INFEZIONI SNC

SAPIENZA
UNIVERSITÀ DI ROMA

Claudio M. Mastroianni

Infezioni SNC

- Meningiti
- Nevrassiti o encefaliti
- Ascesso cerebrale
- Encefalopatia trasmissibile spongiforme (prioni)

Central nervous system infections

- Despite advances in antimicrobial and antiviral therapy, **meningitis and brain abscess** are infections that result in significant morbidity and mortality

- A multidisciplinary approach, including intensive care, is often required in the treatment of these infections

MENINGITE

Infiammazione delle meningi in risposta a microrganismi con caratteristiche alterazioni del LIQUIDO CEFALO-RACHIDIANO.

ASCESSO CEREBRALE

Focale infezione suppurativa localizzata del parenchima cerebrale, circondata da una capsula vascolarizzata e causata comunemente da patogeni come batteri, funghi o parassiti.

Meningiti batteriche

- **Acquisite in comunità**
  - 3-6 casi /100.000 anno (più elevata in bambini e adolescenti)

- **Nosocomiali**
  - 1- 6% tra i pazienti “neurochirurgici”

MENINGITI BATTERICHE

ACQUISITE IN COMUNITA'

- *S. pneumoniae* (47-51% casi)
- *N. meningitidis* (25-37% casi)
- *L. monocytogenes* (4-8% casi)
- Altri patogeni

INFEZIONI NOSOCOMIALI

Coinvolti microbi diversi in relazione alla causa scatenante (conseguono soprattutto a procedure invasive, traumi cranici complicati, batteriemie).

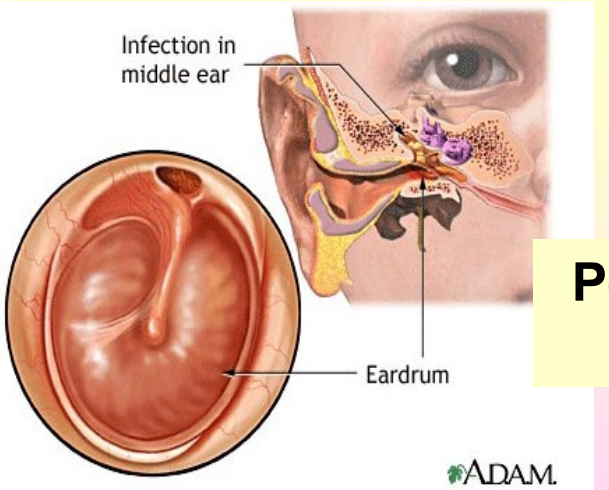
MENINGITI BATTERICHE ACQUISITE IN COMUNITA'

STREPTOCOCCUS PNEUMONIAE

E' la causa più comune di meningite batterica negli adulti.

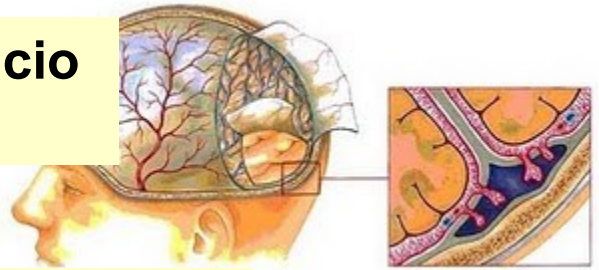
Estensione diretta dell'infezione dai seni paranasali o dall'orecchio medio

Localizzazione batteriemica a livello dell'endotelio meningeo o del plesso corioideo



MENINGI

Peptidoglicano stimola rilascio di citochine (IL-8,MIP-1)



Ipertensione endocranica, edema e ipoperfusione cerebrale, che determinano segni meningei, obnubilamento o coma

MENINGITI BATTERICHE

STREPTOCOCCUS PNEUMONIAE

- Crescono in catenelle
- Cocchi Gram positivi
- Catalasi negativi
- Causano α-emolisi su agar sangue

FATTORI FAVORENTI L'INFEZIONE PNEUMOCOCCICA

- Infezioni respiratorie, infiammazione, influenza
- Inquinamento dell'aria
- Allergie
- Fumo di sigaretta
- BPCO
- Interruzione anatomica delle meningi (lesioni della dura)
- Deficit della formazione di anticorpi
- Mieloma multiplo
- Leucemia linfatica cronica, linfomi
- Deficit del complemento
- Asplenia
- Anemia falciforme
- Infanzia e vecchiaia
- Diabete mellito
- Alcolismo
- Malnutrizione
- Cirrosi epatica
- Insufficienza renale
- Infezione da HIV

MENINGITI BATTERICHE

NEISSERIA MENINGITIDIS

EPIDEMIOLOGIA

L'infezione da N. *meningitidis* è ubiquitaria.

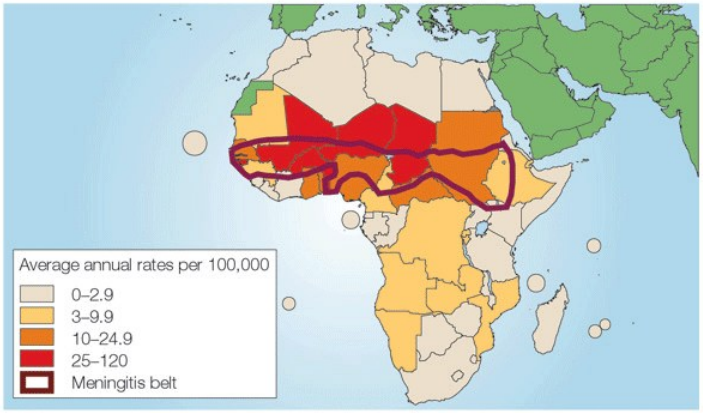
- **CASI SPORADICI**
- **PICCOLI FOCOLAI EPIDEMICI IN ISTITUTI O COMUNITA'**
- **ESTESE EPIDEMIE**

Incidenza: 1-2 casi/100000 all'anno (forme sporadiche)

5-10 casi/100000 all'anno (forme ipersporadiche)

10-1000 casi/100000 all'anno (sierogruppo A epidemico)

La cosiddetta "cintura africana della meningite" (Africa sub-sahariana) continua a registrare frequenti episodi sporadici ed epidemie di malattia meningococcica.



Nature Reviews | Microbiology

Norway, 1969
B:B:15:P1.7,16

A, C

B, C

Spain, 1974
B:4:P1.19,15

Oregon, 1994
B:15:P1.7,16

B, C, Y

Cuba, 1980
B:4:P1.19,15

Japan, 1979
B:15:P1.7,16

A, W-135, C, X

Brazil, 1985
B:4:P1.19,15

Australia, 1982
B:15:P1.7,16

B, C

Chile, 1985

B, C

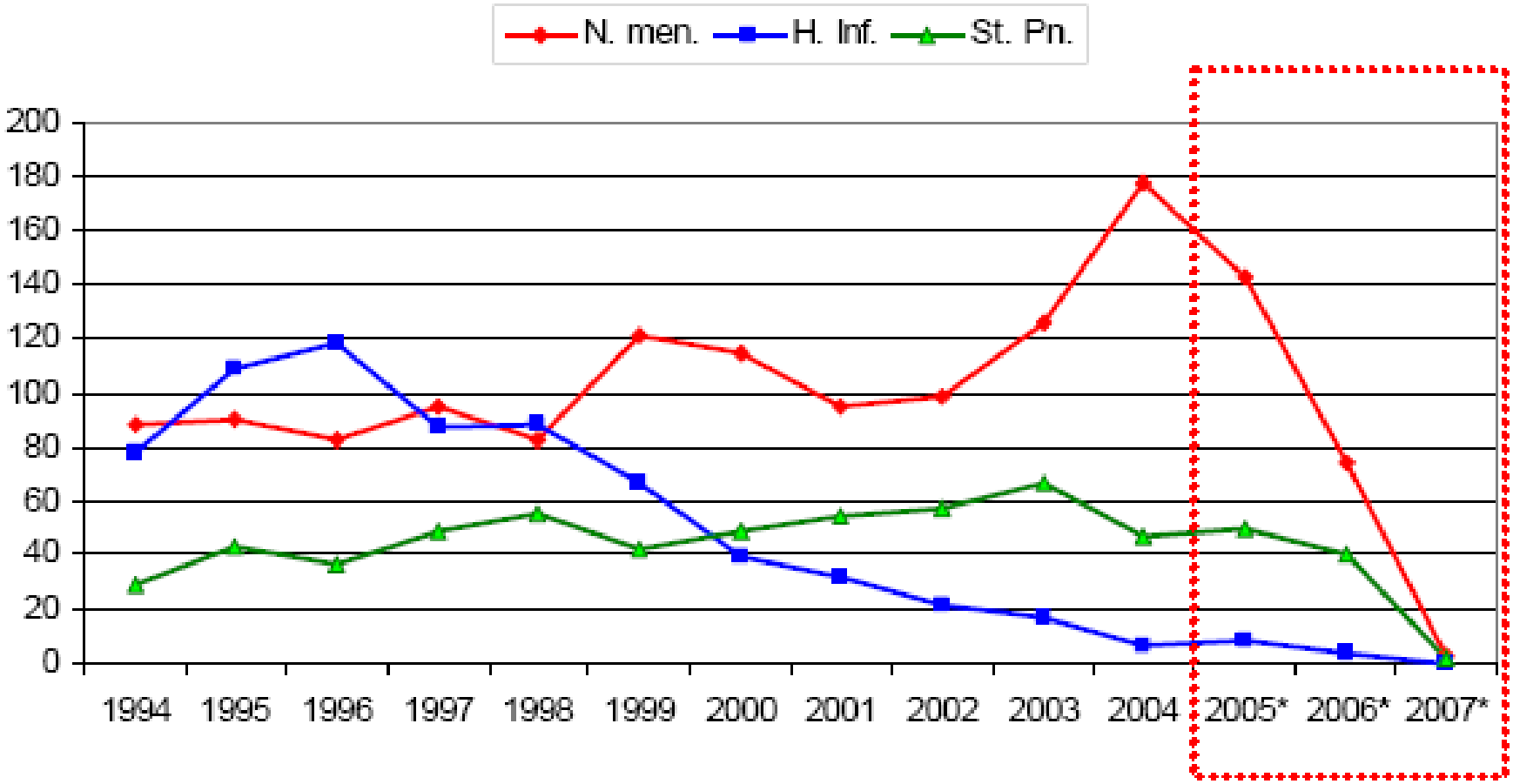
South Africa, 1980
B:4:P1.19,15

New Zealand, 1992 to present
B:4:P1.4

Distribuzione mondiale dei maggiori sierogruppi di meningococco e delle epidemie di sierogruppo B (in viola). La cintura delle meningiti in Africa sub-sahariana

Meningiti batteriche in Italia al 24-02-07

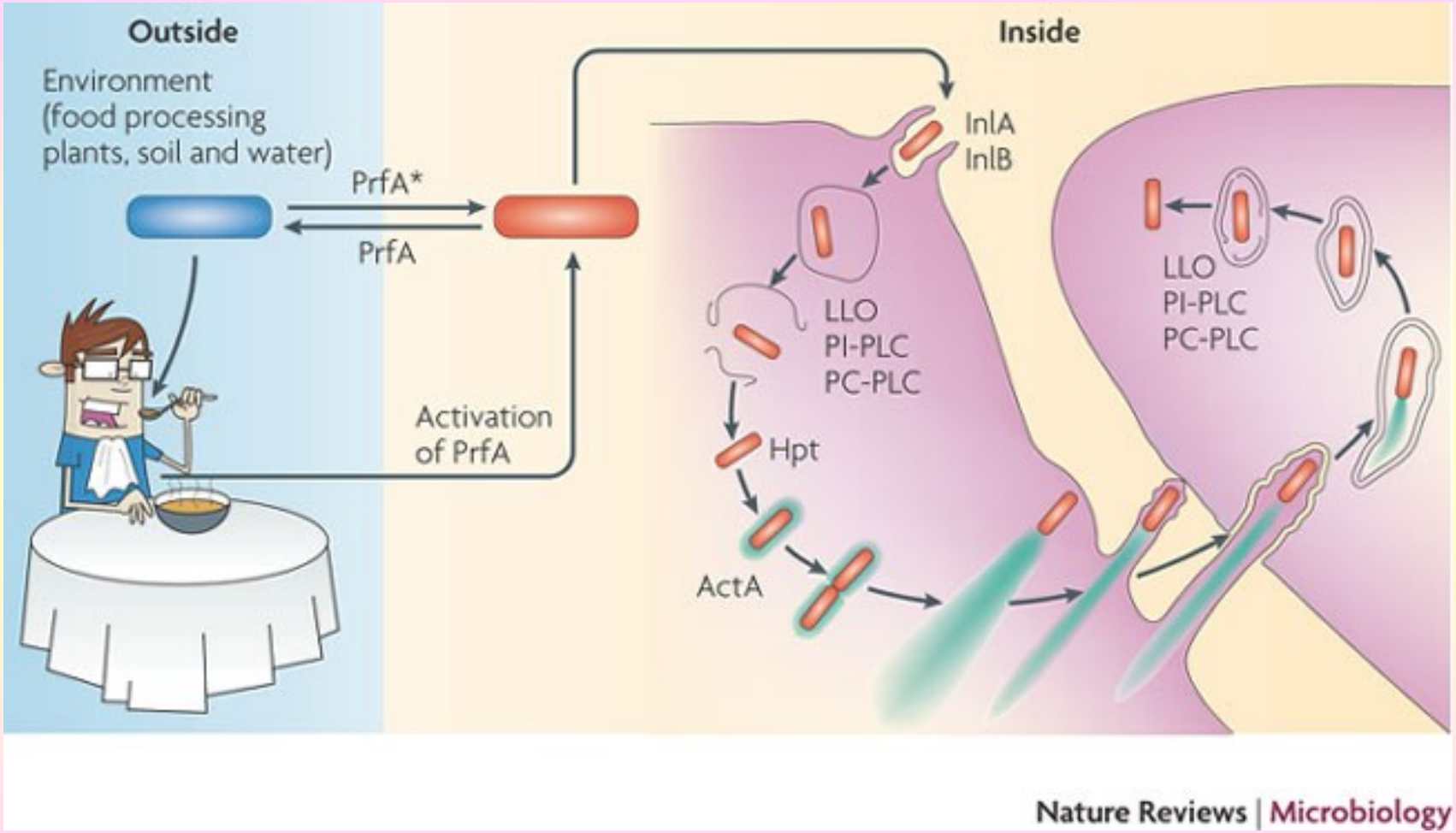
(*2005 - 2007 : dati provvisori*)




Infezione da HIV
Deficit dei fattori della via terminale del complemento
Deficit della properdina
Asplenia anatomica o funzionale
Deficienza dell'attività battericida della via alternativa del complemento
MALATTIA
Recente infezione virale delle alte vie respiratorie
Soggiorno nello stesso ambiente di una persona affetta da malattia meningococcica o di un portatore
Affollamento all'interno di istituti o famiglie
Esposizione attiva o passiva al fumo di tabacco

MENINGITI BATTERICHE ACQUISITA IN COMUNITA'

LISTERIA MONOCYTOGENES



La trasmissione attraverso una fonte alimentare è la causa di malattia umana. I cibi più implicati nelle epidemie di listeriosi sono: cavoli contaminati, latte pastorizzato, formaggi, prodotti di carne di tacchino e insaccati, burro

Periodo di incubazione: 2-6 settimane

Listeria Monocytogenes

- Ingestion of a large inoculum may cause gastroenteritis in healthy individuals bacteremia and meningitis can occur in individuals over 50 years of age or among persons with deficiencies in cell-mediated immunity

- *L monocytogenes* rarely causes meningitis in younger, healthy individuals

- Screening for HIV infection is warranted if *L monocytogenes* meningitis occurs in this patient group.

MENINGITI BATTERICHE

EZIOLOGIA DELLE MENINGITI BATTERICHE IN BASE ALL'ETA' E FATTORI DI RISCHIO

0- 4 settimane	*S.agalactiae* *E. coli* *S. pneumoniae* *L. monocytogenes*	Complicanze neonatali Complicanze neonatali Liquorrea Infezione materna
1-3 mesi	*E. coli* *H. influenzae* *L. monocytogenes*	Colonizzazione nosocomiale Liquorrea, sinusite, otite Immunodeficit
3 mesi-18 anni	*H. influenzae* *N. meningitidis* *S. pneumoniae*	Liquorrea, sinusite, otite Epidemie, deficit del complemento Liquorrea, sinusite, otite, asplenia
18-50 anni	*N. meningiditis* *S.pneumoniae*	Deficit C5-C8 del complemento Otite media, sinusite, liquorrea, asplenia, alcoolismo
› 50 anni	*L. monocytogenes* *S. pneumoniae*	Diabete mellito, immunodeficit Otite media, sinusite, liquorrea, asplenia, alcoolismo

Nosocomial bacterial meningitis

- Growing concern in critical care medicine.
- Neurosurgical procedures (eg, cerebrospinal fluid shunt placement) or cerebrospinal fluid leakage (eg, recent head injury) predisposes to nosocomial meningitis.
- The incidence of nosocomial meningitis ranges from 1% to 6% among neurosurgical patients.
- Although *S. pneumoniae* is one of the most common cause of nosocomial meningitis, *Staphylococcus* spp is frequently isolated in meningitis after neurosurgery (37%).
- Aerobic, Gram-negative bacilli (especially *Enterobacteriaceae*) cause up to 33% of nosocomial meningitis.

Journal of Hospital Infection (2004) 57, 300-307

Available online at www.sciencedirect.com

SCIENCE DIRECT

ELSEVIER

www.elsevierhealth.com/journals/jhin

Outbreak of nosocomial meningitis caused by *Acinetobacter baumannii* in neurosurgical patients

M.M. Wroblewska[a,b,*], L. Dijkshoorn[c], H. Marchel[b], M. van den Barselaar[c], E. Swoboda-Kopec[a,b], P.J. van den Broek[c], M. Luczak[a,b]

[a]*Department of Medical Microbiology, Medical University in Warsaw, 5 Chalubinskiego Street, 02-004 Warsaw, Poland*
[b]*Central Clinical Hospital in Warsaw, Warsaw, Poland*
[c]*Department of Infectious Diseases, Leiden University Medical Center, Leiden, The Netherlands*

Received 11 September 2003; accepted 24 March 2004

INVITED ARTICLE REVIEWS OF ANTI-INFECTIVE AGENTS

Louis D. Saravolatz, Section Editor

Treatment of *Acinetobacter* Infections

Joel Fishbain[1] and Anton Y. Peleg[2,3,4]

[1]Division of Infectious Diseases, St John Hospital and Medical Center, Detroit, Michigan, and [2]Division of Infectious Diseases, Massachusetts General Hospital and Beth Israel Deaconess Medical Center, Boston, Massachusetts; [3]Alfred Hospital and [4]Department of Microbiology, Monash University, Melbourne, Australia

Clinical Infectious Diseases 2010; 51(1):79–84

1058-4838/2010/5101-0013$15.00
DOI: 10.1086/653120

MENINGITI A LIQUOR LIMPIDO

VIRALI

- *Virus echo*
- *Virus coxsackie*
- *Virus polio*
- *Virus della parotite*
- *Virus herpes simplex 1 e 2*
- *Virus della varicella-zoster (VZV)*
- *HIV*
- *Virus Toscana*
- *Cytomegalovirus (CMV)*
- *Virus di Epstein-Barr (EBV)*
- *West Nile Virus*

MICOTICHE

- *Cryptococcus neoformans*
- *Coccidioides immitis*
- *Histoplasma capsulatum*

BATTERICHE

- *Mycobacterium tubercolosis*
- *Brucella* spp
- *Leptospira* spp
- *Treponema pallidum*
- *Borrelia burgdoferi*

PARASSITARIE

- *Toxoplasma gondii*
- *Tripanosoma* spp

West Nile virus infection in Veneto region, Italy, 2008-2009

L Barzon[1,2], L Squarzon[1,2], M Cattai[2], E Franchin[1,2], S Pagni[1,2], R Cusinato[2], G Palù (giorgio.palu@unipd.it)[1,2]

1. Department of Histology, Microbiology and Medical Biotechnology, University of Padua, Italy
2. Regional Reference Centre for Infectious Diseases, Microbiology and Virology Unit, Azienda Ospedaliera di Padova, Padua, Italy

CASO CLINICO

Donna di 40 anni,

dell'Ecuador, agente di polizia nel suo paese, madre di una ragazza di 15 anni,

in Italia da 6 anni,

in gravidanza (quinto mese di gravidanza trigemellare), sottoposta a terzo tentativo di FIVET per idrosalpingite bilaterale con occlusione tubarica.

5 mesi dopo
FIVET:

viene ricoverata in ostetricia per una sintomatologia caratterizzata da

cefalea, febbre e otalgia

(insorta dopo cerchiaggio)

RMN encefalo:

“ lesioni “a bersaglio” sovratentoriale dx (nucleo caudato, talamoecc) con edema perilesionale.

Alterazione flogistica iperemico-essudativa della mastoide di dx in stretta contiguità con strutture vestibolari orecchio dx.

↓

Intervento IN URGENZA di mastoidectomia

↓

“Incisone retroauricolare……, asportazione di materiale da ritenzione Di aspetto granuleggiante di colorito grigiastro…”

Esami batteriologici negativi

“PUS sterile”

Il giorno dopo l'intervento….

Febbre
Cefalea
Rigidità nucale
Emiparesi sinistra

↓

TRASFERIMENTO IN RIANIMAZIONE

Puntura lombare

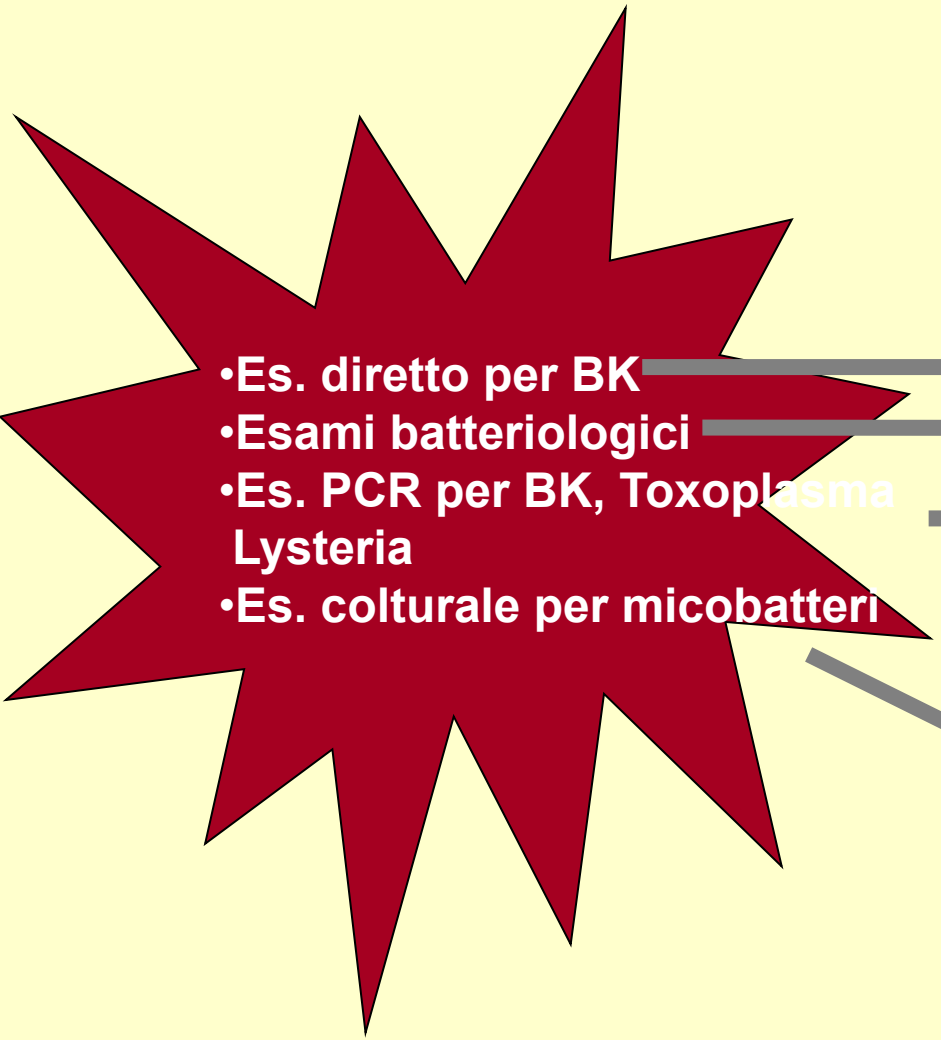
Liquor limpido
600 cellule mononucleate
Virus neurotropi: PCR negative
Glucosio: 40
Proteine: 450 g/dl

Sierologia per Lysteria monocytogenes: pos (1:1200)

Inizia terapia

AMPICILLINA 2 gr X 6 e.v.
+
MEROPENEM 1 gr X3 e.v.

Ripete RMN:
Localizzazione encefalica e meningea da L. monocytogenes



negativo

negativo

PCR Positiva *M. tuberculosis*, Negativa per Toxo e listeria

coltura positiva per *M. tuberculosis*

MENINGITI BATTERICHE

QUANDO SOSPETTARE UNA MENINGITE BATTERICA?

Symptom or Sign	Relative Frequency (%)
Headache	≥85
Fever	≥80
Meningismus	≥80
Altered sensorium	>75
Vomiting	35
Seizures	30
Focal neurologic findings	10 ~35
Papilledema	<5

MENINGITI BATTERICHE

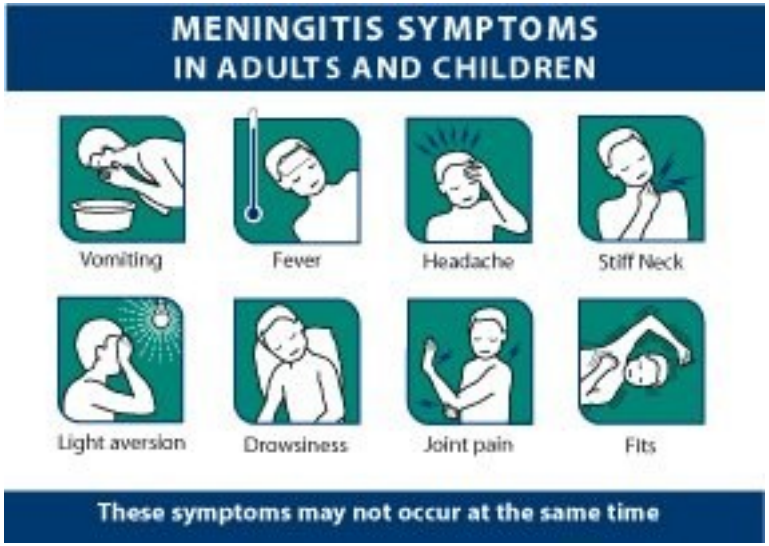
QUANDO SOSPETTARE UNA MENINGITE BATTERICA?

