
Bacterial endocarditis	Vancomycin + gentamicin
Congenital heart disease	Third-generation cephalosporin*
Unknown	Vancomycin + metronidazole + third-generation cephalosporin*‡

Sepsis associated encephalopathy

- Poorly understood CNS condition
- Manifests as lethargy, delirium
- Pathogenesis
  - bacterial invasion of brain
  - endotoxins
  - derangement of neurotransmitters
  - microvascular changes

Is Your Patient Encephalopathic Because of His or Her Antibiotic Therapy?

CID, Feb 2016

- Delusions/hallucinations - macrolides/quinolones/procaine penicillin
- Myoclonus & seizures (54% nonconvulsive) - penicillin or cephalosporins
- Cerebellar findings - metronidazole
- Language alteration (aphasia) - cefipime

Thanks..