Notevole variabilità delle manifestazioni cliniche, soprattutto nei neonati e nei pazienti più anziani.

Nell'adulto, la sensibilità della triade della meningite batterica (FEBBRE + RIGIDITA' NUCALE + ALTERATO STATO DI COSCIENZA) è circa del 40%.

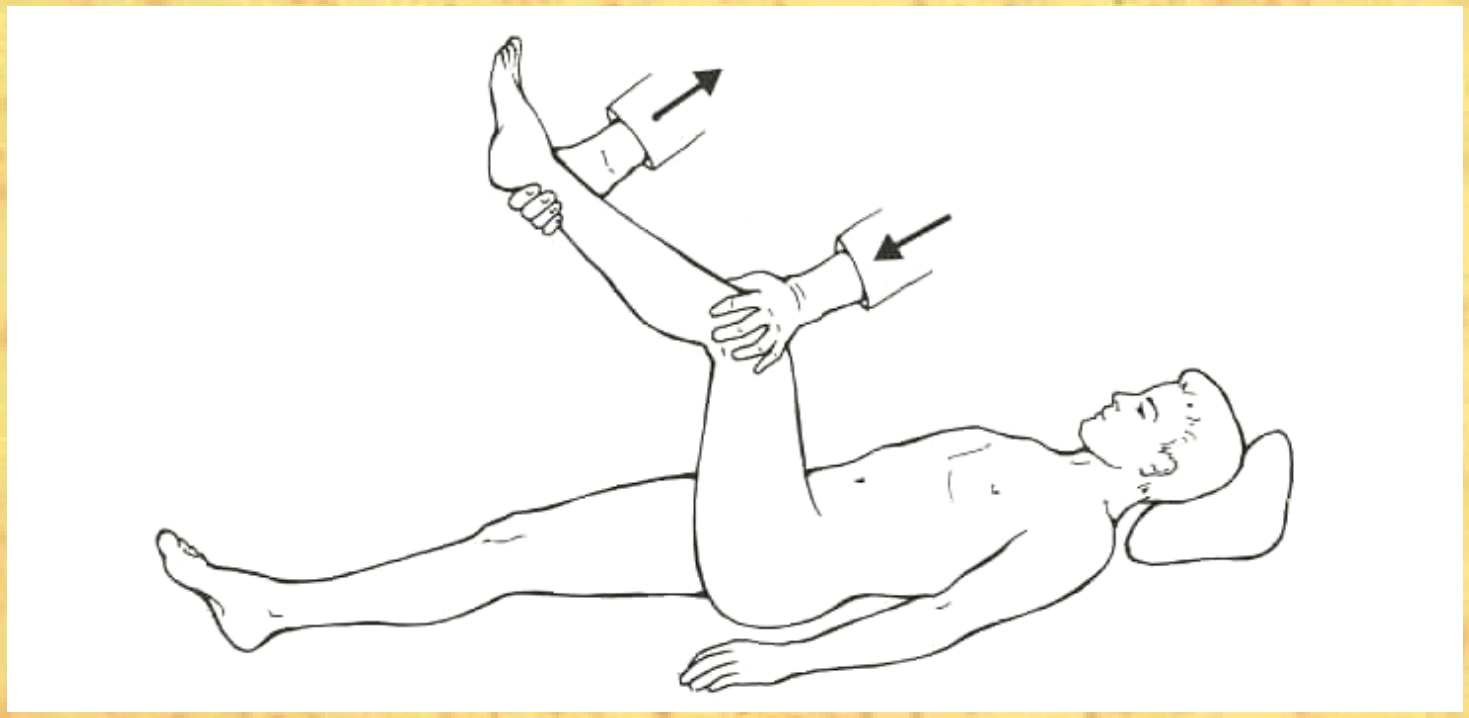
Nell'adulto e nei bambini con più di 2 anni:

- **alta probabilità di meningite nei pazienti con febbre, meningismo, e cefalea o alterazioni della coscienza**
- **alta probabilità in un paziente con febbre + *porpora***
- **considerare meningite anche in presenza di febbre + convulsioni o segni neurologici focali**



Segni di irritazione meningea

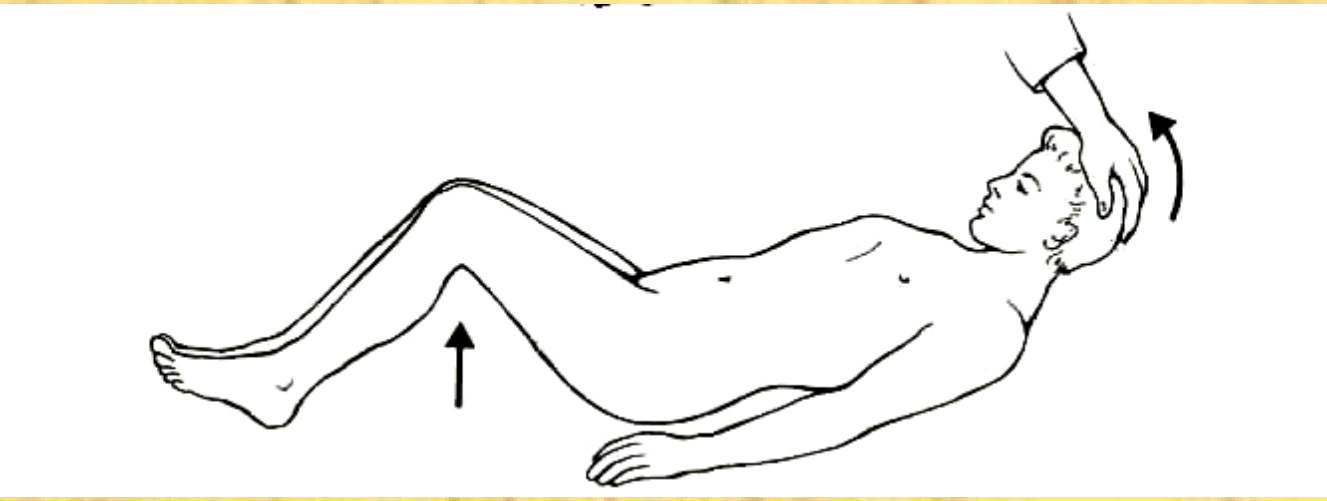
Segno di Laségue



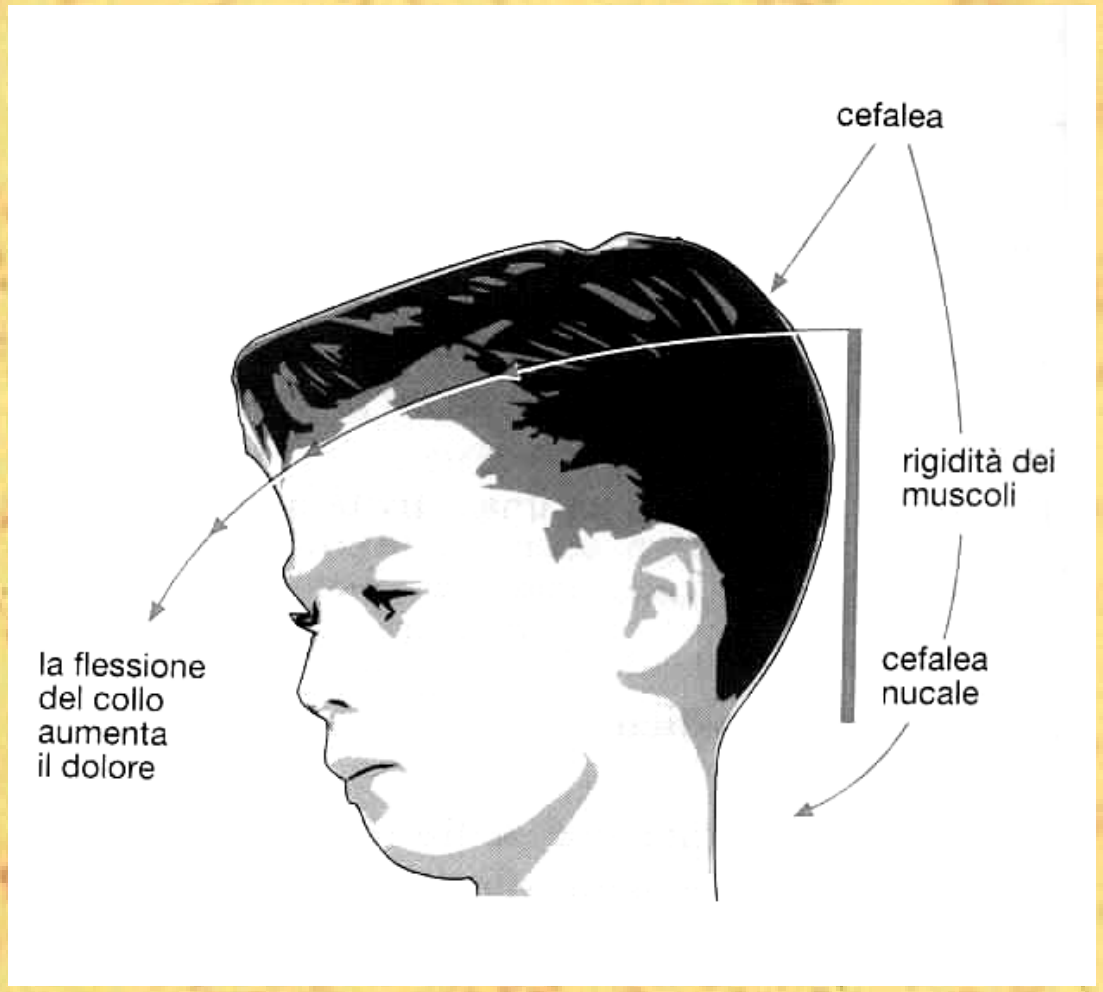
Il segno di Laségue si ricerca nel paziente supino, con la coscia flessa sul bacino: tentando di estendere progressivamente il ginocchio si provoca dolore e una contrazione muscolare che limita il movimento

Segni di irritazione meningea

Segno di Brudzinki



Il segno di Brudzinki consiste nella flessione spontanea delle cosce e delle gambe quando si tenta di flettere passivamente la nuca, per evitare lo stiramento delle radici il paziente decombe accocolato (posizione a cane di fucile)


cefalea
rigidità dei muscoli
la flessione del collo aumenta il dolore
cefalea nucale

Quadro clinico

- **Non contare sui segni di Kerning e Brudzinski**
- **Bassa sensibilità e accuratezza diagnostica**

Quadro clinico

Rash cutaneo ⟶ ***Neisseria meningitidis***

rash eritematoso e maculare

↓

rash petecchiale e purpurico


LATEX
CE

Infezione meningococcica nei bambini
Evoluzione rapida 12-24 ore

- **Segni di allarme**
  - **Febbre**
  - **Nausea-vomito**

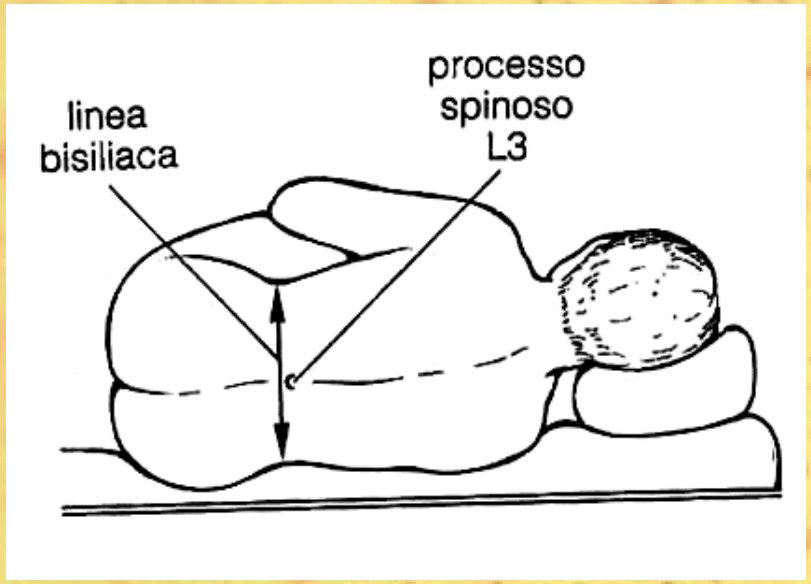
Insorgenza precoce: 4-6 ore

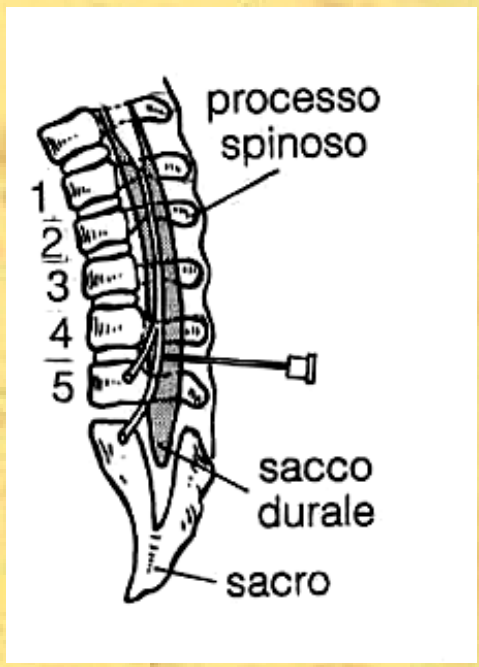
  - **Astenia, diminuzione tono muscolare e dolore agli arti inferiori**
  - **Cute fredda alle estremità (mani e piedi)**
  - **Modificazione del colorito cutaneo**

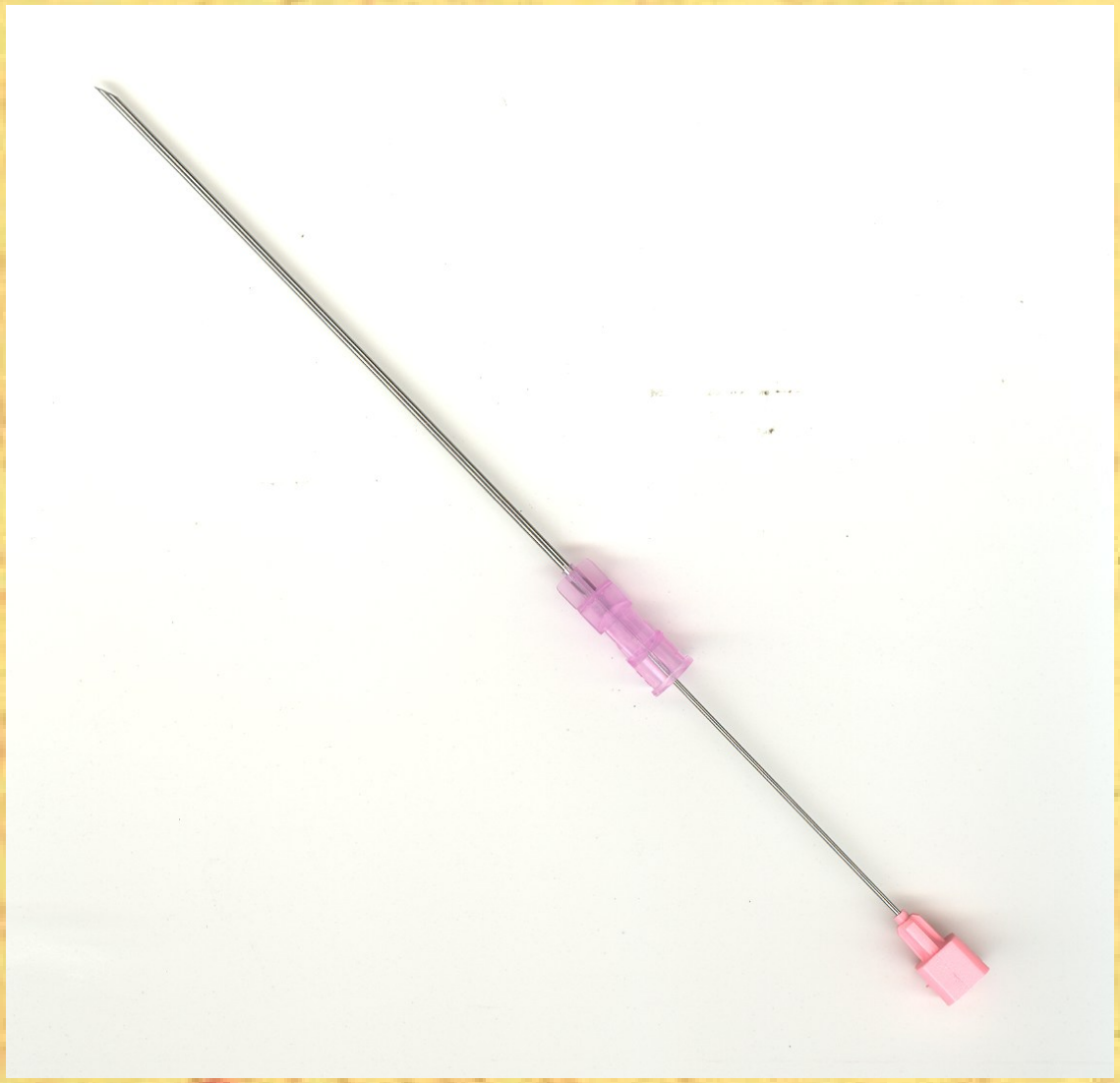
ESAME DEL LIQUOR

- L'esame del liquido-cerebro spinale (CSF) è di fondamentale importanza in tutte le forme di meningite
- La puntura lombare (o rachicentesi) deve essere eseguita in tutti i pazienti con sospetta meningite
- Deve essere procrastinata solo in presenza di sintomi o segni indicativi di una lesione endocranica (rischio di incuneamento del bulbo, in particolare per lesioni della fossa cranica posteriore)

Rachicentesi







Ago per rachicentesi

ESAME DEL LIQUOR

- Normalmente alla rachicentesi il liquor fuoriesce ad una pressione di 35-40 cm H2O (in decubuto assiso) o di 15-20 cm H2O (decubito laterale)
- L'aspetto è limpido, incolore, trasparente
- Il contenuto di proteine varia da 20 a 30 mg/dl
- La glicorrachia corrisponde al 60-70% dei valori glicemici (pari a circa 40-70 mg/dl)
- Gli elementi cellulari, in gran parte linfociti, non sono più di 5/ul

ALTERAZIONI LIQUORALI

- In caso di meningite il liquor può fuoriuscire ad una pressione aumentata (fino a 250-300 cm H2O)

- Aspetto

  1) meningiti a liquor torbido

  2) meningiti a liquor limpido

LIQUOR TORBIDO

Proteinorrachia ↑↑
glicorrachia ↓↓
cellule ↑↑ (PMN++, linfociti +/-)

- **Batteri gram -/+**
  eccetto: *M. tuberculosis, Brucella spp.*, Leptospire, *Tr. Pallidum, L. monocytogenes, Salmonella spp.*
- **Micoplasmi (alcuni)**
- **Miceti del genere Candida e Mucor**
- **Alcuni protozoi:Naegleria e Acanthamoeba**

LIQUOR LIMPIDO

Glicorrachia ↓↓
cellule ↑ linfociti++
protidorrachia ↑↑

- *M. tubercolosis*
- Brucelle, leptospire, salmonelle, *Tr. Pallidum*, *Listeria*
- Miceti: *H. capsulatum*, *Cr. Neoformans*, *C. immitis*

Glicorrachia -/ ↑
cellule ↑ linfociti++
protidorrachia ↑

- Virus
- Rickettsie, clamidie
- Parassiti: Toxoplasma, Tripanosoma

MENINGITI BATTERICHE

QUALI SONO I TEST NECESSARI PER LA DIAGNOSI DI MENINGITE BATTERICA?

- **BIOCHIMICA, CITOLOGIA E MICROBIOLOGIA SU UN CAMPIONE DI LIQUOR**

- **UNA O PIU' EMOCOLTURE**

Esami colturali sul CSF possono risultare negativi quando si riceve terapia antibiotica prima dell' esame del liquor.

COMPLETA STERILIZZAZIONE DEL LIQUOR:

N. meningitidis **= entro 2 ore dalla somministrazione cefalosporina III generazione**

S. pneumoniae **= entro 4 ore dall'inizio di terapia antibiotica**

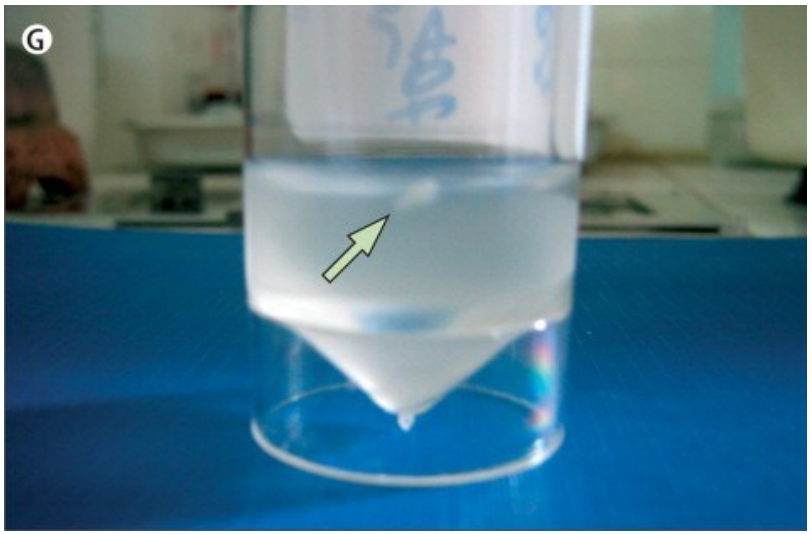
In queste situazioni, emocolture e tests non colturali possono essere di aiuto nella diagnosi

MENINGITI BATTERICHE

QUALI SONO I TEST NECESSARI PER LA DIAGNOSI DI MENINGITE BATTERICA?

COLORAZIONE DI GRAM DEL CSF E ESAMI COLTURALI

Una rapida colorazione di Gram del CSF può determinare una tempestiva identificazione dell'agente eziologico anche quando l'esame colturale del liquor è negativo.



SENSIBILITA' COLORAZIONE GRAM:

90% meningite pneumococcica

80% meningite meningococcica

50% menigite da bacilli Gram negativi

30% meningite da *L. monocytogenes*

Centrifugazione dei campioni può aumentare resa dell' esame diretto dopo colorazione Gram.

MENINGITI BATTERICHE

QUALI SONO I TEST NECESSARI PER LA DIAGNOSI DI MENINGITE BATTERICA?

METODI NON COLTURALI

Latex agglutination	Sensibile verso *H. influenzae tipo b,* meno verso *N. meningitidis*
Cryptococcal antigen latex agglutination	Eccellente sensibilità/ specificità nella diagnosi di meningite criptococcica
PCR su CSF	Particolarmente utile nel caso di meningiti virali. Importante anche PCR per meningococco e pneumococco se esame diretto è negativo
CSF Immunochromatography	Molto sensibile per *S. pneumoniae*

MENINGITI BATTERICHE

QUANDO E' NECESSARIA TAC ENCEFALO PRIMA DELLA PUNTURA LOMBARE?

La rachicentesi è fondamentale per la diagnosi di meningite. Questa procedura può esporre al rischio di erniazione cerebrale, a seguito di squilibrio pressorio causato da ostacoli alla circolazione liquorale, o come conseguenza di lesioni cerebrali che producono effetto massa.

L' ipertensione endocranica è comune nelle forme più gravi di meningite, ma NON controindica la puntura lombare.

SOSPETTA MENINGITE BATTERICA

IMAGING CEREBRALE SOLO IN CASO DI

- **SEGNI NEUROLOGICI FOCALI**
- **ALTERAZIONI DELLO STATO DI COSCIENZA (GCS < 11)**
- **CRISI CONVULSIVE RECENTI O IN ATTO**

The Dilemma Between Diagnosis and Early Treatment

- **Lumbar puncture should not delay initiation of antimicrobial therapy in cases in which bacterial meningitis is suspected**

- **A delay in treatment is strongly associated with adverse outcome**

- **The most common factors associated with delay of antimicrobial therapy are cranial imaging before lumbar puncture and transfer of the patient to another hospital.**

The Dilemma Between Diagnosis and Early Treatment

- **The mean time to administration of antimicrobial agents from presentation is between 1 and 4.9 hours**
- **Delayed administration of antimicrobial agents greater than 6 hours after presentation is associated with increased mortality and neurologic sequelae**
- **CT scan of the brain is routinely performed before lumbar puncture, despite the low prevalence (2%) of pre-existing mass effect or space-occupying lesions in the general patient population**

Neuroimaging

- **Cranial CT or MRI does not aid in the diagnosis of acute bacterial meningitis.**
- **Should be considered during the course of illness in patients with:**
  - **persistent or prolonged fever**
  - **clinical evidence of increased intracranial pressure**
  - **focal neurologic findings or seizures**
  - **enlarging head circumference (in neonates)**
  - **persistent neurologic dysfunction**
  - **persistently abnormal CSF parameters or cultures**

MENINGITI BATTERICHE

QUANDO E' NECESSARIA TAC ENCEFALO PRIMA DELLA PUNTURA LOMBARE?

1. Immunodepressione	Infezione da HIV/AIDS, terapie immunosoppressive, trapianti
2. Storia di malattia del SNC	Masse cerebrali, stroke, infezioni focali
3. Crisi epilettiche di recente comparsa	Entro 1 settimana dalla comparsa, alcuni sconsigliano l'esecuzione di puntura lombare nei pazienti con crisi convulsive prolungate
4 . Papilledema	Indicativo di aumentata pressione intracranica
5. Alterazioni dello stato di coscienza	-
6.Deficit neurologici focali	Midriasi, anomalie della motilità oculare, alterazioni del campo visivo, paralisi dello sguardo, immobilità degli arti

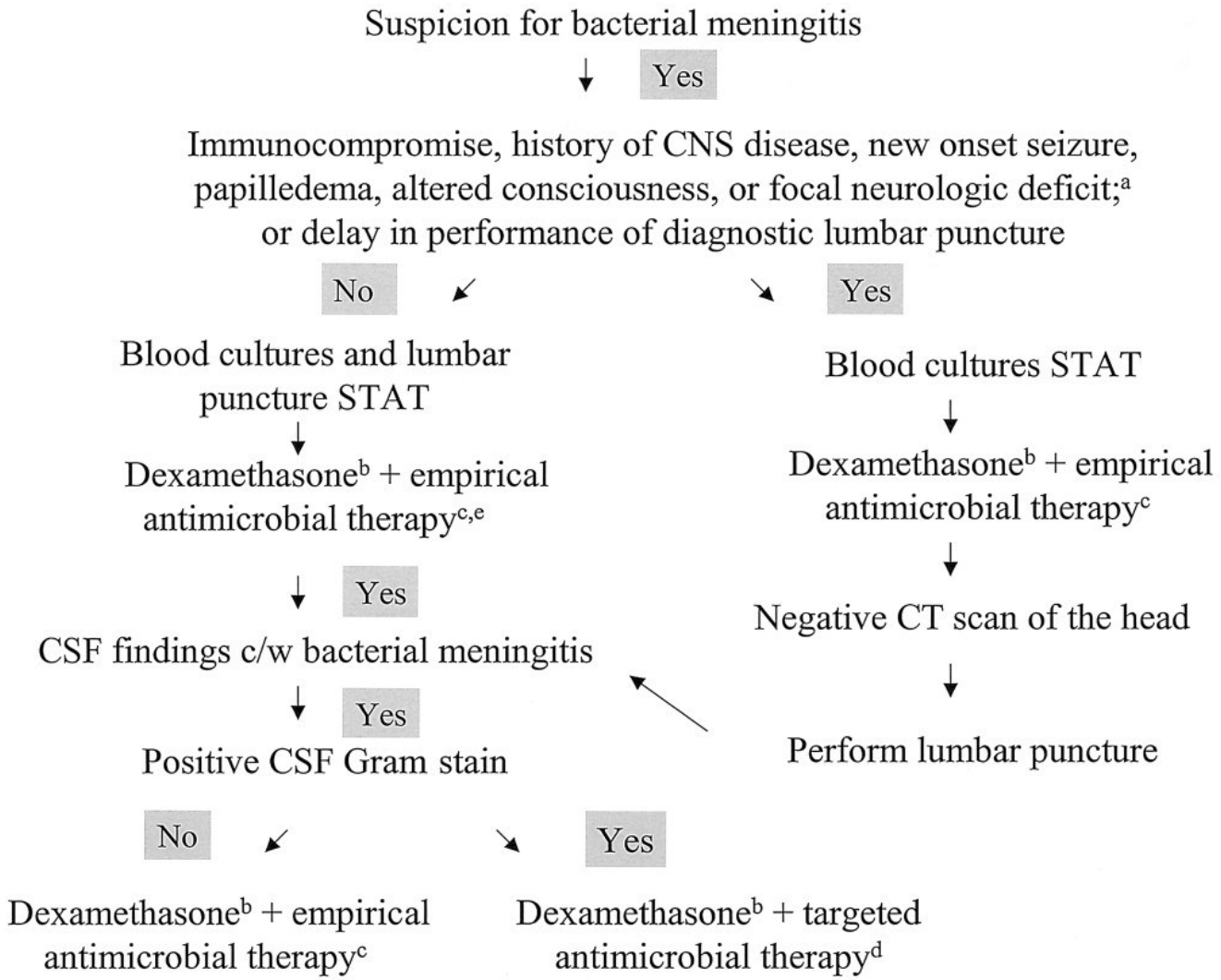


Figure 2. Management algorithm for adults with suspected bacterial meningitis. “Stat” indicates that the intervention should be done emergently. aSee table 2. bSee text for specific recommendations for use of adjunctive dexamethasone in adults with bacterial meningitis. cSee table 4. dSee table 3. eDexamethasone and antimicrobial therapy should be administered immediately after CSF is obtained.

DIAGNOSI O TRATTAMENTO PRECOCE ?

La terapia antibiotica dovrebbe essere somministrata non più tardi di 3 ore e possibilmente entro 1 ora dall'arrivo in ospedale, indipendentemente dal momento di esordio della sintomatologia.

Quando si rende necessaria TAC encefalo, la prima dose di antimicrobico deve essere assunta prima di effettuare gli esami strumentali.

MENINGITI BATTERICHE

IN QUALI CASI LA SOMMINISTRAZIONE DI ANTIBIOTICI PRECEDE LA PUNTURA LOMBARE?

Ogni circostanza in grado di ritardare l'esecuzione di una rachicentesi comporta la necessità di iniziare antibioticoterapia.

Questo è vero soprattutto in presenza di:

1. **PURPURA FULMINANS**
2. **CONTROINDICAZIONI ALLA P.L.**
3. **IMPOSSIBILITA' DI VALUTARE IL PAZIENTE ENTRO 90 MINUTI**

Relative contraindications to lumbar puncture (delay lumbar puncture until clinically stable)

- Clinical signs of raised intracranial pressure (bradycardia, hypertension, abnormal respiration)
- Rapidly deteriorating conscious level
- Coagulopathy or purpuric or petechial rash
- Focal neurological signs or seizures, or continuous seizure activity
- Cardiovascular compromise
- Infection of the skin at the site of lumbar puncture

Table 1

MENINGITI BATTERICHE ACQUISITE IN COMUNITA'

Terapia antibiotica empirica

Table 1. Recommendations for Empirical Antimicrobial Therapy in Adults with Community-Acquired Bacterial Meningitis.*

Predisposing Factor	Common Bacterial Pathogen	Antimicrobial Therapy
Age		
16–50 yr	*Neisseria meningitidis, Streptococcus pneumoniae*	Vancomycin plus a third-generation cephalosporin†‡
>50 yr	*S. pneumoniae, N. meningitidis, Listeria monocytogenes,* aerobic gram-negative bacilli	Vancomycin plus a third-generation cephalosporin plus ampicillin‡§
Presence of a risk factor¶	*S. pneumoniae, L. monocytogenes, Haemophilus influenzae*	Vancomycin plus a third-generation cephalosporin plus ampicillin‡§

* For additional information, including alternative antimicrobial therapies, see Table 1 in the Supplementary Appendix, available with the full text of this article at www.nejm.org.

† Only in regions with very low rates of penicillin resistance (<1 percent), monotherapy with penicillin may be considered, although many experts recommend combination therapy for all patients until the results of in vitro susceptibility testing are available.

‡ Cefotaxime and ceftriaxone are the third-generation cephalosporins recommended.

§ Only in regions with very low rates of penicillin resistance and cephalosporin resistance, combination therapy with amoxicillin (ampicillin) and a third-generation cephalosporin may be considered.

¶ Risk factors include alcoholism and altered immune status.

MENINGITI BATTERICHE NOSOCOMIALI

Terapia antibiotica empirica

- Cefalosporine anti-Pseudomonas
- Carbapenemici
- Anti-MDR
  - Colistina
- Anti-MRSA
  - Vancomicina
  - Linezolid
  - Daptomicina

MENINGITI BATTERICHE

STREPTOCOCCUS PNEUMONIAE

TERAPIA

Diagnosi di meningite pneumococcica; sensibilità antibiotica non nota

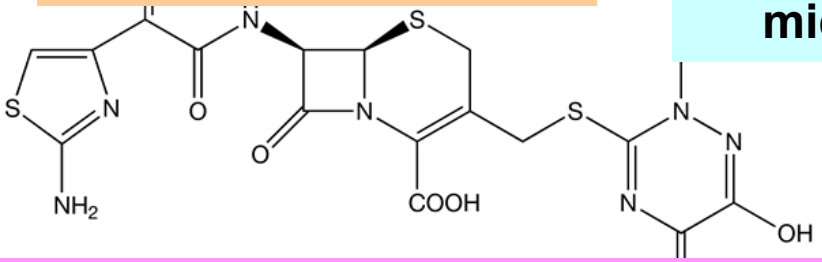
→

Trattare con ceftriaxone, (1-2 g ogni 12 ore) più vancomicina (500 mg ogni 6 ore), fino all'antibiogramma

↓

Disponibilità dell'antibiogramma: continuare trattamento con il solo ceftriaxone se il microrganismo è sensibile;

Pazienti allergici alle penicilline: trattare con meropenem piuttosto che con un β-lattamico

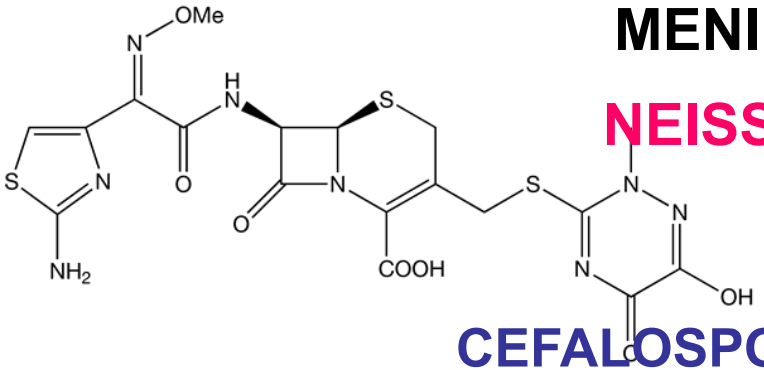


NB: Cefalosporina è efficace sulla maggior parte degli isolati e ha buona penetrazione nel CSF, mentre vancomicina ha penetrazione minore nel liquor

Il trattamento va proseguito per 10 giorni.. Non necessaria la chemiprofilassi per i contatti di pazienti con meningite pneumococcica.

MENINGITI BATTERICHE

NEISSERIA MENINGITIDIS



TERAPIA

<u>CEFALOSPORINE DI III GENERAZIONE</u>:

Cefotaxime (2g e.v. ogni 4 ore)

Ceftriaxone (2g e.v. ogni 12 ore)

<u>In alternativa</u>:

Penicillina G (18-24 mUI/die e.v.)

Il trattamento deve essere continuato per almeno 7 giorni.

Abbondante reidratazione

Ventilazione assistita

Farmaci vasopressori

Proteina C attivata (DROTRECOGINα) nei pazienti con sepsi grave e disfunzione di più di un organo (24μg/kg/h in infusione endovenosa continua per 96 ore)

MENINGITI BATTERICHE

NEISSERIA MENINGITIDIS

PREVENZIONE

VACCINAZIONE

Vaccino tetravalente (sierogruppi A, C, Y, W135), costituito dai polisaccaridi capsulari meningococcici. E' efficace nell'80-95% degli adulti e la durata dell'immunità post-vaccinale è di 5 anni. Non è disponibile ancora un vaccino contro il sierogruppo B (perché il polisaccaride che lo forma è scarsamento immunogeno per l'uomo).

Vaccino inefficace per bambini con meno di 2 anni.

CHEMIOPROFILASSI ANTIMENINGOCOCCICA

Consigliata solo per i contatti stretti di soggetti con malattia meningococcica.

- **Rifampicina (600 mg 2 volte/die per 2 giorni per os)**
- **Ciprofloxacina (500 mg in monosomministrazione per os)**
- **Ofloxacina (400 mg in monosomministrazione)**
- **Ceftriaxone (250 mg in monosomministrazione i.m.)**

MENINGITI BATTERICHE

LISTERIA MONOCYTOGENES

TERAPIA

ADULTI NON IN GRAVIDANZA:

Ampicillina (12 g/die e.v. divisi in 6 dosi)

oppure

Trimetroprim-sulfametoxazolo (15/75 mg/kg/die e.v, in 3 dosi uguali ogni 8 ore) negli allergici alla penicillina

Continuare la terapia antibiotica per 2-3 settimane dopo defervescenza

(la meningite negli immunodepressi va trattata per almeno 4-6 settimane). Non è richiesta la chemioprofilassi per i contatti delle persone affette.

MENINGITI BATTERICHE NOSOCOMIALI

Microrganismo	Terapia raccomandata	Alternative
Staphylococcus aureus (meticillino sensibile)	Oxacillina	Vancomicina, Linezolid, Daptomicina
Staphylococcus aureus (meticillino resistente)	Vancomicina (± Rif)	Linezolid, Daptomicina, TMP-SMZ
P. aeruginosa	Cefepime, ceftazidime meropenem	Colistina
A. baumannii	Meropenem	Colistina

MENINGITI BATTERICHE

QUAL E' LA DURATA DELLA TERAPIA ANTIBIOTICA IN CASO DI MENINGITE BATTERICA?

MICRORGANISMO	DURATA DELLA TERAPIA (giorni)
Neisseria meningitidis	7
Haemophilus influenzae	7
Streptococcus pneumoniae	10-14
Streptococcus agalactiae	14-21
Bacilli aerobi gram negativi *	21
Listeria monocytogenes	>= 21

*** La terapia nei neonati è proseguita per 2 settimane dopo la prima coltura negativa del CSF**

MENINGITI BATTERICHE

QUALI SONO LE INDICAZIONI PER RIPETERE PL DOPO L'INIZIO DEL TRATTAMENTO?

Nei pazienti affetti da meningite batterica e che hanno risposto alla terapia antibiotica, analisi ripetute del CSF per documentarne la sterilizzazione e la normalizzazione dei parametri biologici non sono indicate di routine.

RIPETERE P.L.

Nei pazienti che non hanno risposto clinicamente dopo 48 ore di terapia antibiotica

Pazienti con meningite pneumococcica causata da ceppi penicillino- o cefalosporino-resistenti

Dopo 48-72 ore di terapia nel caso di meningiti da germi non comuni

MENINGITI BATTERICHE

Ruolo degli steroidi

Il ruolo dei corticosteroidi (DESAMETASONE) nella terapia delle meningiti batteriche, deriva dalla capacità di ridurre il grado di infiammazione, interferendo con la formazione di edema cerebrale, ipertensione endocranica, vasculite dei vasi cerebrali e danno neuronale.

Benefici derivati dall'impiego di desametasone sono stati riscontrati solo in caso di meningite pneumococcica, ma vanno sempre somministrati nella terapia empirica

USO RACCOMANDATO DI DESAMETASONE : 0,15 mg/kg per 2-4 giorni (prima dose assunta 10-20 minuti prima o contemporaneamente alla prima dose di antibiotici)

RICHIEDE ATTENTO MONITORAGGIO nelle meningiti causate da ceppi resistenti di Pneumococco: riduce infiammazione meningea e perciò anche la penetrazione degli antibiotici nel liquor (vancomicina)

Terapie adiuvanti
Modulazione della risposta ifiammatoria

- Beneficio clinico degli steroidi nella fase acuta della malattia
- La risposta infiammatoria dell'ospite continua anche dopo la somministrazione degli antibiotici inducendo un danno al SNC
- E' quindi necessario modulare la cascata degli eventi infiammatori evitando il danneggiamento dei tessuti dell'ospite
- Importanza nella prevenzione del danno infiammatorio e neuronale

MENINGITI VIRALI

MENINGITI VIRALI

- La sintomatologia delle meningiti virali, qualunque sia il virus causale, non ha elementi patognomonici
- Spesso il quadro dell'encefalite è preminente: confusione, coma, comizialità, emiparesi
- Possono orientare verso una diagnosi eziologica il criterio epidemiologico o l'evidenza di un'infezione preesistente o concomitante con caratteristica sintomatologia extrameningea
- Diagnosi: microbiologico del liquor
- Esami sierologici

MENINGITI VIRALI
Enterovirus

- *VIRUS COXSACKIE* (tutti i tipi del gruppo B ed alcuni tipi del gruppo A)
- prevalente: estivo-autunnale
- più frequente: agammaglobulinemia, trapiantati, neonato
- esantema, faringite, congiuntivite, dolori addominali
- pericardite, miocardite
- letalità: 10%

MENINGITI VIRALI
Enterovirus

- virus *ECHO*
- prevalente: estivo-autunnale
- *ECHO 6-9* : si accompagna a manifestazioni esantematiche di tipo roseoliforme, morbilliforme o scarlattiniforme
- evoluzione benigna

MENINGITI VIRALI

- *PAROTITE EPIDEMICA*
- 10-20% dei casi
- La sindrome meningea compare in genere dopo la tumefazione ghiandolare, ma può anche precederla o verificarsi in assenza di parotite
- E' possibile, seppur rara, l'evoluzione verso quadri di encefalite e di mielite

MENINGITI VIRALI

- Il virus *HERPES SIMPLEX* può provocare una meningite o una meningoencefalite per riattivazione di un'infezione latente oppure in seguito ad un'infezione primaria o ad una reinfezione esogena
- La meningite in qualche caso si associa ad herpes labiale o genitale

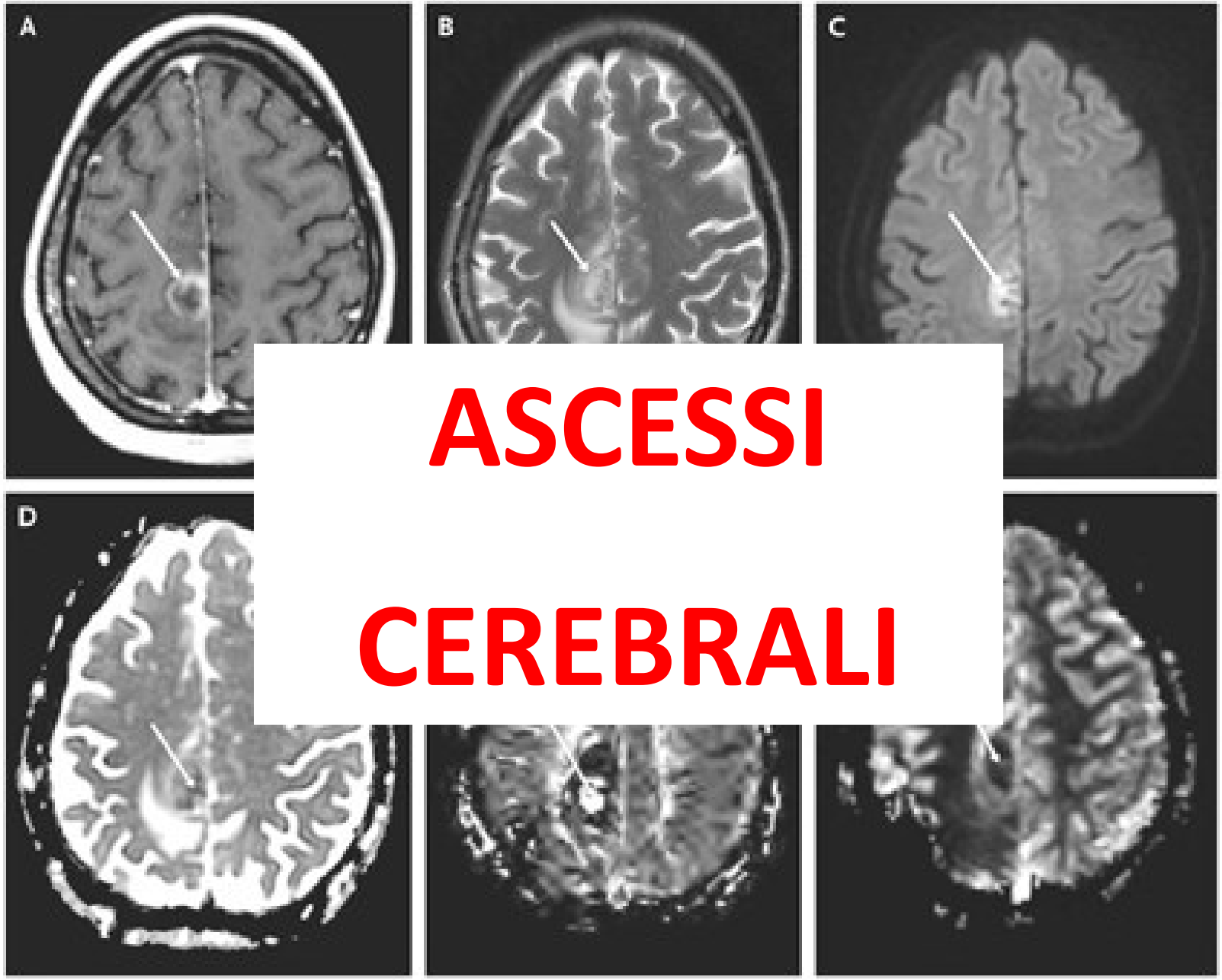
MENINGITI MICOTICHE

MENINGITI MICOTICHE

- **L'agente eziologico più frequente è rappresentato da *CRYPTOCOCCUS NEOFORMANS***
- **Può causare meningite (liquor limpido), encefalite o, raramente, quadri focali dovuti ad ascessi o infezioni granulomatose**
- **Si osserva in soggetti immunodepressi, in particolare in corso di malattia da HIV**

MENINGITI MICOTICHE

- Funghi del genere Mucor, Candida e Aspergillus possono causare meningiti (a liquor torbido)
- Sono quasi sempre conseguenza di infezioni generalizzate
- Insorgono in soggetti immunocompromessi



ASCESSI CEREBRALI

ASCESSI CEREBRALI

L’ascesso è la più comune infezione suppurativa focale a livello cerebrale.

I progressi nella diagnosi e nel trattamento delle infezioni dell’orecchio, dei seni paranasali e delle infezioni orofacciali hanno ridotto l’incidenza degli ascessi cerebrali, che sono diventati poco frequenti, interessando circa 1500-2500 persone l’anno negli Stati Uniti.

ASCESSI CEREBRALI

FATTORI PREDISPONENTI:

-Infezioni in un sito adiacente (otite media, sinusite)

-Traumi cranici penetranti

-Disseminazione ematogena a partire da un focolaio posto a distanza (endocardite, ascessi intra-addominali, infezioni delle vie urinarie)

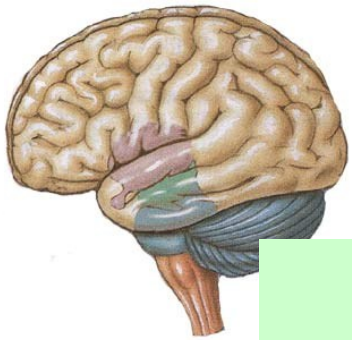
-Immunocompromissione (farmaci immunosoppressori, trapianti d'organo, HIV)

ASCESSI CEREBRALI

CONDIZIONI PREDISPONENTI	MICRORGANISMI COINVOLTI
OTITE MEDIA O MASTOIDITE	Streptococchi, *Bacteroides* spp., *Prevotella* spp., *Enterobacteriaceae*
SINUSITE	Streptococchi, *Bacteroides* spp., *Enterobacteriaceae*, *S.aureus*, *Haemophilus* spp
INFEZIONE ODONTOGENA	Infezioni miste da *Fusobacterium* spp., *Prevotella* spp e *Bacteroides* spp.
TRAUMA O INTERVENTO NEUROCHIRURGICO	*S.aureus*, streptococchi, *Enterobacteriaceae, Clostridium* spp.
ASCESSO POLMONARE, EMPIEMA, BRONCHIECTASIE	*Fusobacterium* spp., *Bacteroides* spp., *Actinomyces* spp., *Prevotella* spp., streptococchi, *Nocardia* spp.

ASCESSI CEREBRALI

CONDIZIONI PREDISPONENTI	MICRORGANISMI COINVOLTI
ENDOCARDITE BATTERICA	*S.aureus*, streptococchi
CARDIOPATIA CONGENITA	Streptococchi, *Haemophilus* spp.
NEUTROPENIA	Bacilli aerobi Gram-,*Aspergillus* spp.,*Mucorales, Candida* spp.
TRAPIANTO	*Aspergillus* spp.,*Mucorales, Candida* spp.,*Enterobacteriaceae, Nocardia* spp.
AIDS	*Toxoplasma gondii, M.tubercolosis, Nocardia* spp.,*Listeria monocytogenes*



ASCESSI CEREBRALI

PATOGENESI

CEREBRITE PRECOCE

Infiltrazione perivascolare di cellule infiammatorie a livello di un focolaio di necrosi coagulativa (1-3 giorni)

CEREBRITE TARDIVA

Espansione del focolaio purulento (4-9 giorni)

FORMAZIONE PRECOCE DELLA CAPSULA

Enhancement contrastografico ad anello nelle immagini neuroradiologiche (10-13 giorni)

FORMAZIONE TARDIVA DELLA CAPSULA (dopo 14 giorni)

ASCESSI CEREBRALI

Symptom or Sign	Frequency (%)
Headache	70
Mental status changes	70
Focal neurologic deficits	>60
Fever	45–50
Seizures	25-35
Nausea and vomiting	25-50
Nucheal rigidity	25
Papilledema	25

Neuroimaging

- The wide availability of imaging studies has improved the diagnosis of brain abscess.
- CT with intravenous contrast may reveal single- or multiple-ring enhancing lesions, particularly in well-established or chronic brain abscess.
- MRI with gadolinium contrast is more sensitive and specific than CT scan with contrast study to diagnose brain abscess

Management of brain abscess

- Multidisciplinary approach involving intensivists, neurosurgeons, radiologists, and infectious disease specialists
- As brain abscesses are frequently polymicrobial, empiric antimicrobial therapy should cover Gram-positive, Gram-negative, and anaerobic microorganisms
- Once a causative microorganism is identified, antimicrobial therapy can be tailored
- Steroid treatment
- Surgical treatment

ASCESSI CEREBRALI

TERAPIA ANTIBIOTICA

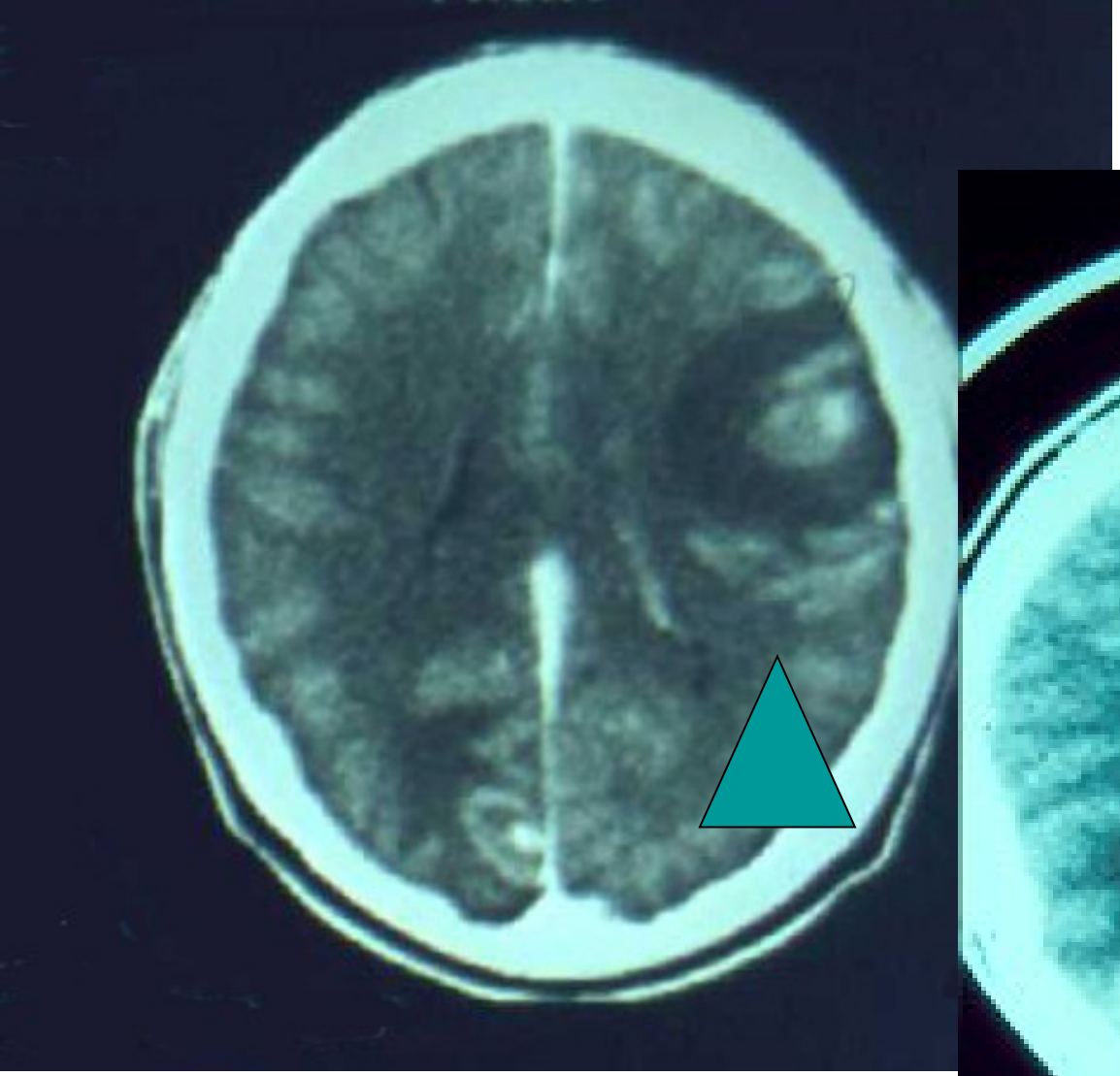
FONTE PRIMARIA	ORGANISMI PROBABILI	REGIME ANTIBIOTICO SUGGERITO
Meningite	Dipende dall'età	Cefalosporine di III generazione
Otite/mastoidite	Streptococchi, *Enterobacteriaceae, Bacteroides* spp., *S.aureus, Haemophilus* spp.	ceftazidime e metronidazolo + antistafilococco (flucloxacillina/vancomicina),
Sinusite	Streptococchi, *Bacteroides* spp.,*Haemophilus* spp.,*S.aureus*	cefalosporine di III generazione e metronidazolo + Antistafilococco
Trauma cranico	*S.aureus*, streptococchi, *Enterobacteriaceae, Pseudomonas*	Antistafilococcici e cefalosporine di III generazione
Infezione di shunt ventricoloperitoneale	*S.aureus*, streptococchi, *Enterobacteriaceae, Pseudomonas aeruginosa*	Antistafilococco, ceftazidime e metronidazolo

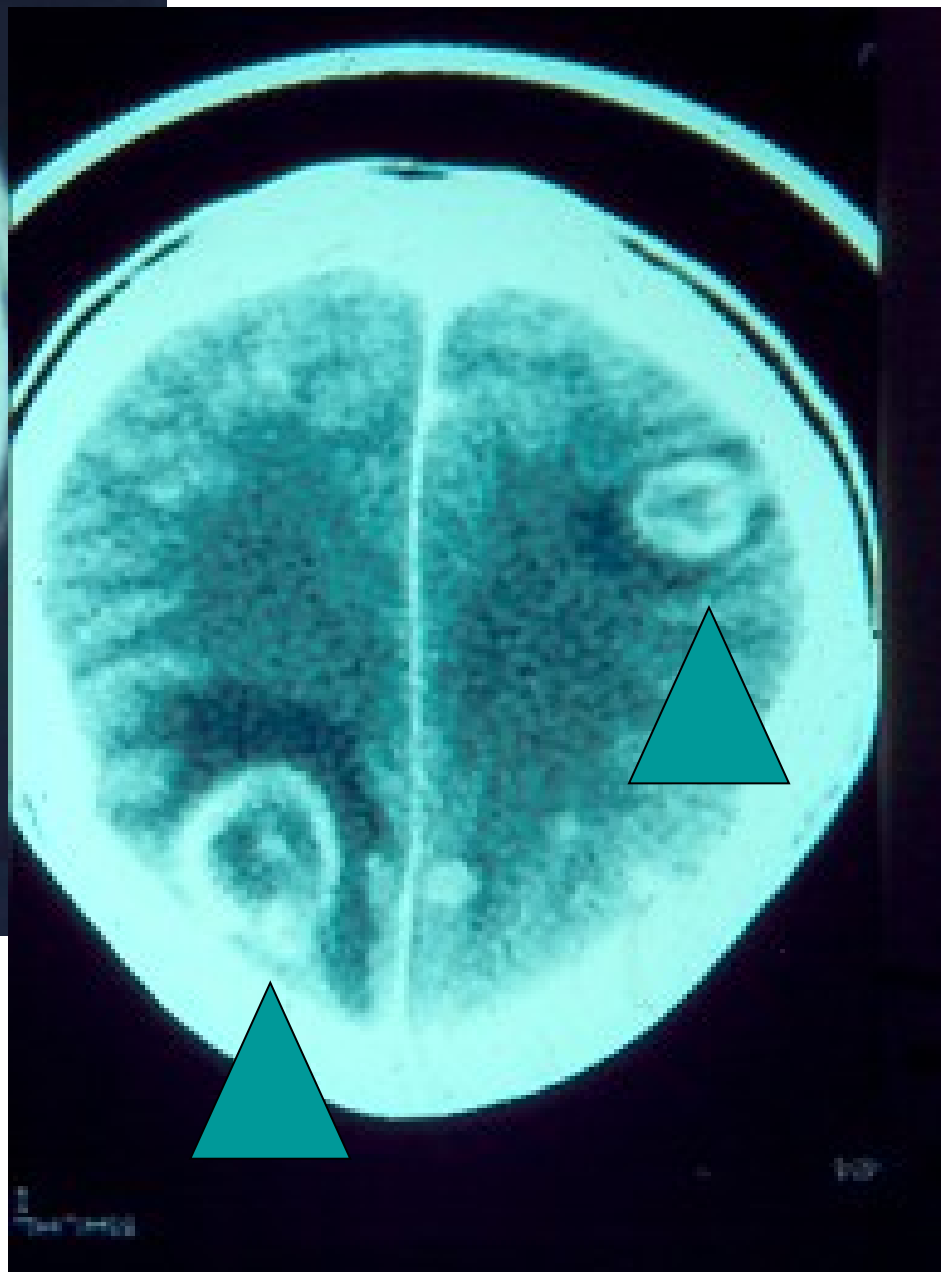
Surgical treatment

- **Most experts feel that brain abscesses greater than 2.5 cm in diameter should be surgically treated (ie, open craniotomy or stereotactic aspiration), because of poor response with antimicrobial therapy alone**

- **Indications for closed drainage and aspiration of brain abscess versus open craniotomy are controversial**

- **A traumatic brain abscess may require craniotomy to remove foreign material or bone chips.**





Toxoplasmosi

ENCEFALITI

SAPIENZA
UNIVERSITÀ DI ROMA

Claudio Mastroianni

Dipartimento di Sanità Pubblica e Malattie Infettive
UOC Malattie Infettive,
Polo Pontino

DEFINITION

- Encephalitis is defined as inflammation of the brain parenchyma associated with neurologic dysfunction
- Diagnosis is typically made by a combination of clinical, laboratory, neuroimaging, and electrophysiologic findings.

Diagnostic criteria (1)

- Major criterion (required)
- Patients presenting to medical attention with altered mental status (defined as decreased or altered level or consciousness, lethargy, or personality change) lasting 24 hours with no alternative cause identified

Diagnostic minor criteria (2 required for possible encephalitis; 3 required for probable or confirmed encephalitis)

- Documented fever >38°C (100.4°F) within the 72 hours before or after presentation
- Generalized or partial seizures not fully attributable to a preexisting seizure disorder
- New onset of focal neurologic findings
- CSF leukocyte count >5/mm3
- Abnormality of brain parenchyma on neuroimaging suggestive of encephalitis that is either new from prior studies or appears acute in onset
- Abnormality on EEG that is consistent with encephalitis and not attributable to another cause

STUDY	DEFINED ETIOLOGY	UNDETERMINED	AUTOIMM.
USA CID, 2006	29%	63%	8%
FRENCH CID, 2007	52%	37%	11%
UK Lancet, 2011	42%	37%	21%
USA Neurology, 2013	37%	47%	16%

Causes of encephalitis and differences in their clinical presentations in England: a multicentre, population-based prospective study

Julia Granerod, Helen E Ambrose, Nicholas W S Davies, Jonathan P Clewley, Amanda L Walsh, Dilys Morgan, Richard Cunningham, Mark Zuckerman, Ken J Mutton, Tom Solomon, Katherine N Ward, Michael P T Lunn, Sarosh R Irani, Angela Vincent, David W G Brown, Natasha S Crowcroft, on behalf of the UK Health Protection Agency (HPA) Aetiology of Encephalitis Study Group

Lancet, 2011

	Immunocompetent patients* (n=172)	Immunocompromised patients† (n=31)	Total
Herpes simplex virus	37 (22%, 16–28)	1 (3%, 0·1–17)	38
Acute disseminated encephalomyelitis	23 (14%, 9–19)	--	23
Antibody-associated encephalitis	15 (9%, 5–14)	1 (3%, 0·1–17)	16
Mycobacterium tuberculosis	9 (5%, 2–10)	1 (3%, 0·1–17)	10
Varicella zoster virus	4 (2%, 0·6–6)	6 (19%, 7–37)	10
Streptococci	4 (2%, 0·6–6)	--	4
Enterovirus	3 (2%, 0·4–5)	--	3
Dual finding	--	3 (10%, 2–26)	3
Toxoplasma gondii	--	2 (6%, 1–21)	2
Epstein-Barr virus	--	1 (3%, 0·1–17)	1
Human herpesvirus-6	--	1 (3%, 0·1–17)	1
HIV	--	1 (3%, 0·1–17)	1
JC virus	--	1 (3%, 0·1–17)	1
Listeria monocytogenes	--	1 (3%, 0·1–17)	1
Pneumococcus	--	1 (3%, 0·1–17)	1
Other‡	13 (8%, 4–13)	--	13
Unknown	64 (37%, 30–45)	11 (35%, 19–55)	75

Data are number (%, 95% CI). The dual findings are the same as for table 2. *Includes cases for whom immune status was unknown. †Reasons for immunocompromised status: 18 HIV positive; three on chemotherapy; ten with other reasons or exact reason unknown. ‡Other causes include *Pseudomonas* spp, *Coxiella burnetii*, *Enterococcus faecium*, meningococcus, pneumococcus, influenza A, sclerosing subacute panencephalitis, paraneoplastic encephalitis, multiple sclerosis, and encephalitis secondary to systemic vasculitis.

Table 2: **Causes of encephalitis in immunocompetent versus immunocompromised patients**

Nonviral and noninfectious causes of encephalitis

- **Bacterial**

Bartonella henselae
Bartonella quintana
Borrelia burgdorferi
Brucella species
Leptospira interrogans
Listeria monocytogenes
Mycobacterium tuberculosis
Mycoplasma pneumoniae
Rickettsia rickettsii
Treponema pallidum

Protozoal

Naegleria fowleri
Acanthamoeba species
Cysticercosis
Echinococcus species
Plasmodium falciparum
Trypanosoma species
Toxoplasma gondii

Fungal

Blastomycosis
Coccidioidomycosis
Cryptococcosis
Histoplasmosis

Noninfectious

Autoimmune
Central nervous system hemorrhage
Collagen vascular disease
Exposure to certain toxins or drugs
Inborn errors of metabolism
Malignant disease

Primo approccio al paziente con encefalite

I passaggi fondamentali del percorso diagnostico pre-eziologico

- Anamnesi:
  - generale
  - specifica
  - immunocompetenza (HIV, trapianti, emopatie, tumori, immunosoppressori e steroidi, terapie a bersaglio molecolare, eta' > 70 anni)

- Quadro clinico:
  - riconducibile al coinvolgimento specifico di un lobo/sistema neuronale?
  - associazione con un meningismo?

- LCS:
  - esame fisico-chimico, IEF (generalmente basso profilo infiammatorio negli immunodepressi)

- RMN:
  - encefalo e midollo

Encefaliti e stato immunologico

Encefaliti di interesse comune:

- HSV 1,2
- VZV
- enterovirus
- adenovirus
- arbovirus
- morbillo
- toscana
- WNV

Encefaliti dell'immunodepresso:

- Tutte le precedenti
- HHV6
- CMV
- EBV
- JCV
- funghi
- parassiti
- TBC

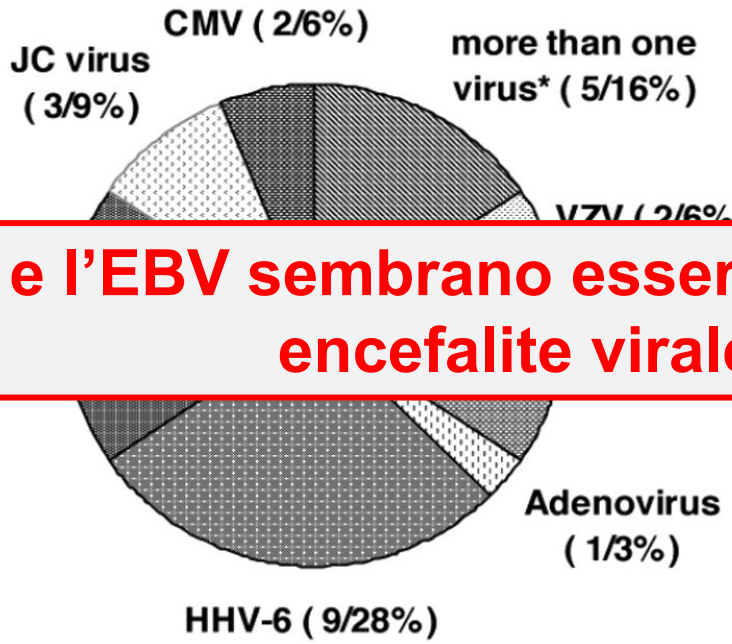
Rischio encefalitico in rapporto al background

	Allo-Trapianto CSE	HIV	Immunocompetenti
+	HHV-6	CMV	HSV
	EBV	JCV	VZV
	HSV	EBV	
	JCV	VZV	
	CMV	HSV	
	VZV		
-	Adenovirus		

frequenza

Spectrum and frequency of causative viruses

(numbers of patients and percentages in parentheses)



L'HHV6 e l'EBV sembrano essere le cause più comuni di encefalite virale nel post trapiantato

*Including CMV + HHV-6 + JC virus; HHV-6 + HHV-7; CMV + HHV-6; HSV + EBV; CMV + VZV + HSV + EBV.

Schmidt-Hieber, M. et al. Haematologica 2011;96:142-149

Elementi per la diagnosi pre-eziologica

LCS: comparison (Level A, Class II)

Parameter (normal)	Bacterial/ lysteria	HSV, VZV, HH6, CMV, WN, TV, measles	JCV/ TOXO/	Fungal/ Secondarism	vasculitis /PINS
Opening Pressure (<170 mm)	>300	200	200	>300	200
WBC (<5)	>1000	<1000	<5	<1500	<200
% PMNs (0)	>80%	1%-10%	0	1%-50%	0
Glucose (>40)	<40	>40	<40	<40	>40
Protein (<50)	>200	<200	<50	>200	100-200
Oligoclonal banding	-	+	-	-	-/+
lactate	+	-	-	++	-

Modified from Somand, 2009 and Marchioni, 2005

brain and spinal MRI: distribution of damage

DISEASES	BRAIN	SPINE
HSV, HH6	Temporal/limbic	Normal
ADEM/PINS	Multi, deep white matter	Multi + caudal roots
morbillo	Multi, cortical enhancement	Normal
VZV, CMV, EBV	Multi, DWI	Multi
PML	Multi (no enhance)	Normal
methastasis	Multi + lepto	Multi + caudal roots
FUNGAL/TOXO	Multi + lepto	Multi + caudal roots (rare toxo)
BACTERIC	Multi + lepto	Normal
VASCULITIS	Multi + lepto, DWI+	rare

Encefaliti virali da danno neurogeno o gliale diretto:

-HSV

-HHV 6

-JCV

Encefaliti virali da danno indiretto (prevalentemente vasculitico):

-morbillo

-VZV

-EBV

-CMV

Encefalite erpetica

- ✓ Herpes Simplex Virus 1
- ✓ Diffusione per via nervosa ai bulbi olfattori o per riattivazione nel ganglio trigeminale
- ✓ Encefalite necrotico emorragica
- ✓ Manifestazioni cliniche:

  irritabilità, disturbi comportamentali, stato confusionale

  febbre (assente nel 10-20%)

  allucinazioni, crisi epilettiche, deficit neurologici

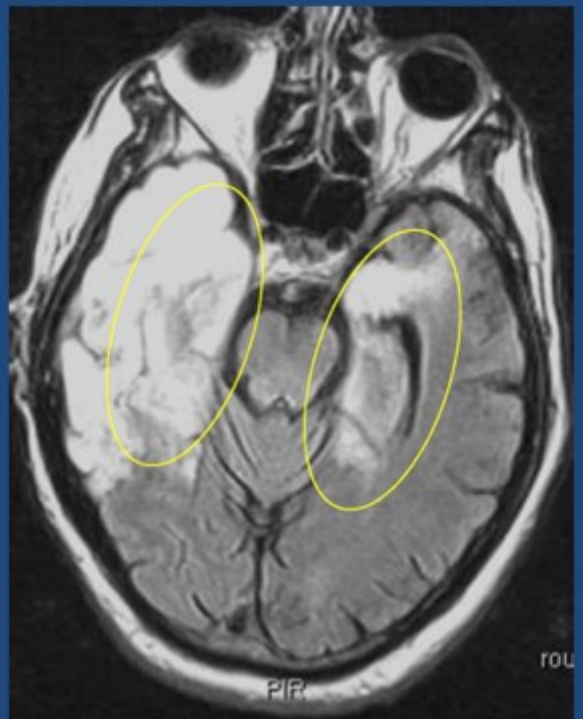
CT nei primi 3 giorni spesso negativa

Encefalite erpetica - RM

Sede tipica: sistema limbico

temporale mesiale, frontale basale mesiale

insula, girus ginguli



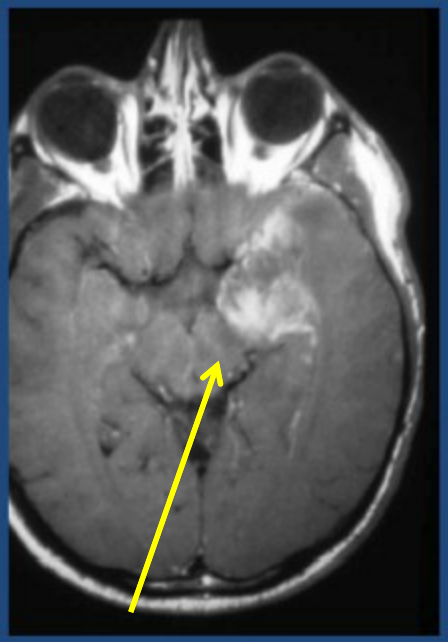
Possono essere interessati anche convessità e lobi occipitali

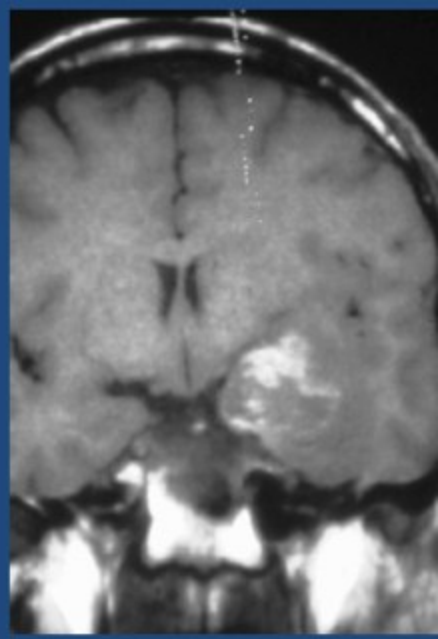
Spesso bilaterale anche se asimmetrica

Rara la sede mesencefalopontina

T2W

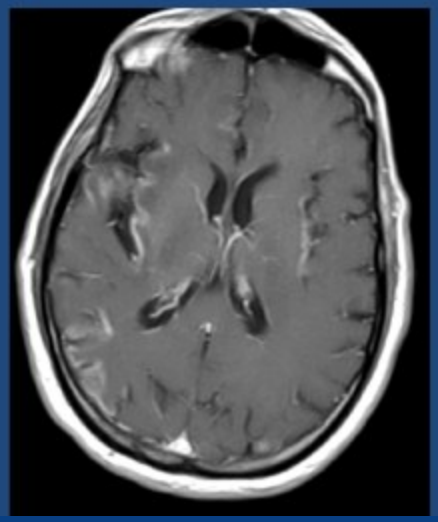
T1W

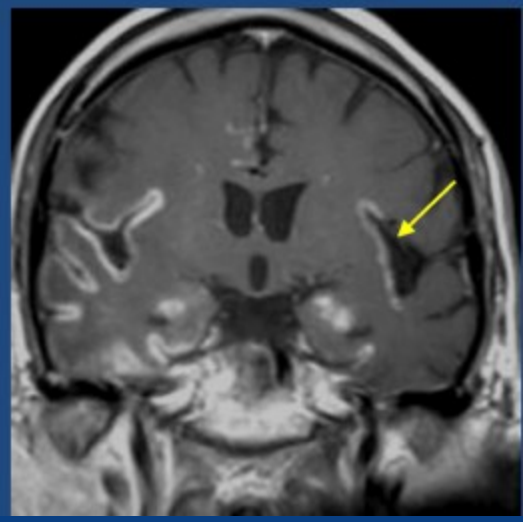




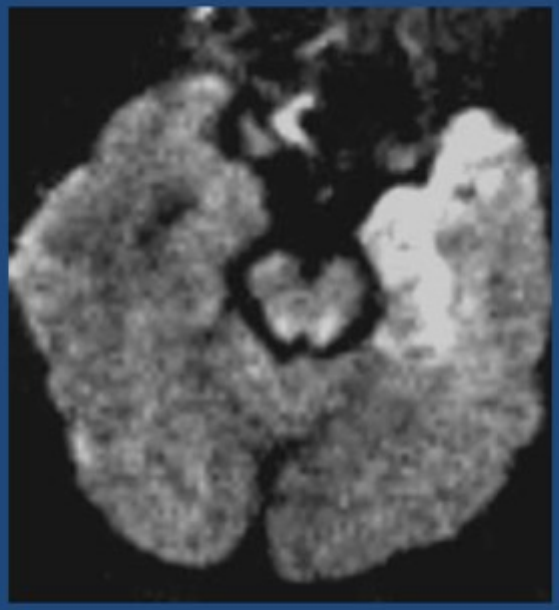
Enhancement giriforme corticale

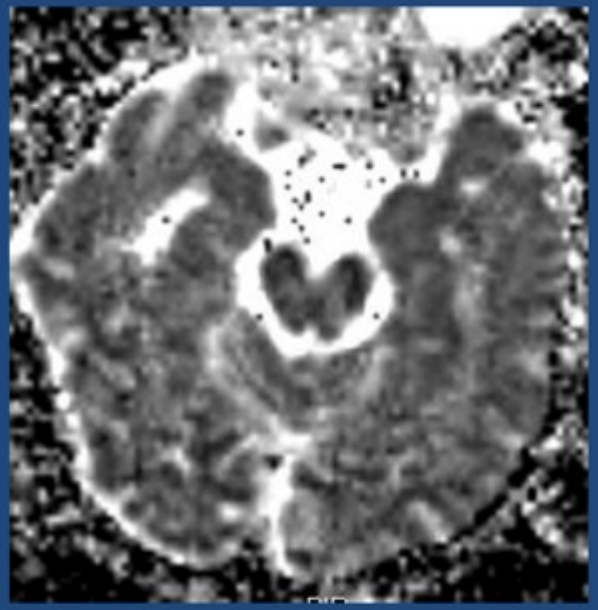
Componenti a segnale paramagnetico T1 e T2 per la presenza di materiale emorragico





Encefalite erpetica





DWI e ADC variabili.

Pattern più tipico: riduzione diffusione da edema citotossico

Encefaliti virali da danno neurogeno o gliale diretto:

-HSV

-HHV 6

-JCV

Encefaliti virali da danno indiretto (prevalentemente vasculitico):

-MORBILLO

-VZV

-EBV

-CMV

Condizioni neurologiche in cui è stato sospettato il ruolo dell'HHV 6

- Encefalite limbica:	documentata	post trap
- Encefaliti extra –limbiche	non documentate	immunocompet.
- Convulsioni febbrili	non documentate	immunocompet.
- Sclerosi temporale mesiale	non documentata	immunocompet.

NIH Public Access
Emerging Viral Infections of the Central Nervous System
Tyler LK, Arch Neurol. 2009

Encefalite limbica

Sintesi:

- sindrome Korsakoff -like	100 %
- epilessia temporale	82 %
- RMN (sistema limbico)	84 %
- alterazioni del LCR	41%

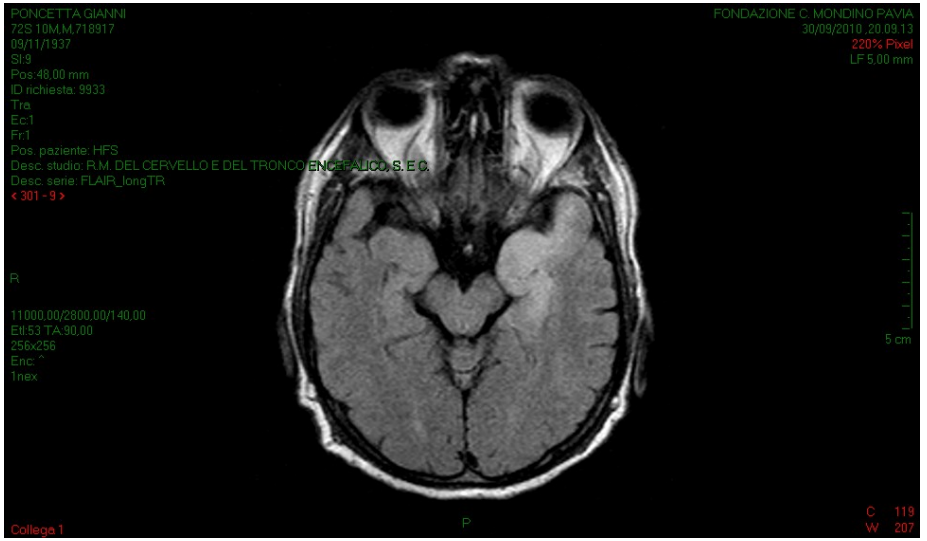
Encefalite da HSV

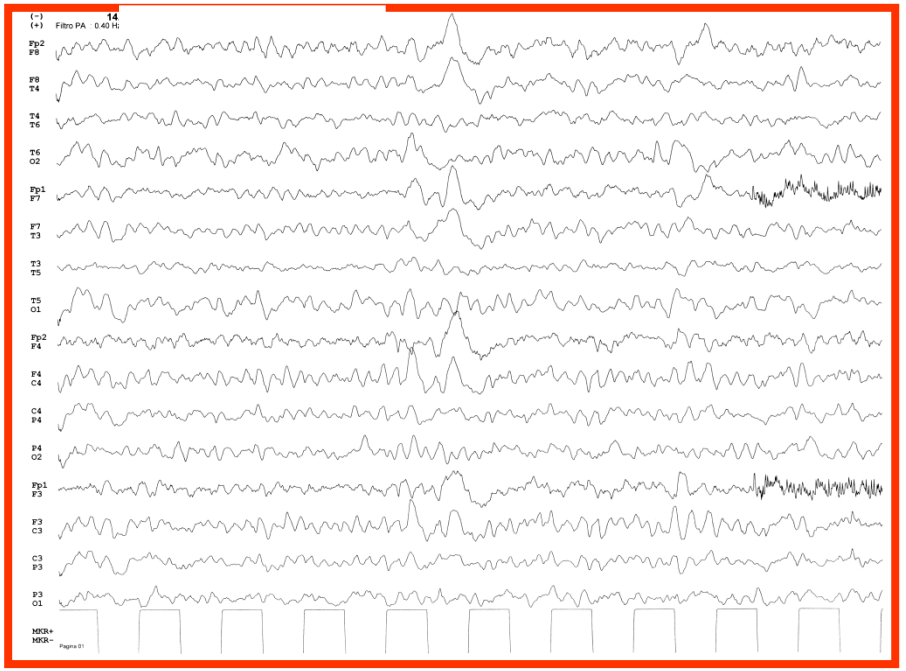
sintomi «classici»:
-esordio critico
-crisi del lobo temporale
-fase intercritica: “Sindrome temporale”

LCS:
-Pleiocitosi linfomonocitoide variabile
-Danno della BEE lieve-moderato
-Banding oligoclonale
-Rapporto anticorpale siero/LCS

RMN:
-Lesioni temporali mono o bilat iperintense in T2
-Enhancement

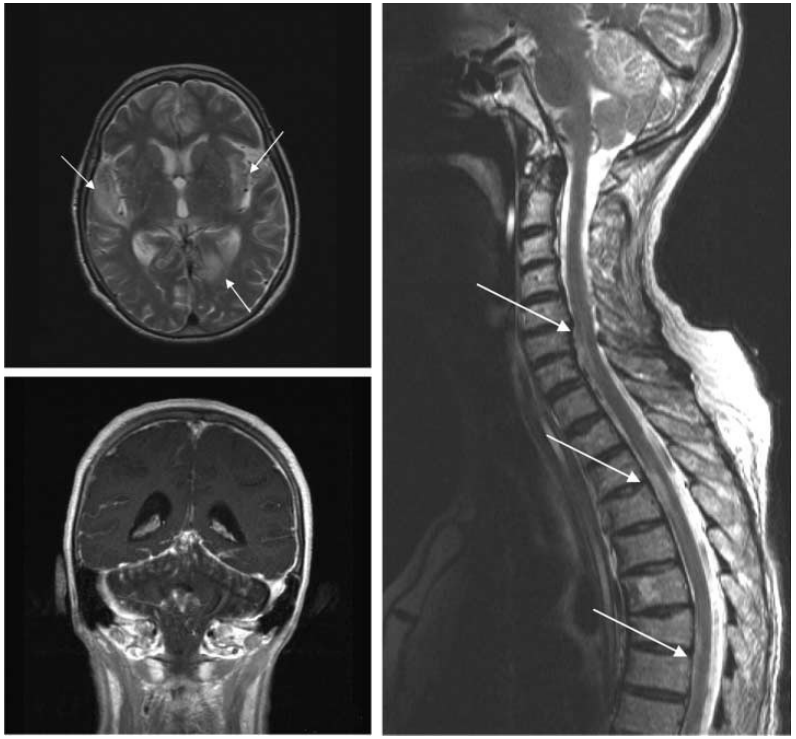
-EEG: aspecifico e congruo con la clinica





Encefaliti da VZV

Danno vasculitico con notevole variabilità fenotipica in rapporto allo stato immunitario:

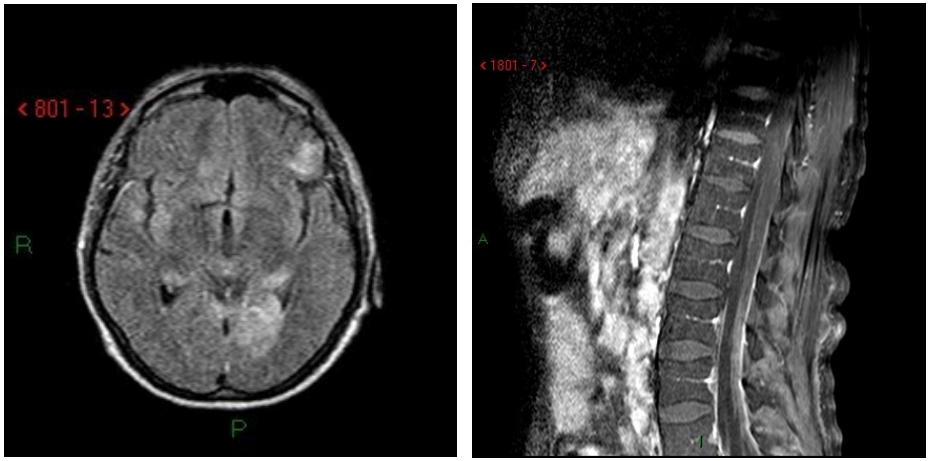


Encefalomielite senza rash:

-prevale nell' immunocompromesso
-dipende da un danno dei piccoli vasi
-non preceduto da rash cutaneo

Sindrome segmentaria:

-prevale nell'immunocompetente
-dipende da un danno dei vasi di medio-grosso calibro satelliti del metamero cutaneo interessato



Clinical case

- A 53-year-old male with medical history of hypertension was admitted for the onset of diplopia associated with fever and headache.
- Primary varicella-zoster virus (VZV) infection in childhood was reported.
- Physical examination was unremarkable, except for binocular diplopia in all directions of gaze and enhanced in the lower quadrants.

- .Patient was alert and oriented and no meningeal irritation signs were revealed. Blood examination tests shows normal differential count and inflammatory markers.
- Elettroencefalogram (EEG) shows moderate slow-sharp anomalies in short spikes on medium anterior derivations.
- A brain CT and MRI scan was normal.

- A lumbar puncture was performed: cerebrospinal fluid analysis (CSF) showed:
  - mononucleated white blood cells count of 144/mm3
  - proteins 60 mg/dl
  - glucose 61 mg/dl

- A quantitative real-time PCR **for VZV-DNA documented a viral load > 300.000.000 copies/ml.**
- Intravenous acyclovir was started at the dose of 1000 mg tid and dexamethasone 8 mg bid.
- CSF VZV DNA PCR was repeated in day 9 (detected < 150 cp/mL) and in day 19 (not detectable).

- Partial improvement of diplopia was observed after seven days.
- The diplopia progressively improved, also after steroid tapering and suspension.
- The patient was discharged on day 20, when he reported the complete disappearance of diplopia.
- Acyclovir was continued up to day 26 in oral formulation (800 mg five time a day).

Encefaliti da EBV

- EBV replica spesso nel SNC e a livello sistemico nei pz immunocompromessi
- in quasi il 50% dei casi replica con altri patogeni e il suo ruolo è aspecifico
- i pazienti sottoposti a trapianto di cellule staminali sembrano più predisposti a sviluppare encefaliti specifiche da EBV
- Il coinvolgimento cerebrale può avvenire nel contesto di una PTLD potenzialmente reversibile

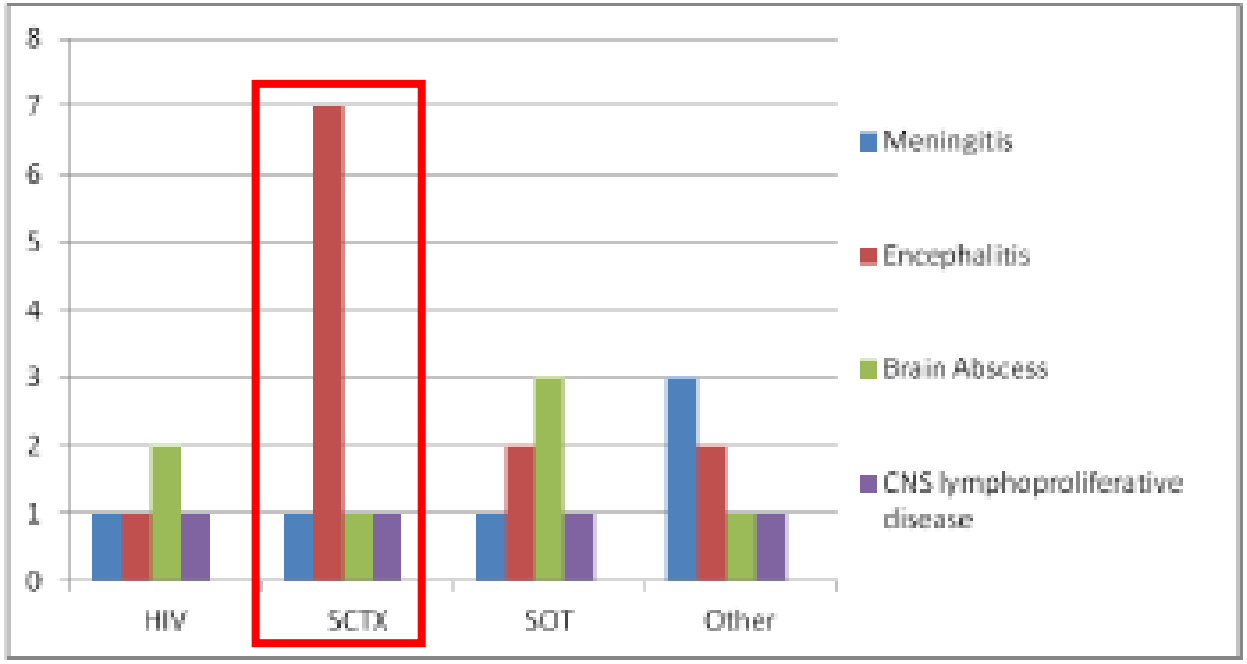


Figure 1 Clinical manifestations of patients with EBV DNA in CSF. Y-axis: number of patients. HIV = HIV infection, HSCT = stem cell transplantation, SOT = solid organ transplantation. *Brain abscess" also includes fungal lesions.

- L'encefalite e la meningite da EBV sono più frequenti nei post trapiantati di midollo
- La malattia linfoproliferativa è la diagnosi più complessa

Martelius, BMC Infectious Dis, 2011

Encefaliti virali da danno neurogeno diretto:

-HSV

-HHV 6

-JCV

Encefaliti virali da danno indiretto (prevalentemente vasculitico):

-morbillo

-VZV

-EBV

-CMV

Virology Journal

BioMed Central

Review

Open Access

Severe cytomegalovirus infection in apparently immunocompetent patients: a systematic review

Table 1: Synopsis of data from previous reviews on severe CMV infections and in immunocompetent patients.

Reference Year of publication	Number of patients	Site involved	Patient demographics	Comorbidity	Antiviral treatment	Outcome
[2]/2007	11	Portal vein thrombosis	55% M/MA 34 y and one infant 4 m	Known thromboembolic risk factors in 64%	ND	Complete thrombus resolution in 73% of patients 2/11 received antiviral treatment
[3]/2005	44	Colitis	61.5% M/61.1(25–71)	18 IM (8 with renal failure, 6 with DM, 2 pregnant), 18 with NM and 10 NC	18.8% in the IM 44% in the NM group 40% in the NC group	MR and SR: 56.3% and 18.8% in the IM, 22% and 33% in the NM group, 10% and 50% in the NC group
[4]/2003	4	Vascular thrombosis and pulmonary embolism	40% M/29–38 y and one neonate	One patient APA, and another FVLH	Ganciclovir one patient, none another ND for 3 patients	Good for personal 2 patients (1 of them received treatment) ND for 3
[5]/2001	15	Colitis	MA 63+/-20 y	ND	34% received AT	31% in the AT group died 36% of those that did not receive AT died**
[6]/2000	19	Meningoencephalitis [16 monophasic (2 of them had multiorgan involvement)] and 3 paroxysmal]	17–78 y	ND	12/16 with monophasic received treatment (8 acyclovir, 3 ganciclovir,1 adenine-arabinoside) None with paroxysmal received treatment	Monophasic without treatment: 4/5 had CR while 1/5 PR With treatment: 13/16 CR, 1/16 PR, 2/16 deaths Paroxysmal: All CR
[7]/1997	27	Hepatitis (15), Nervous system (9), Pneumonitis (2), colitis (1)	44% males, 14–73 y	3 pregnant women	5 ganciclovir, 1 acyclovir, 2 vidarabine, 19 none	1/5 of those who received ganciclovir died, 13/22 of the remaining died
[8]/1985	62	Myocarditis (10), pneumonia (8), encephalitis (7), gastrointestinal infection (8), granulomatous hepatitis (7), haemolytic anaemia (5), icteric hepatitis (3), conjunctivitis (3) severe thrombocytopenia (2), pericarditis (2), meningitis (2), VIII cranial nerve palsy (1), uveitis (1), chorioretinitis (1), rash (2)	ND for the majority 39.8 years old (for patients with granulomatous hepatitis, uveitis, chorioretinitis, gastrointestinal)	ND	ND	All survived except for 3 who died (1 with pericarditis and 2 with gastrointestinal infection) Relapses in one patient with uveitis and persistence in 1 with chorioretinitis

CMV encephalitis

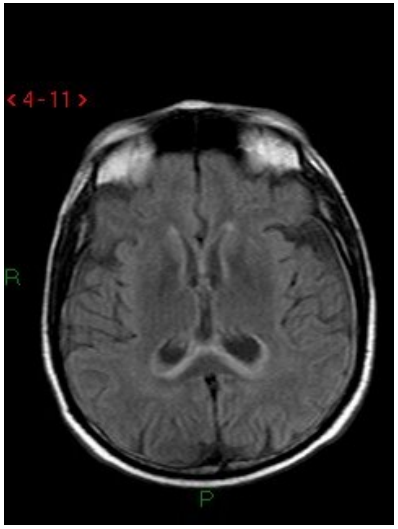
CNS disease due to CMV infection reported in:

- HIV (frequently)
- HSCT (occasionally)

MRI shows changes suggestive of:

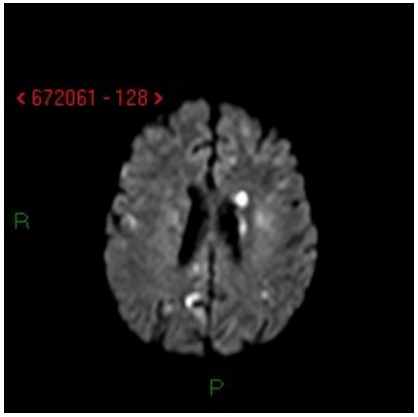
a) Ventriculo-encephalitis: periventricular area

a

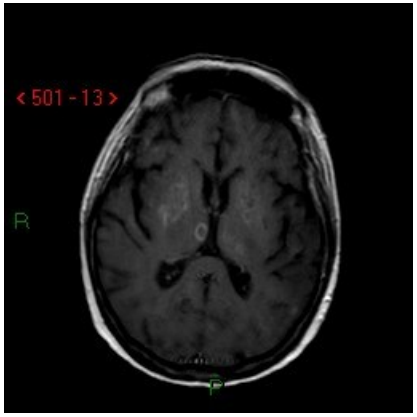


b): multifocal vasculitis

b1



b2



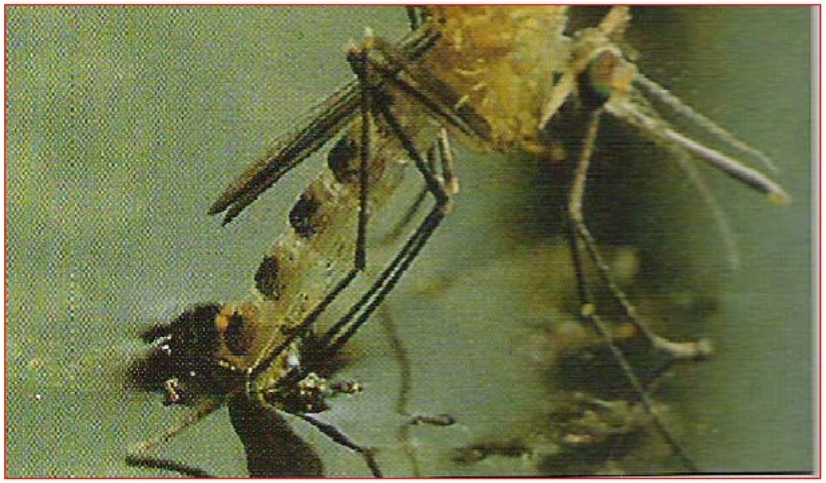
Management

- Specific antiviral therapy is generally limited to infections causes by herpesviruses (especially HSV-1 and VZV) and HIV.
- Aciclovir (10 mg/kg intravenously q8h in children and adults with normal renal function; 20 mg/kg intravenously q8h in neonates) should encephalitis and continued until HSV-1 has been excluded by PCR.
- Empiric therapy for acute bacterial meningitis should be initiated when clinical and laboratory testing is compatible with bacterial infection
- Clinicians should consider conditions that mimic infectious encephalitis, particularly if no etiology is identified in the first week of illness.

- In patients suspected to have postinfectious encephalomyelitis (i.e. ADEM), steroids or other immunotherapies are often recommended.
- High-dose intravenous corticosteroids (methylprednisolone 1 g intravenously daily for at least 3–5 days, followed by an oral taper for 3–6 weeks) are generally recommended for ADEM;

West Nile fever

arbovirus



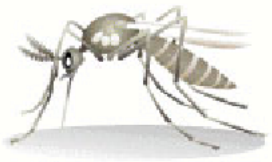
Culex quinquefasciatus

Fever, headache,
lymphoadenopathy,
angina,
Encephalitis
Severe in older people

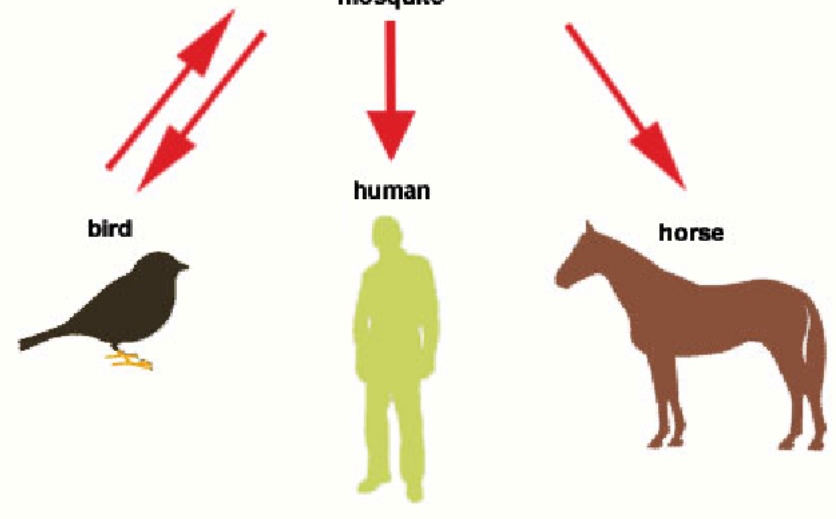
Since 1999 WNV (NY strain) is present in the USA

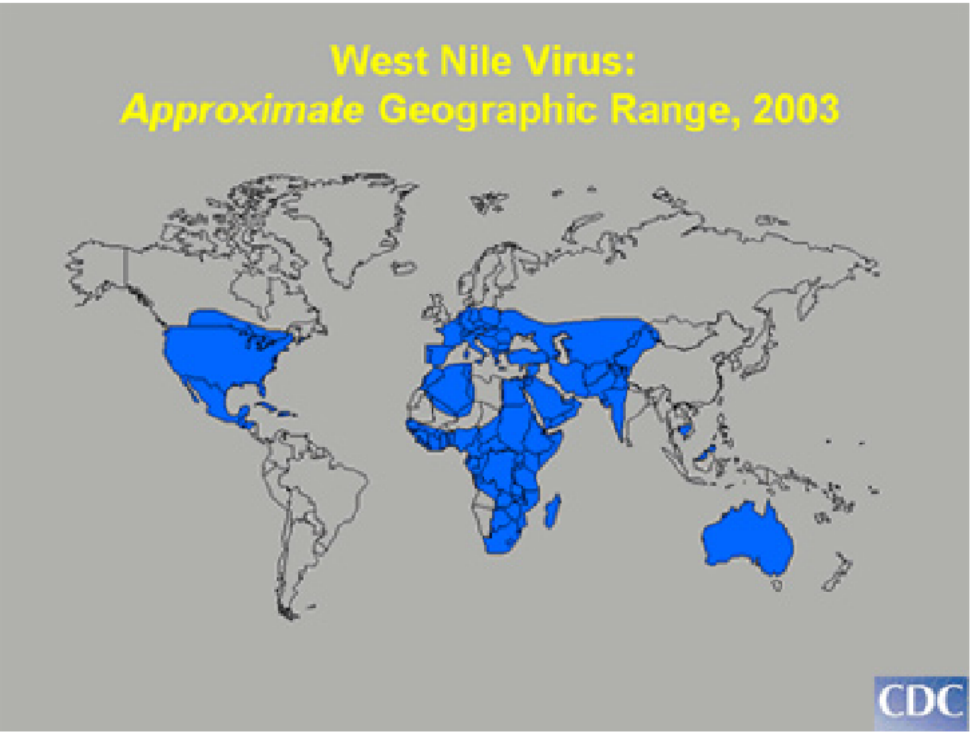
At least 2.6% of the population in the Queens district of NY has been infected. Most cases were benign. However, 7 deaths were recorded

West Nile Virus

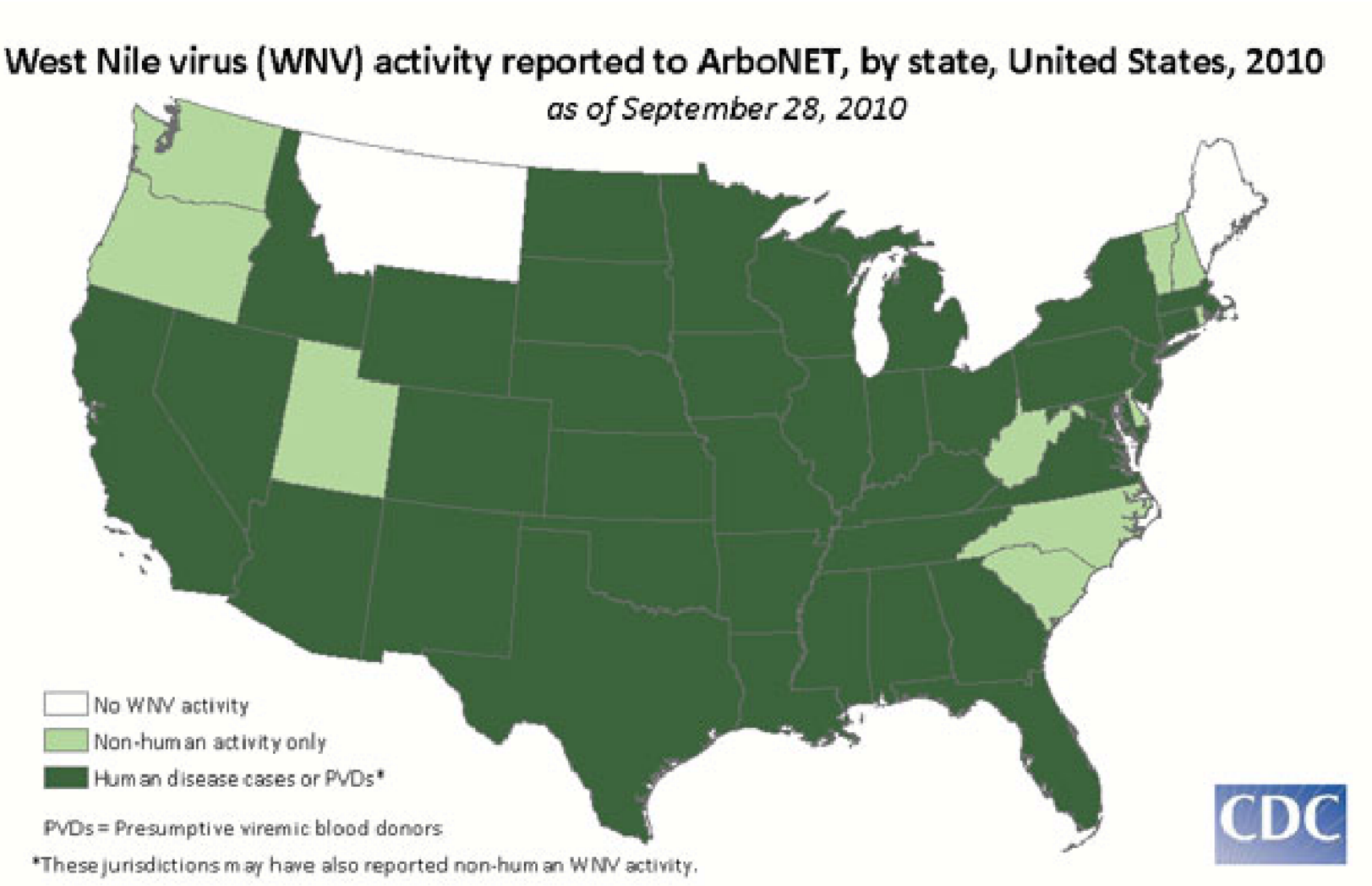


Culex
Aedes





Prior to 1999, the West Nile virus had only been found in Africa, Eastern Europe,



547 cases, 22 deaths

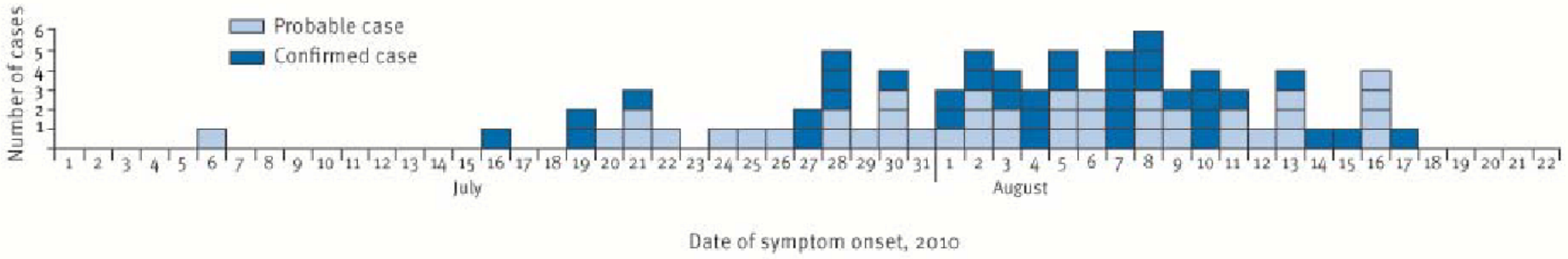
West Nile virus: the need to strengthen preparedness in Europe

H Zeller (evd@ecdc.europa.eu)[1], A Lenglet[1], W Van Bortel[1]
1. European Centre for Disease Prevention and Control, Stockholm, Sweden

Reemergence in Greece

FIGURE 1

Reported cases of West Nile neuroinvasive disease by date of symptom onset, Greece, 1 July – 22 August 2010 (n=81)



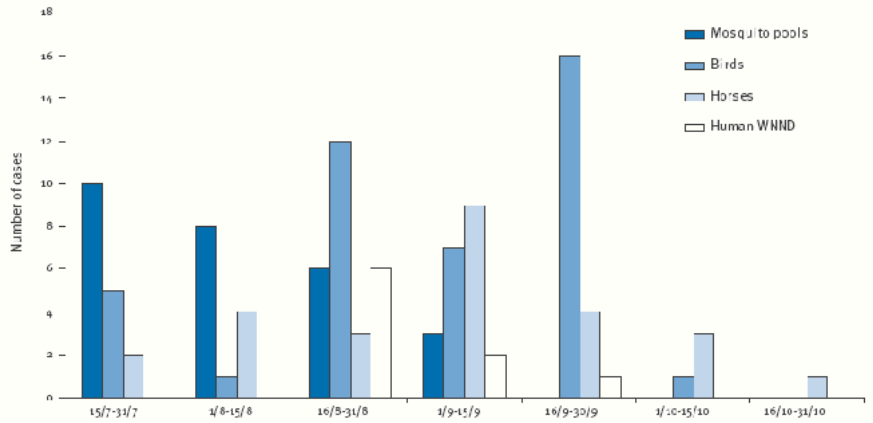
WNV documented in animals and humans in several countries across Europe, mainly in central Europe and in the Mediterranean region.
Over the last 15 years, outbreaks in horses and/or humans were reported from Romania, Hungary and Portugal, Spain, France, Italy and Greece

West Nile virus circulation in Emilia-Romagna, Italy: the integrated surveillance system 2009

P Angelini (pangelini@regione.emilia-romagna.it)[1], M Tamba[2], A C Finarelli[1], R Bellini[3], A Albieri[3], P Bonilauri[2], F Cavrini[4], M Dottori[2], P Gaibani[4], E Martini[5], A Mattivi[1], A M Pierro[4], G Rugna[2], V Sambri[4], G Squintani[5], P Macini[1]

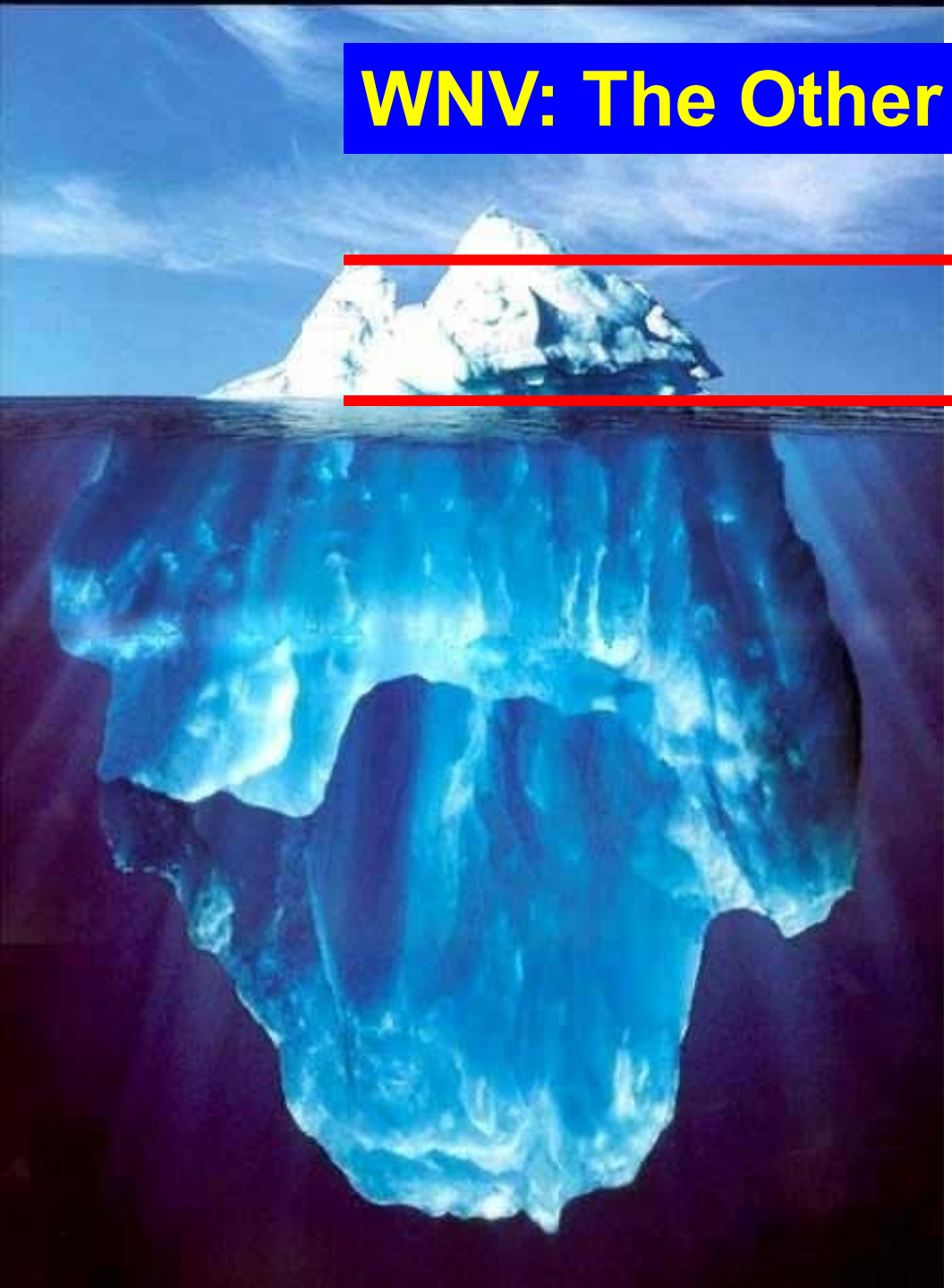
Map of municipalities with confirmed West Nile virus circulation and localisation of human West Nile neuroinvasive disease cases by probable infection site, Emilia-Romagna, Italy, 2009

Distribution of West Nile virus confirmed cases (mosquito pools, birds, horses, and human West Nile neuroinvasive disease) by date, Emilia Romagna, Italy, July October 2009



Euro Surveill.2010;15(16):pii=19547.
Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19547

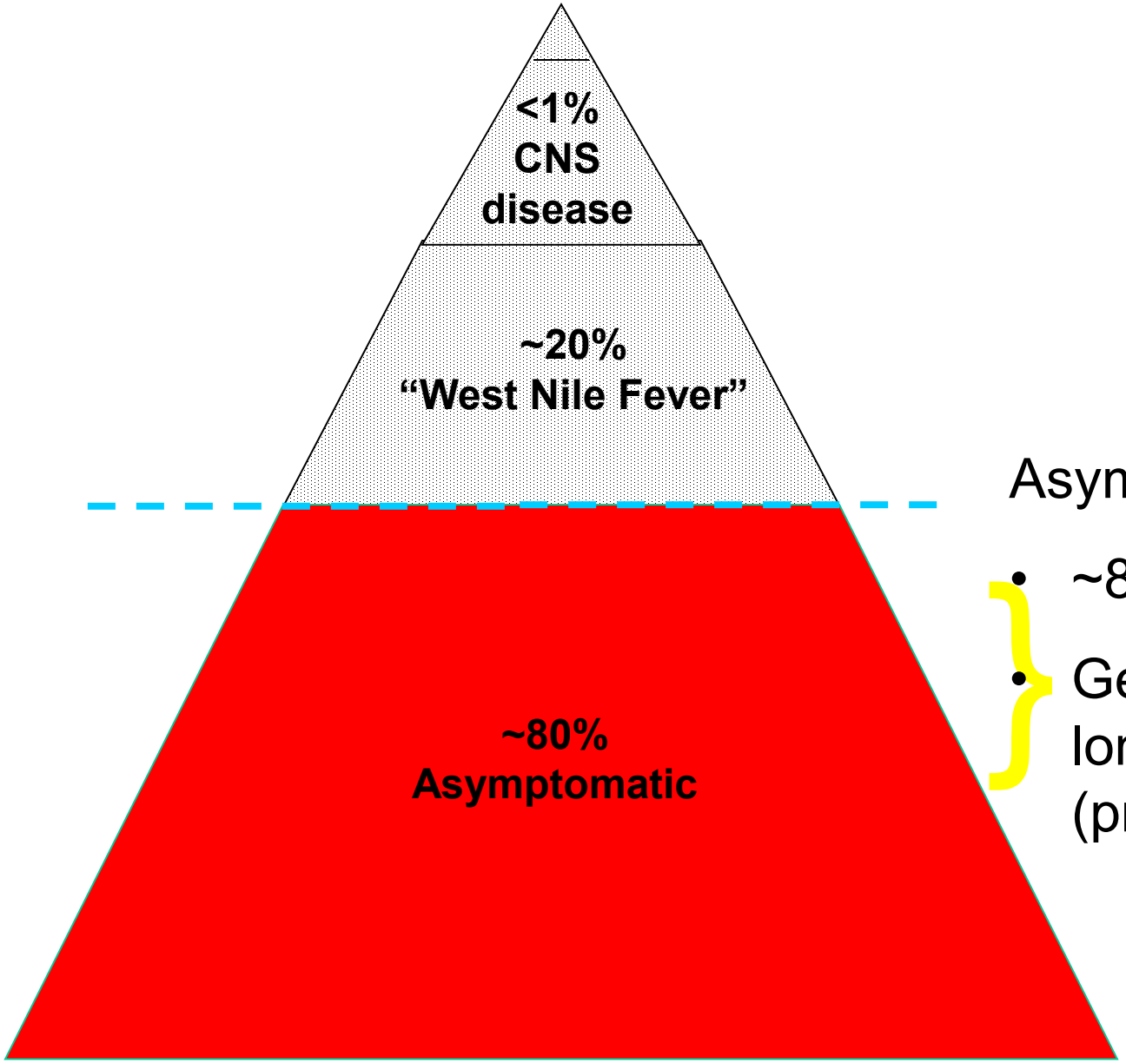
WNV: The Other "Iceberg"



Acute WNV Illness

WNV Long-term effects

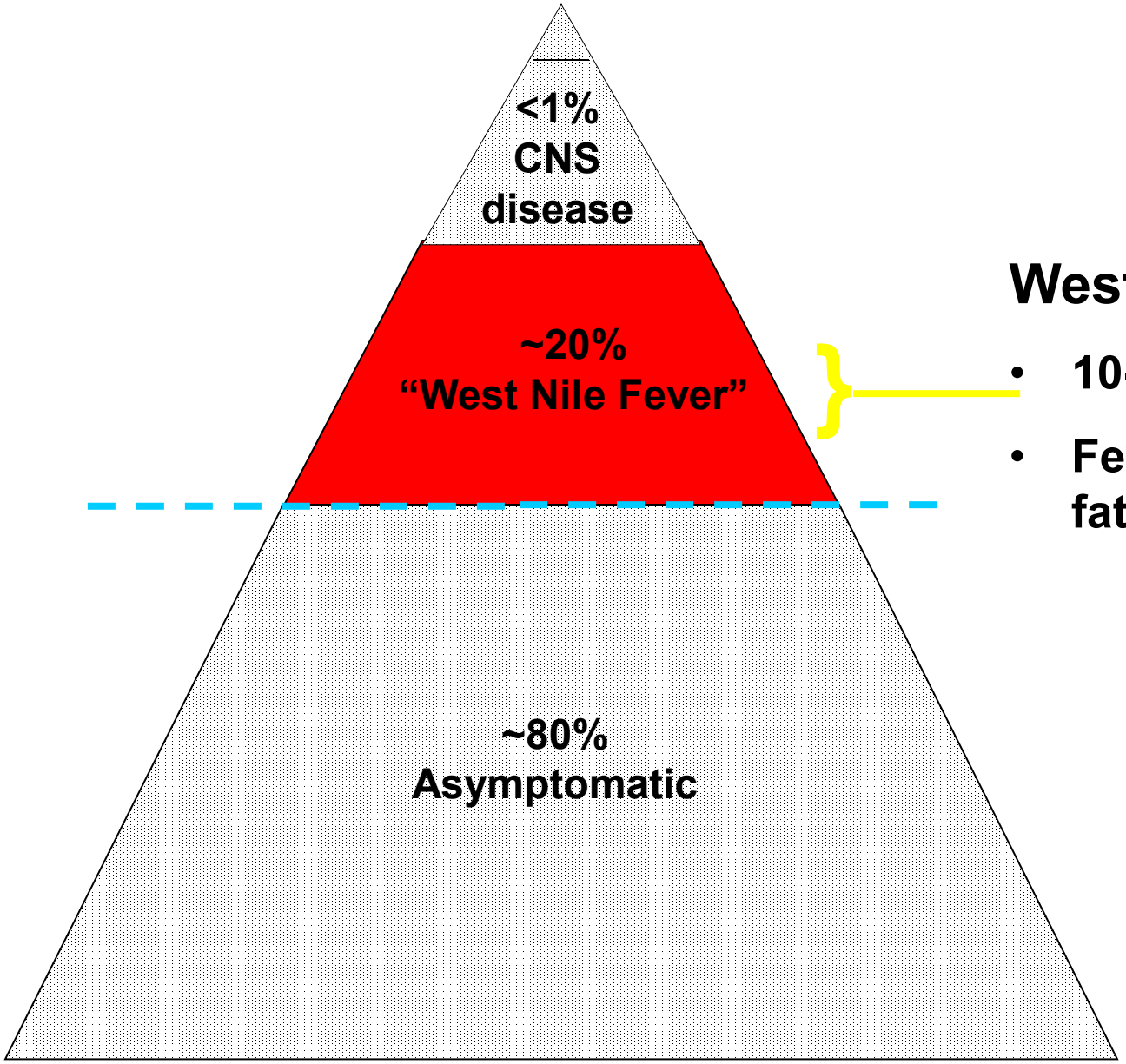
WNV Human Infection "Iceberg"



Asymptomatic Infection

- ~80% of infections
- Generation of life-long immunity (presumed)

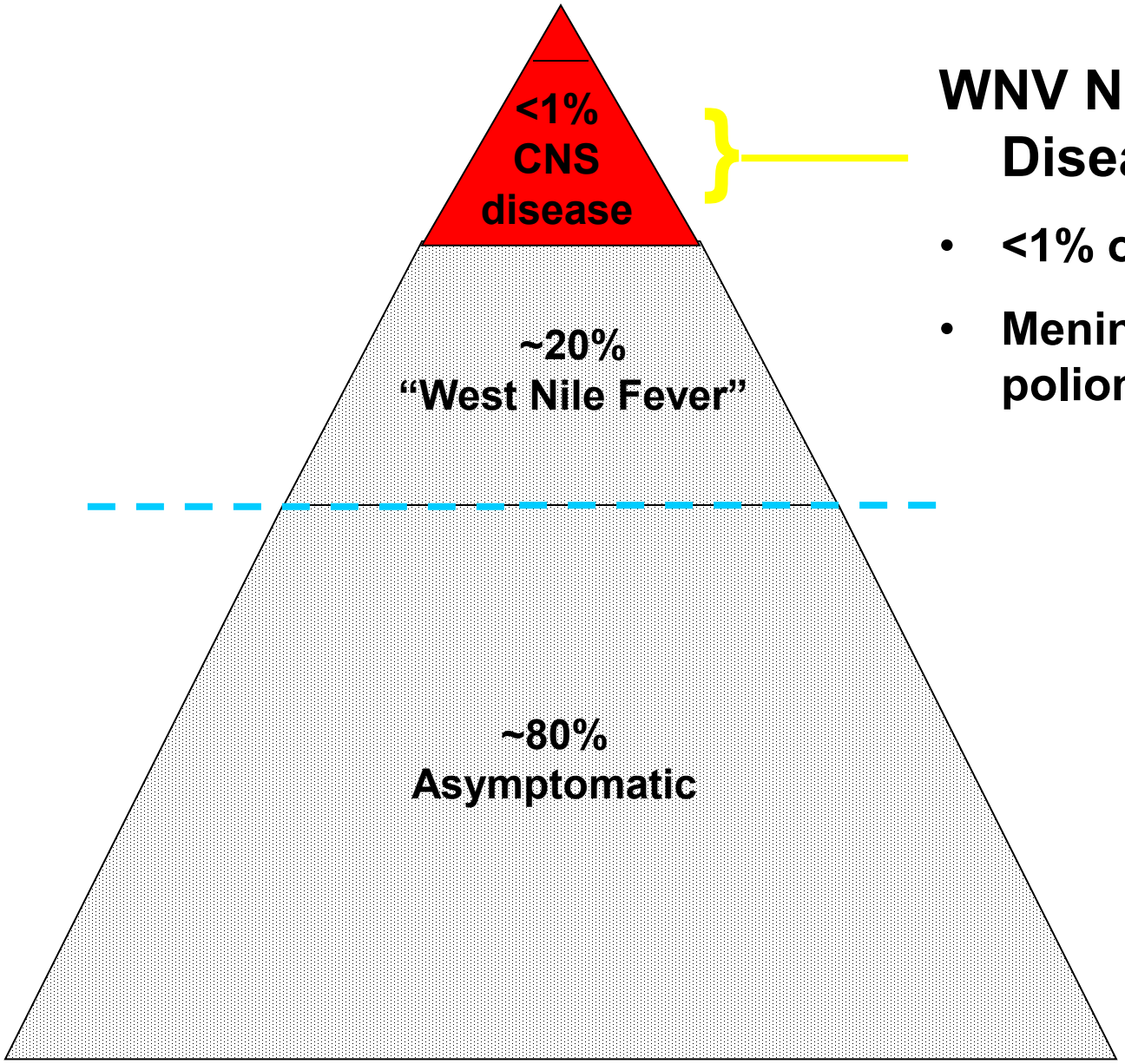
WNV Human Infection "Iceberg"



West Nile Fever

- 10-30% of infections
- Fever, headache, rash, fatigue

WNV Human Infection "Iceberg"



WNV Neuroinvasive Disease (WNND)

- **<1% of all infections**
- **Meningitis, encephalitis, poliomyelitis**

WNV—Treatment

- No definitive treatment—management symptomatic only
- Multiple agents tried: IFN-α, ribavirin, antisense nucleotides, steroids,
  - All: case reports, limited case series with uninterpretable results
  - None: definitive efficacy
- NIH-sponsored randomized, placebo-controlled trial of high-titre WNV intravenous immune globulin
  - Limited by small enrollment; results pending
- WNV vaccine
  - Under Phase I / II clinical trials
  - Promising safety, efficacy profiles
  - Cost-effectiveness of WNV vaccine unclear

WNV—Novel Modes of Transmission

- Blood transfusion-associated transmission
  - First recognized in 2002
  - As of July 2003, US blood donors screened for WNV using nucleic acid amplification testing (NAT)
- Solid organ transplant transmission
- Intrauterine transmission
- Transmission through breast milk (?)

WNV—Novel Modes of Transmission

- Solid organ transplant-associated transmission
  - 2 published transplant-associated outbreaks (2002, 2005)*#
  - Total of 7 cases

    Kidney (3) Liver (2)

    Lung (1) Heart (1)
  - Included 1 cluster in which donor was WNV-IgM / IgG antibody + / nucleic acid PCR –
- Implications for organ donor screening

*Iwamoto et al, NEJM 2003 # CDC, MMWR 2005

WNV And Pregnancy

- One confirmed intrauterine transmission (2002)*
  - 20-year old female with WNND 2 months before delivery
  - Infant with subsequent retinitis, lissencephaly
  - Birth tissues WNV PCR +, infant serum & CSF WNV IgM +
- Subsequent surveillance, 2003 – 2005#
  - 0 / 79 intrauterine transmissions
  - 3 / 79 with infection shortly after birth (transplacental transmission?)

*Alpa et al, Am J Opthamol 2003; CDC, MMWR 2002

O'Leary et al. Pediatrics 2006

West Nile Virus: transplacentar transmission?


Birth Outcomes Following West Nile Virus Infection of Pregnant Women in the United States: 2003-2004

O'Leary et al. Pediatrics 2006

TABLE 2 Frequencies of Birth Abnormalities Among Live-Born Infants of Women

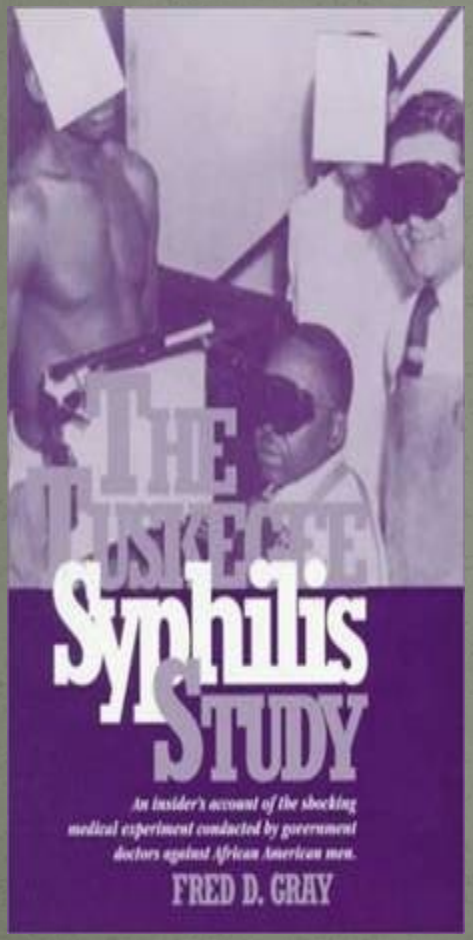
Condition	Among 72 Live Births, % (95% CI)	General Population, %
Major birth defects		
All major defects[a]	10.6 (5.2–20.3)	5.5[a]
Aortic coarctation	1.5 (0.3–8.1)	0.03
Cleft palate	1.5 (0.3–8.1)	0.04
Down syndrome	1.5 (0.3–8.1)	0.13
Lissencephaly	1.5 (0.3–8.1)	0.001
Microcephaly[b]	3.5 (1.0–11.7)	2.28
Polydactyly	1.5 (0.3–8.1)	0.2
Other adverse outcomes		
Glycogen storage disease type 1	1.5 (0.3–8.1)	0.0005
Spontaneous abortion	9.1 (3.4–21.2)[c]	15.0
Low birth weight	4.8 (1.6–13.1)	7.9
Preterm	5.6 (2.2–13.6)	12.3

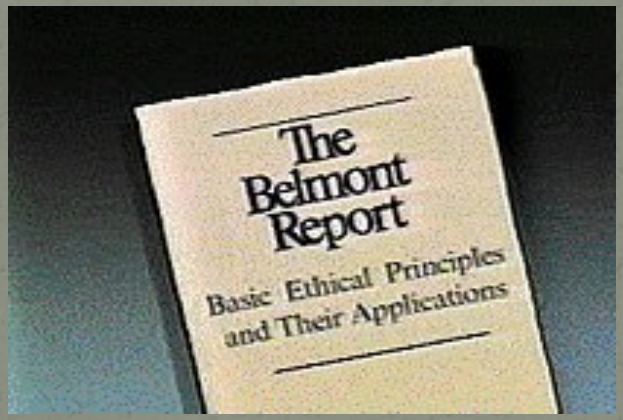
2003-4 study reported on 77 women infected with WNV during pregnancy

- 71 delivered 72 live infants
- 7 had malformations, 3 of whom possibly caused by maternal WNV
- No greater incidence of malformation than in general population
- 4 miscarriage
- 2 elective abortion

2/42 breastmilk + for WNV RT-PCR. 1 breast-fed foollowed: neg at 7 months

TUSKEGEE TRAGEDY AND BELMONT REPORT





Presented by:

Ginumol George
Girish Tandel
Harpreet Notey
Harshajeet Patil
Hitakshi Trivedi

Batch: M.Sc. CR (2009-2011)
Cranfield University.
Date:- March 2010

“Lo studio più infame nella ricerca biomedica nella storia degli Stati Uniti”

Location

- Tuskegee study was conducted in province of America in Alabama.
- It is situated in South Eastern region of the country.

"Tuskegee Study of Untreated Syphilis in the Negro Male"

When?

- 1932 – 1972

Where?

- Macon County, Alabama

Who?

- The US Public Health Service along with the Tuskegee Institute
- 600 African American men[2]
  - 399 with syphilis (Experimental Group)
  - 201 without syphilis (Control Group)

2. "About the USPHS Syphilis Study." Tuskegee University. Tuskegee University, n.d. Web. 20 June 2012. <http://www.tuskegee.edu/about_us/centers_of_excellence/bioethics_center/about_the_usphs_syphilis_study.aspx>.

False Advertising to Patients

- No informed consent
  - "These negroes are very ignorant and easily influenced by things that would be of minor significance in a more intelligent group"[6] (Clark)
- Did not want participants to know they would be autopsied

(Spinal tap)

6. Brandt, Allan M. "Racism and Research: The Case of the Tuskegee Syphilis Study." Hastings Center Magazine, (1978): 1-13. SciFinder. Web. 9 June 2012.

Natural History of Syphilis

Infection

↓ **2 - 6 weeks**

Primary
Chancre, regional adenopathy

↓ **1 - 3 months**

Secondary
Rash, generalized adenopathy

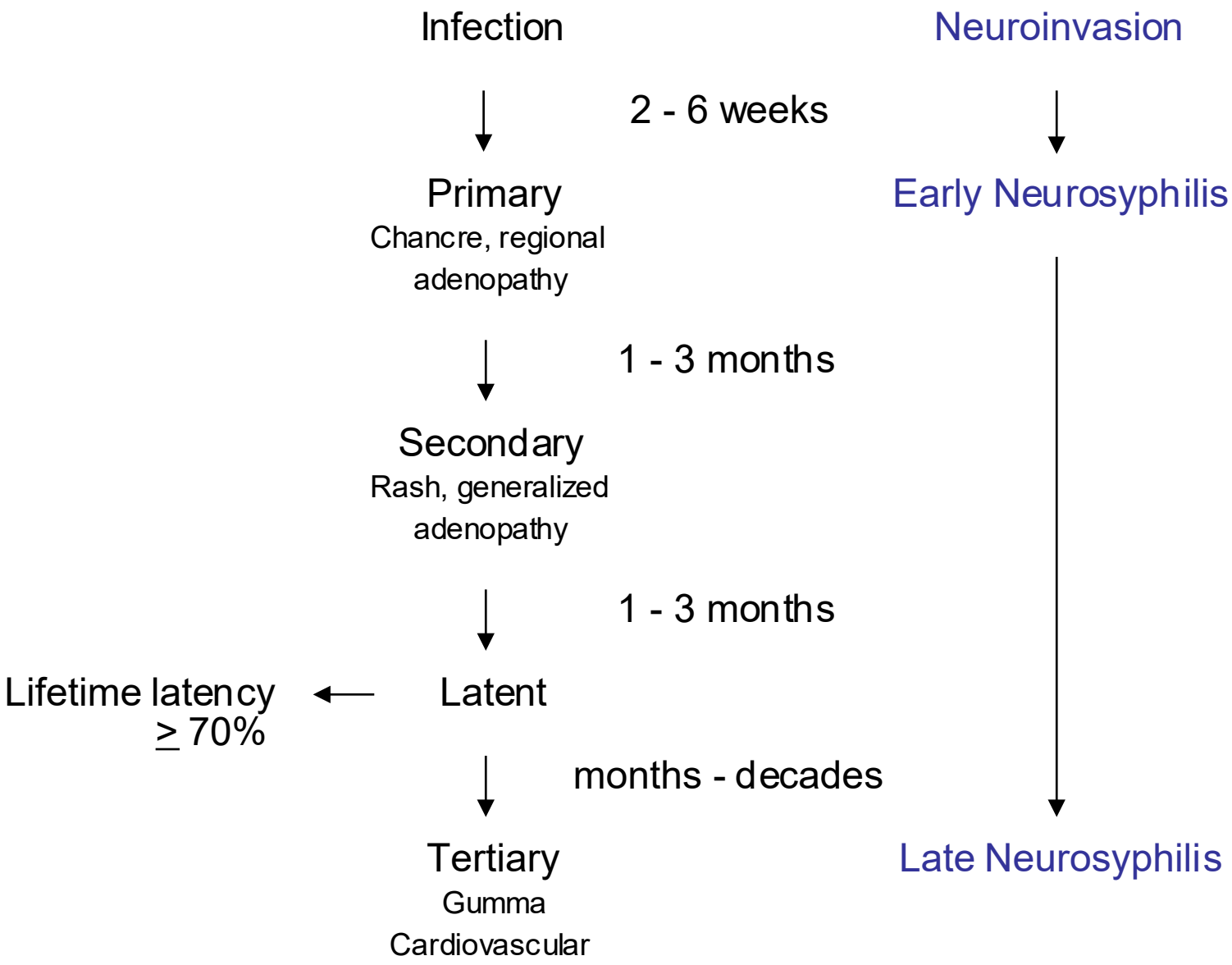
↓ **1 - 3 months**

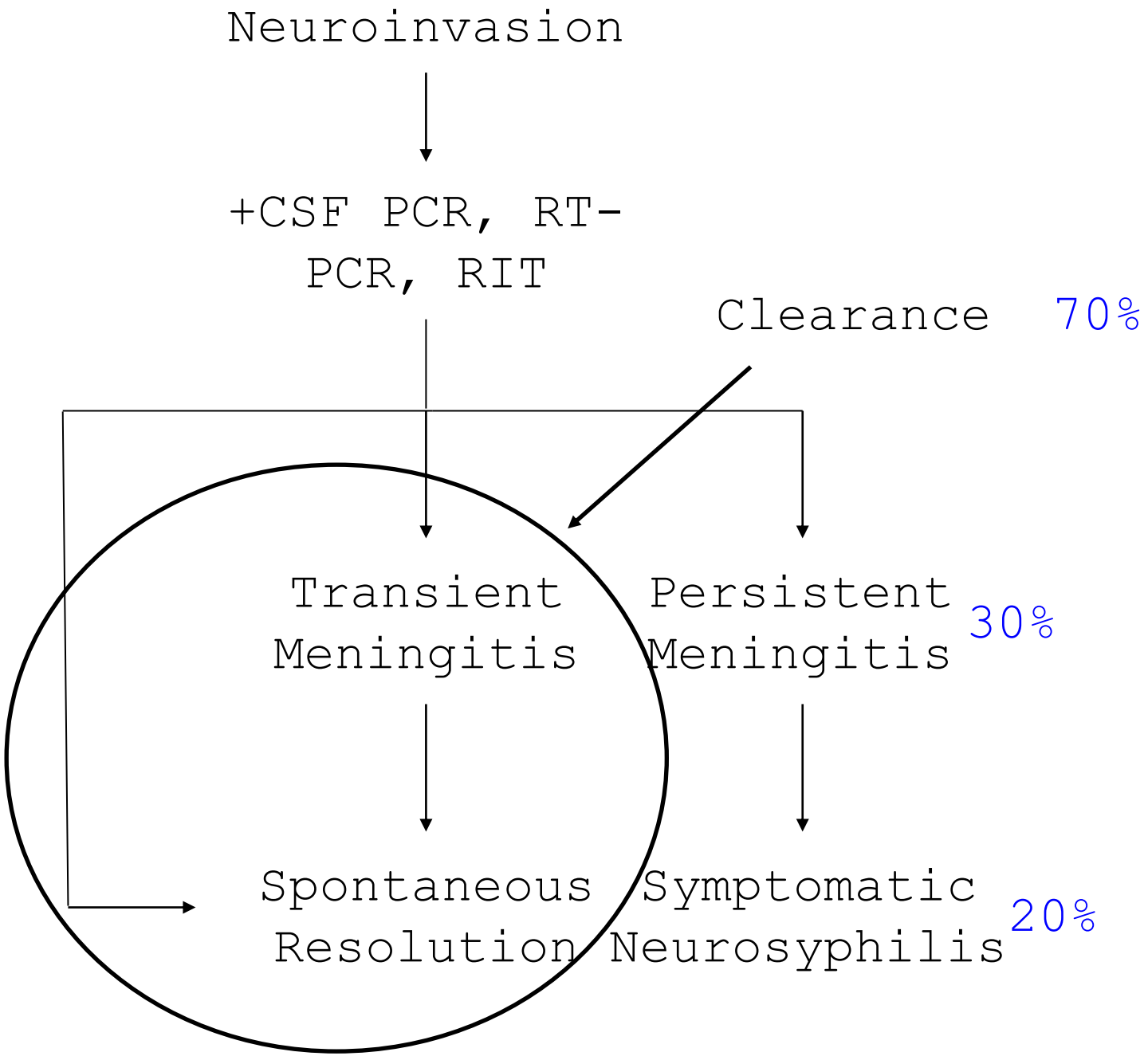
Latent ← **Lifetime latency ≥ 70%**

↓ **months - decades**

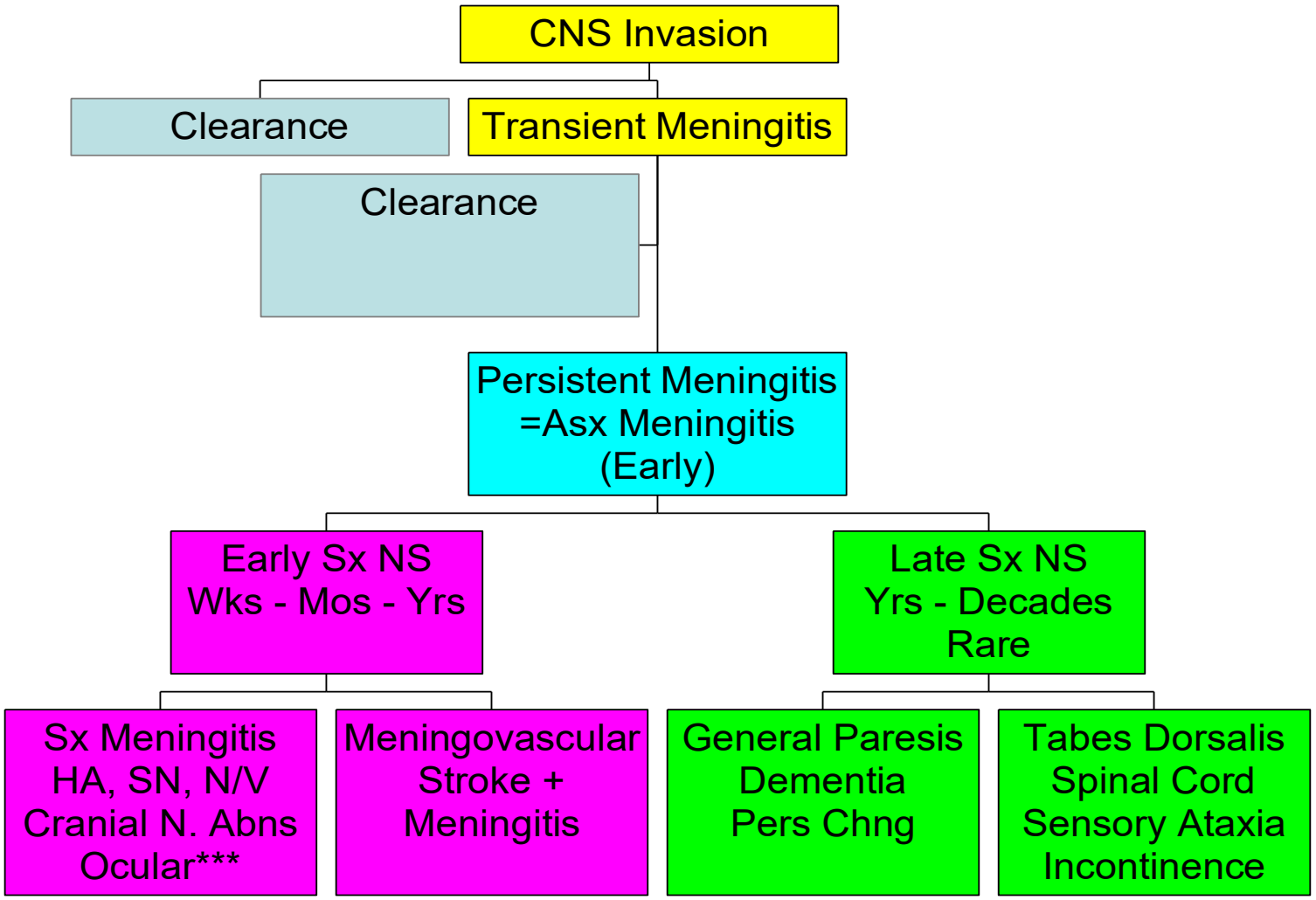
Tertiary
Gumma
Cardiovascular

Natural History of Syphilis




Neuroinvasion
+CSF PCR, RT-PCR, RIT
Clearance 70%
Transient Meningitis
Persistent Meningitis 30%
Spontaneous Resolution
Symptomatic Neurosyphilis 20%

Neurosyphilis Natural Hx



L'interessamento del sistema nervoso avviene già nelle fasi precoci della malattia, benché per lo più in forma latente, e le gravi manifestazioni tardive, di tipo neurologico, derivano dal carente trattamento nello stadio primario dell'infezione.

Neurosyphilis
practical definition

a CSF WBC count of 20 cells/μL or greater and a reactive CSF Venereal Disease Research Laboratory (VDRL) test result

…è così semplice ?

Diagnosi

- **Test sierologici** (VDRL, TPHA)
- **Puntura lombare** (alterazioni chimico-fisico, cellule, VDRL, ricerca diretta treponema, PCR)
- **NeuroImaging** (RMN, SPECT, PET)
- **Test elettrofisiologici** (potenziali evocati somatosensoriali, EEG)

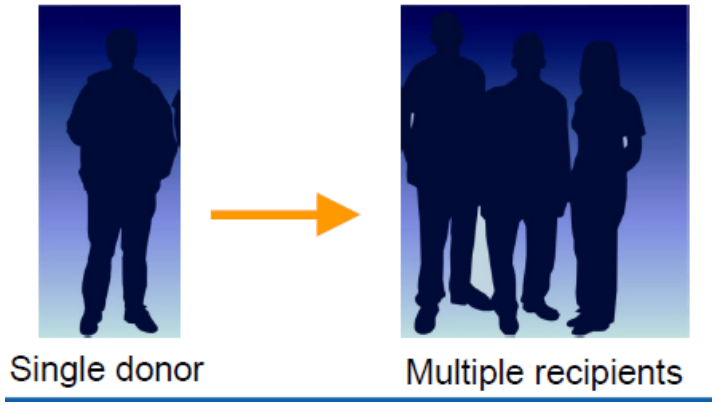
Lumbar puncture

- 10% have CSF **protein values** of less than 46 mg/dL, 70% have CSF protein values of 46-100 mg/dL, and 10% have CSF protein values greater than 100 mg/dL.
- The **CSF WBC count** is normal in 70% of patients, whereas it is 5-10/µL in 20% of patients and greater than 10µL in 10%; it is 4 times more likely to be lymphocytic rather than characterized by polymorphonuclear neutrophils

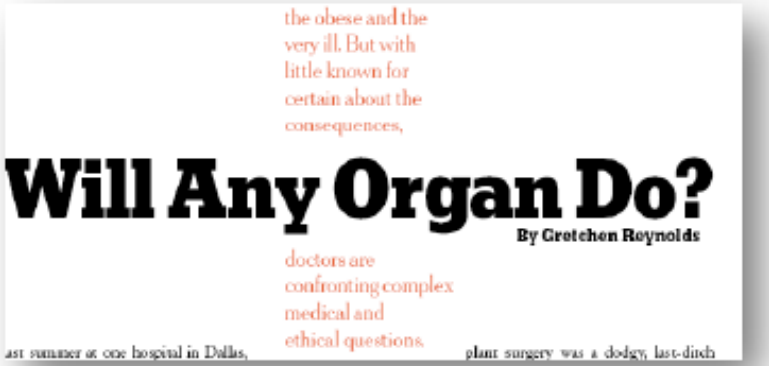
Novel Transplant-Associated Infections

Unexpected Donor-derived Infections Associated with Organ Transplantation

- **Multiple challenges**
  - Unexpected or unrecognized at time of death
  - Not screened for in donor
  - Unknown incidence (presumed low)
  - Associated with significant morbidity and mortality
  - High-profile events



Unexpected Donor-derived Infections



the obese and the very ill. But with little known for certain about the consequences,

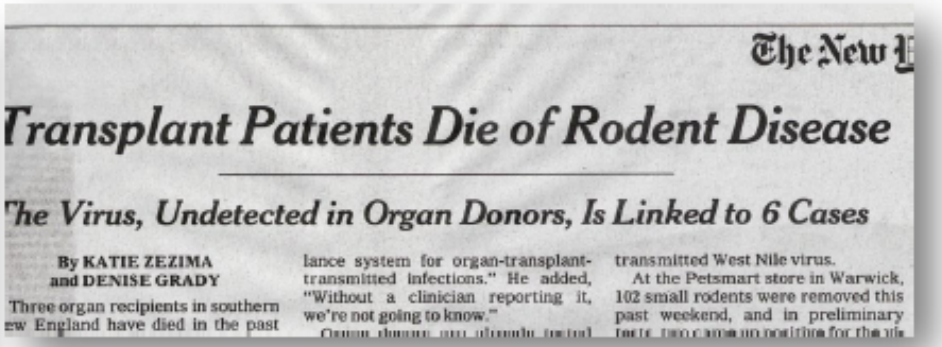
Will Any Organ Do?

By Gretchen Reynolds

doctors are confronting complex medical and ethical questions.

ast summer at one hospital in Dallas, plant surgery was a dodgy, last-ditch

NY Times, 2005 (Rabies)



The New

Transplant Patients Die of Rodent Disease

The Virus, Undetected in Organ Donors, Is Linked to 6 Cases

By KATIE ZEZIMA and DENISE GRADY

Three organ recipients in southern ew England have died in the past

lance system for organ-transplant-transmitted infections." He added, "Without a clinician reporting it, we're not going to know."

transmitted West Nile virus.

At the Petsmart store in Warwick, 102 small rodents were removed this past weekend, and in preliminary

NY Times, 2005 (LCMV)

Officials Re-examining Organ Transplant Rules

Brain Infection in Two Patients Raises Issue

By DENISE GRADY

The plight of two kidney transplant patients who contracted a brain infection from an organ donor is prompting health officials to re-examine their policies on using people with certain neuro-

vising in the patients' treatment.

Dr. Matthew J. Kuehnert, the director of the office of blood, organ and other tissue safety at the disease centers, said that transplant patients are sometimes an early warning system for new in-

NY Times, 2009 (Amoeba)

WEST NILE CASES RAISING QUESTIONS OVER TRANSPLANTS

NO TEST TO SCREEN BLOOD

Weeks Needed to Determine if Operation or a Transfusion Allowed Transmissions

NY Times, 2002 (WNV)

Novel and Emerging Donor-derived Transplant-transmitted Infections, 2002–2014

- **West Nile virus**
  - 6 clusters
- **Lymphocytic choriomeningitis virus**
  - 5 clusters
- **Rabies**
  - 2 clusters
- **Balamuthia**
  - 2 clusters
- **Microsporidiosis**
  - 2 clusters

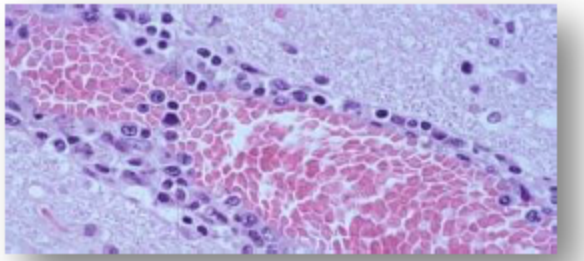
West Nile Virus (WNV) in an Organ Donor and Four Transplant Recipients, August 2002

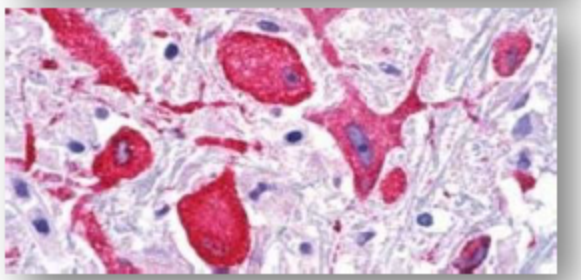
Organ DONOR
- ✓ Female victim of a car accident
- ✓ Received multiple transfusions
- ✓ Patient died

All organ RECIPIENTS became febrile (2 kidney, liver, heart)

One kidney recipient died
- ✓ Thought to have had WNV
- ✓ Seronegative for WNV

But IHC and PCR showed WNV encephalitis





Viral antigens in red, IHC

Stimulated trace back investigation

Blood components from 63 donors
- ✓ Only one component was WNV IgM positive
- ✓ Only one component was WNV PCR positive, but WNV IgM negative

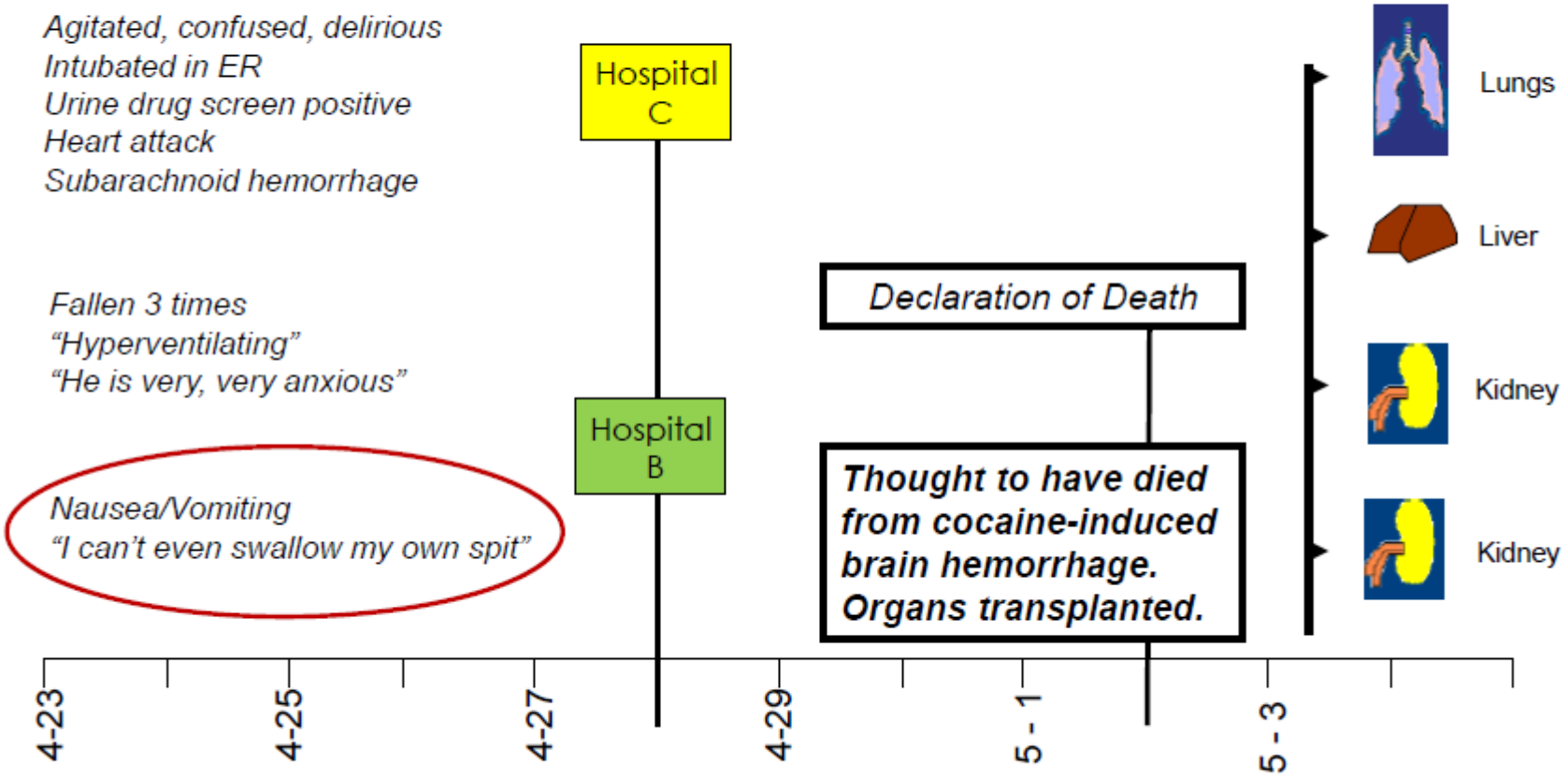
IHC: Immunohistochemistry
PCR: Polymerase chain reaction
Iwamoto M, et al. *NEJM* 2003.

Another Unusual Infection Transmitted from Organ Donor to Four Transplant Recipients

- In 2004, CDC contacted by pathologist in Texas
- Two transplant recipients with unexplained deaths
- Third transplant recipient with altered mental status
- Connection of a common donor among cases was determined by families whose loved ones were in the intensive care unit

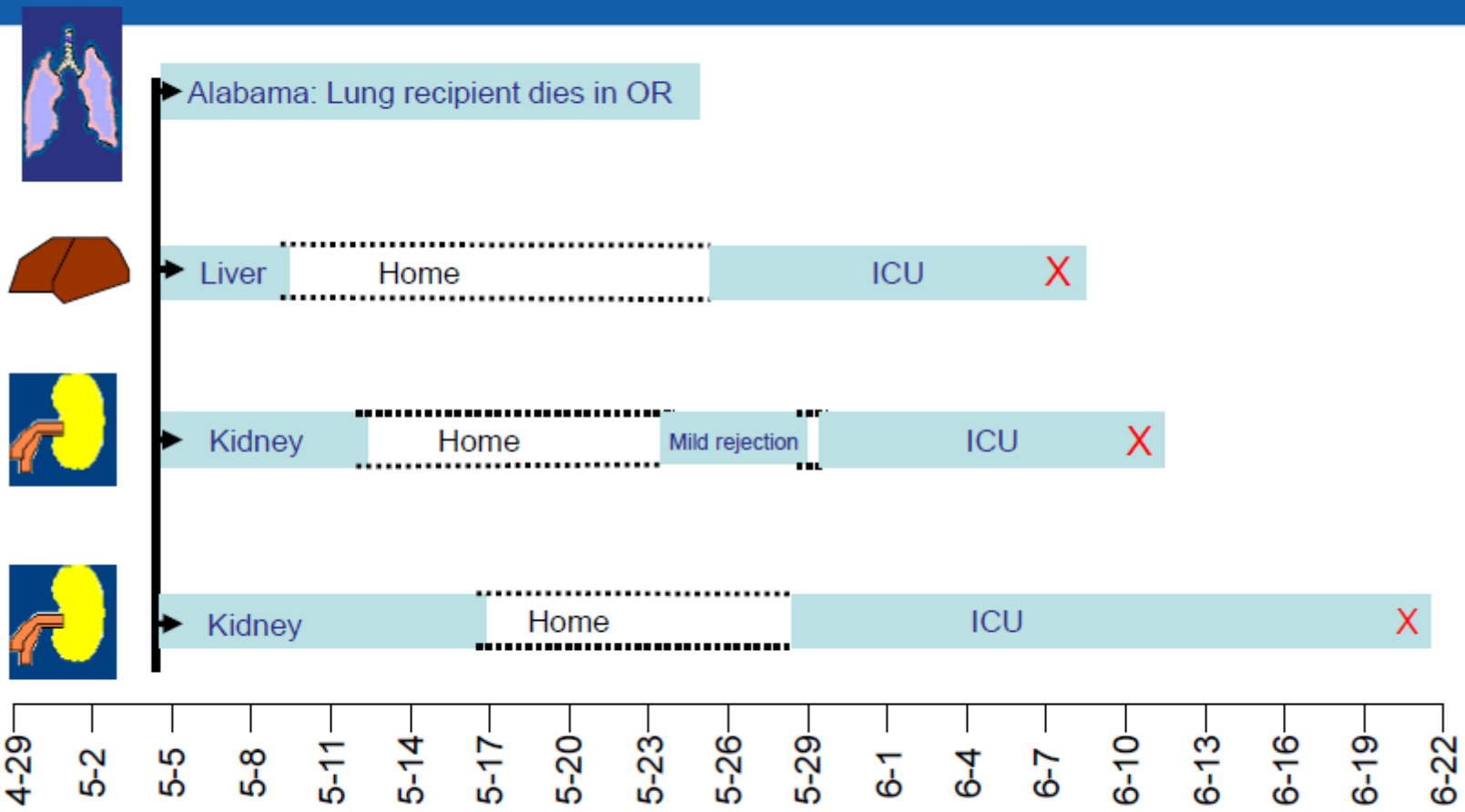
Srinivasan A, et al. *NEJM* 2005.

Twenty year-old Male Donor



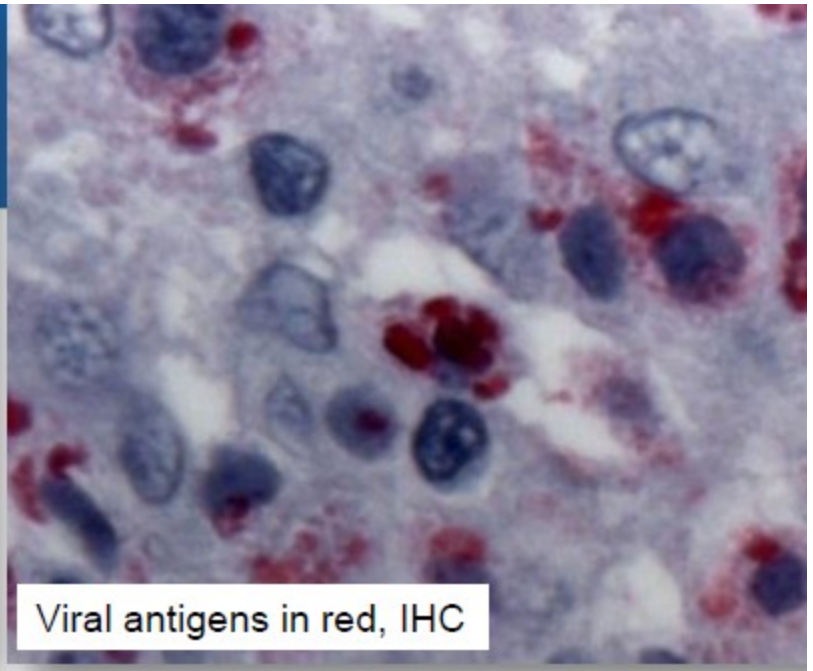
Organ donor timeline, April–May 2004

Background on the Four Recipients at Hospital A, Texas

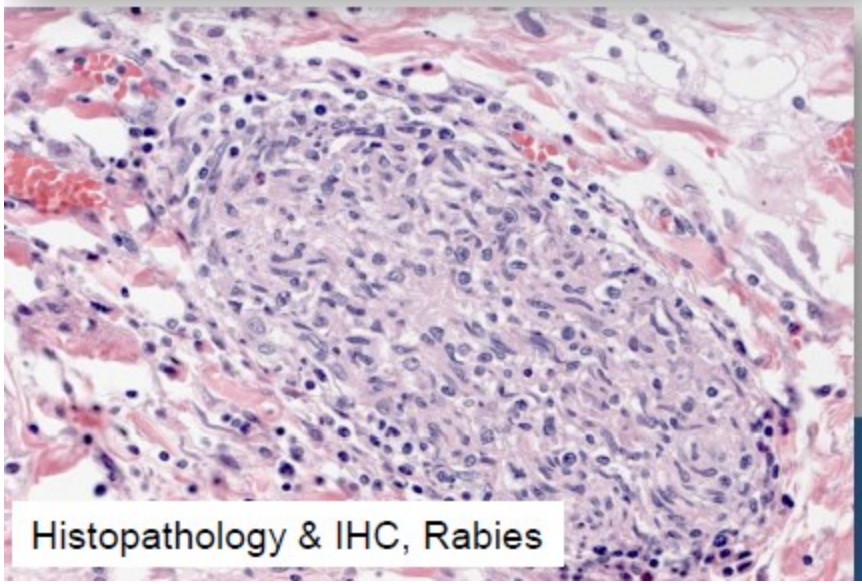


Organ recipient timeline, April–June 2004

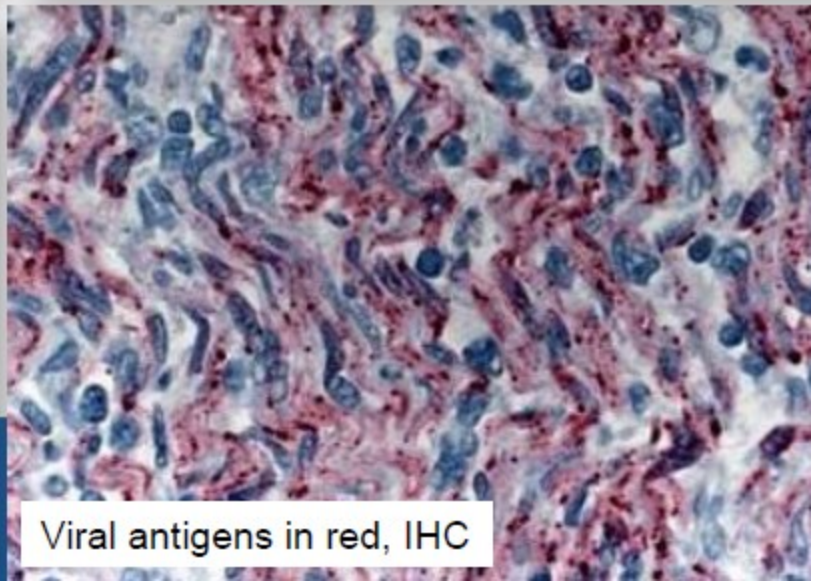
Negri bodies, indicating rabies!



Viral antigens in red, IHC



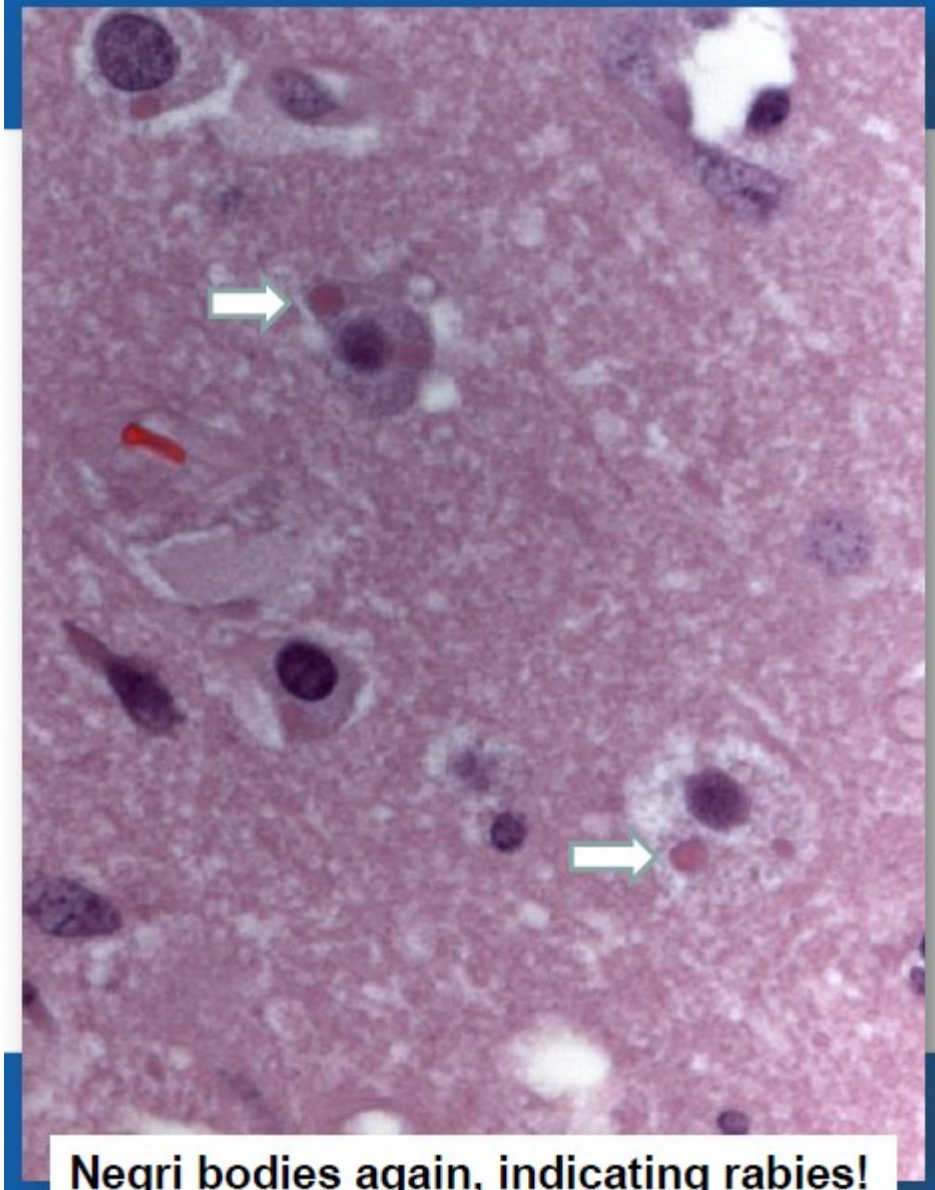
Histopathology & IHC, Rabies



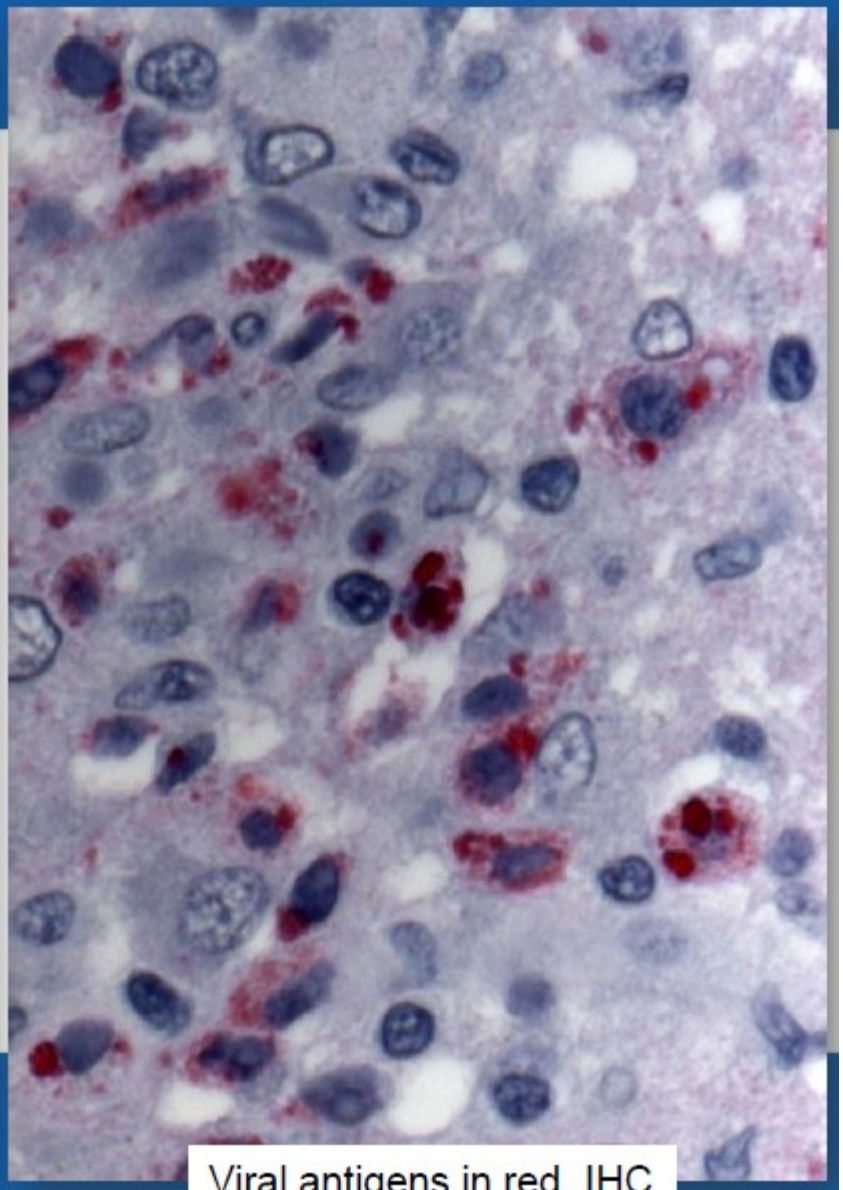
Viral antigens in red, IHC

The Persistent Pathologist…

- **Recalled 4th death due to encephalitis in organ transplant recipient**
- **Reviewed autopsy**
  - Consistent with viral encephalomyelitis due to West Nile virus
  - Received liver transplant
  - Different donor than other cases
- **Specimens sent to CDC for further investigation**



Negri bodies again, indicating rabies!



Viral antigens in red, IHC

Donor's serum positive and sequence from all three recipients was exactly the same

N ENGL J MED 352;11 WWW.NEJM.ORG MARCH 17, 2005

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Transmission of Rabies Virus from an Organ Donor to Four Transplant Recipients

Arjun Srinivasan, M.D., Elizabeth C. Burton, M.D., Matthew J. Kuehnert, M.D., Charles Rupprecht, V.M.D., Ph.D., William L. Sutker, M.D., Thomas G. Ksiazek, D.V.M., Ph.D., Christopher D. Paddock, M.D., Jeannette Guarner, M.D., Wun-Ju Shieh, M.D., Ph.D., Cynthia Goldsmith, M.S., Cathleen A. Hanlon, V.M.D., Ph.D., James Zoretic, M.D., Bernard Fischbach, M.D., Michael Niezgoda, M.S., Waleed H. El-Feky, M.D., Lillian Orciari, M.S., Edmund Q. Sanchez, M.D., Anna Likos, M.D., M.P.H., Goran B. Klintmalm, M.D., Denise Cardo, M.D., James LeDuc, Ph.D., Mary E. Chamberland, M.D., M.P.H., Daniel B. Jernigan, M.D., M.P.H., and Sherif R. Zaki, M.D., Ph.D., for the Rabies in Transplant Recipients Investigation Team*

Rabies variant from Mexican Free-Tailed Bat

The NEW ENGLAND JOURNAL of MEDICINE

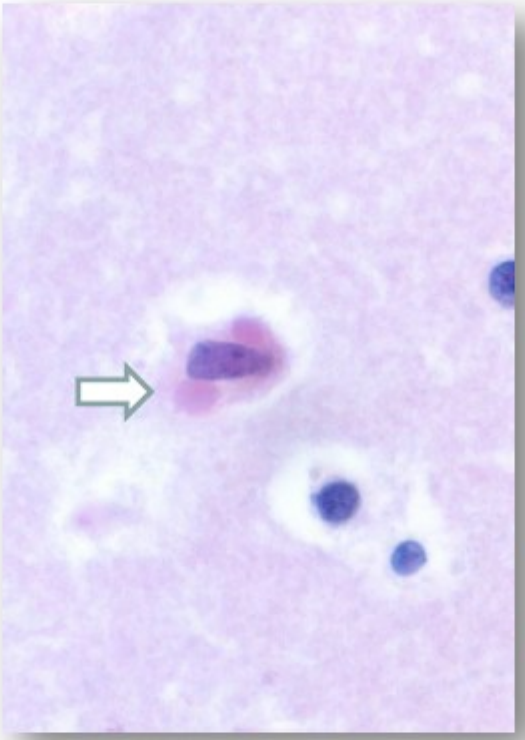
ORIGINAL ARTICLE

Transmission of Rabies Virus from an Organ Donor to Four Transplant Recipients

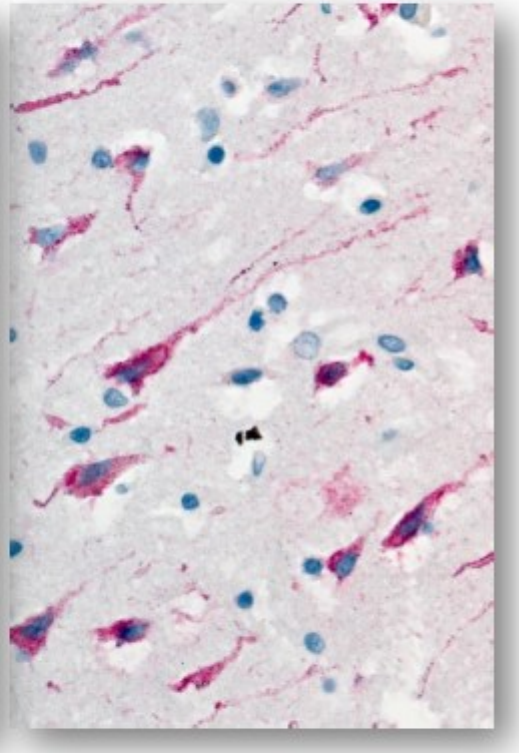
Arjun Srinivasan, M.D., Elizabeth C. Burton, M.D., Matthew J. Kuehnert, M.D., Charles Rupprecht, V.M.D., Ph.D., William L. Sutker, M.D., Thomas G. Ksiazek, D.V.M., Ph.D., Christopher D. Paddock, M.D., Jeannette Guarner, M.D., Wun-Ju Shieh, M.D., Ph.D., Cynthia Goldsmith, M.S., Cathleen A. Hanlon, V.M.D., Ph.D., James Zoretic, M.D., Bernard Fischbach, M.D., Michael Niezgoda, M.S., Waleed H. El-Feky, M.D., Lillian Orciari, M.S., Edmund Q. Sanchez, M.D., Anna Likos, M.D., M.P.H., Goran B. Klintmalm, M.D., Denise Cardo, M.D., James LeDuc, Ph.D., Mary E. Chamberland, M.D., M.P.H., Daniel B. Jernigan, M.D., M.P.H., and Sherif R. Zaki, M.D., Ph.D., for the Rabies in Transplant Recipients Investigation Team*

Raccoon Rabies Virus Variant Transmission Through Solid Organ Transplantation, 2013

- Kidney transplant recipient died 18 months post-transplant
- Donor with a history of raccoon exposure died with fever, vomiting, seizures and dysphagia
- Rabies positive by histopathology and PCR
- Three other organ recipients completed post-exposure prophylaxis and remained asymptomatic with serum rabies neutralizing antibodies



Negri bodies

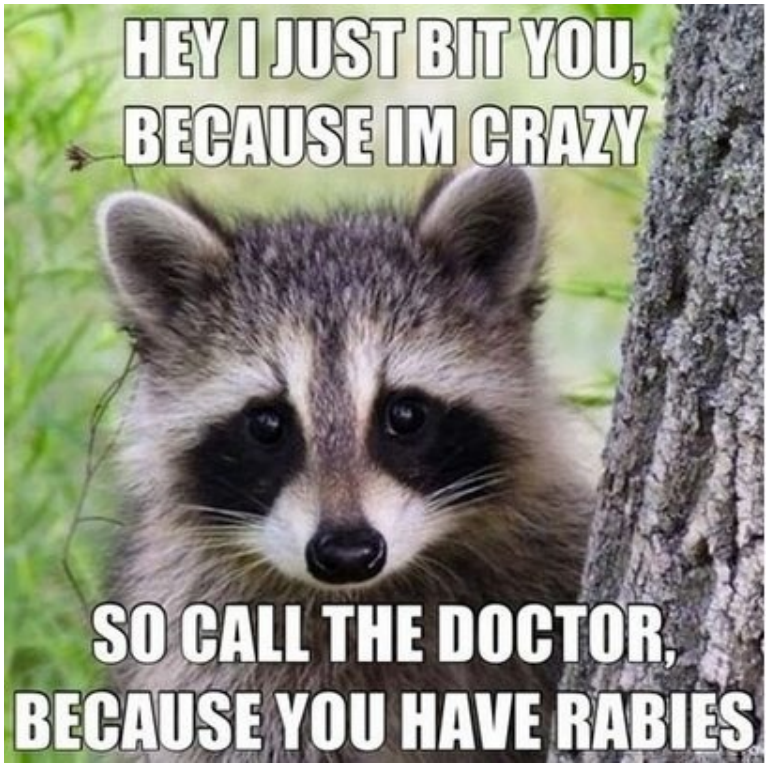


Viral antigens in red, IHC

IHC: Immunohistochemistry
PCR: Polymerase chain reaction
Vora NM, et al. *JAMA* 2013.

Raccoon-Rabies

- Nel 2013 identificato negli Stati Uniti in un donatore morto per “avvelenamento da ciguatera” ed in un suo ricevente una variante del virus della rabbia degli orsetti lavatori!



Zika Virus as a Cause of Neurologic Disorders

Nathalie Broutet, M.D., Ph.D., Fabienne Krauer, M.Sc., Maurane Riesen, M.Sc., Asheena Khalakdina, Ph.D., Maria Almiron, M.Sc., Sylvain Aldighieri, M.D., Marcos Espinal, M.D., Nicola Low, M.D., and Christopher Dye, D.Phil.

Zika Virus

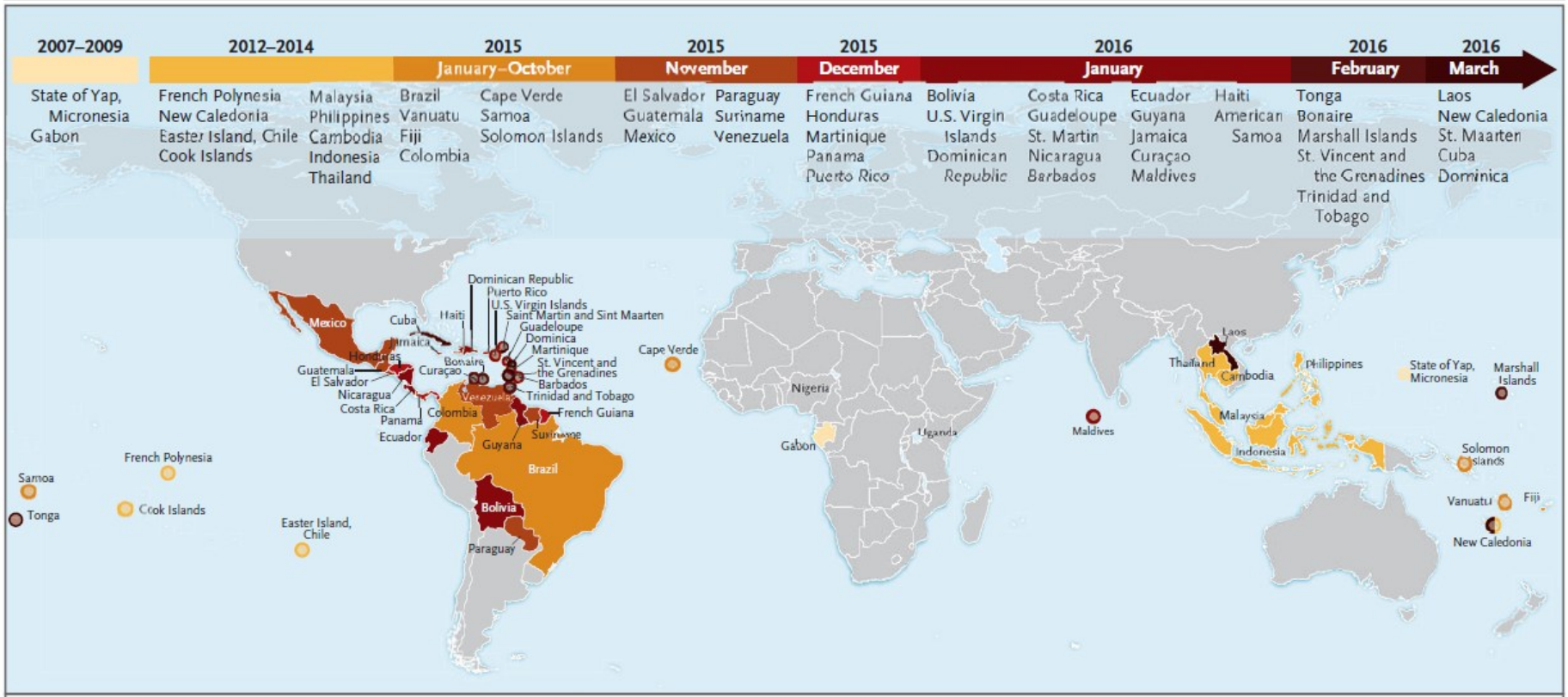
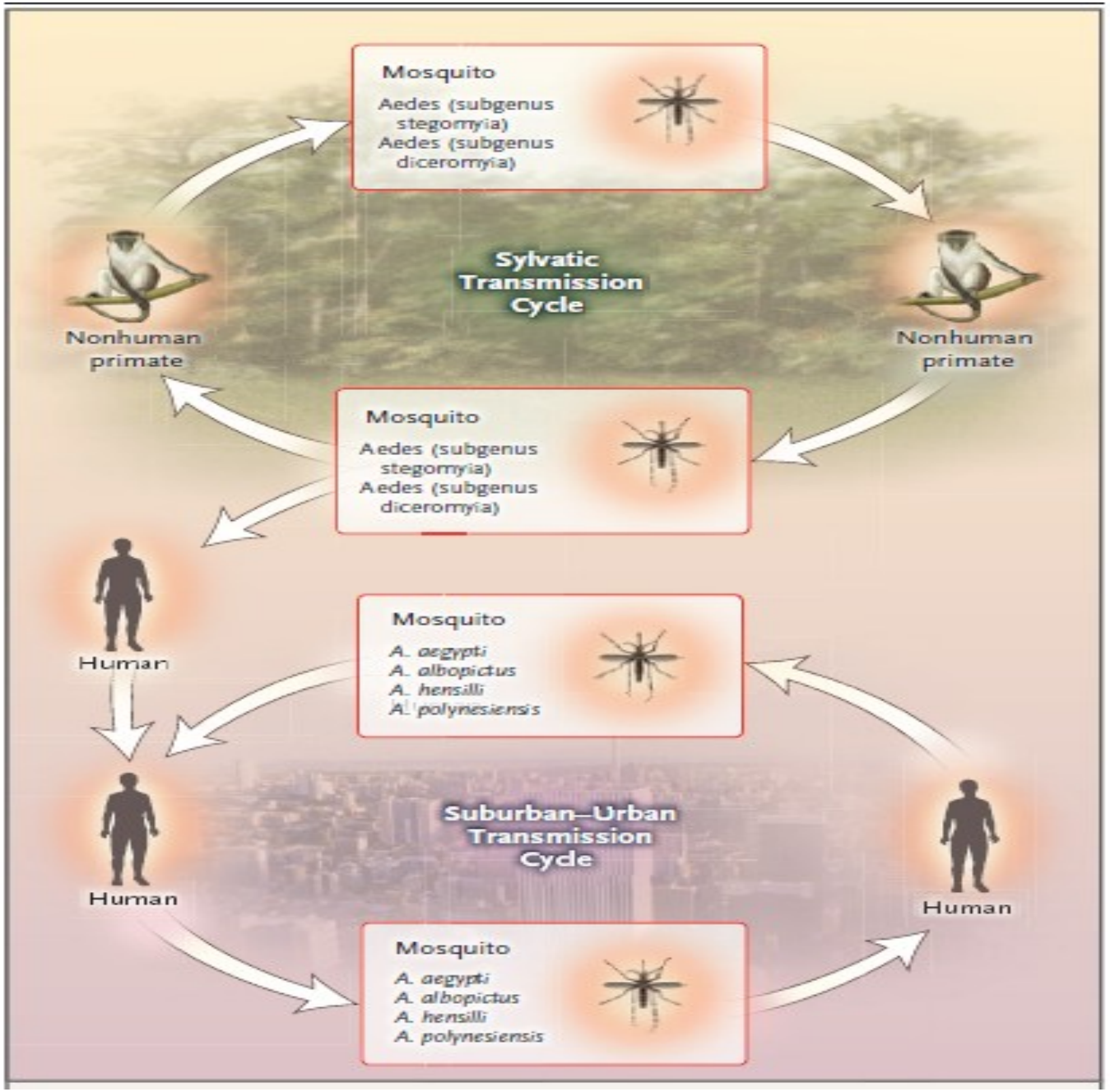
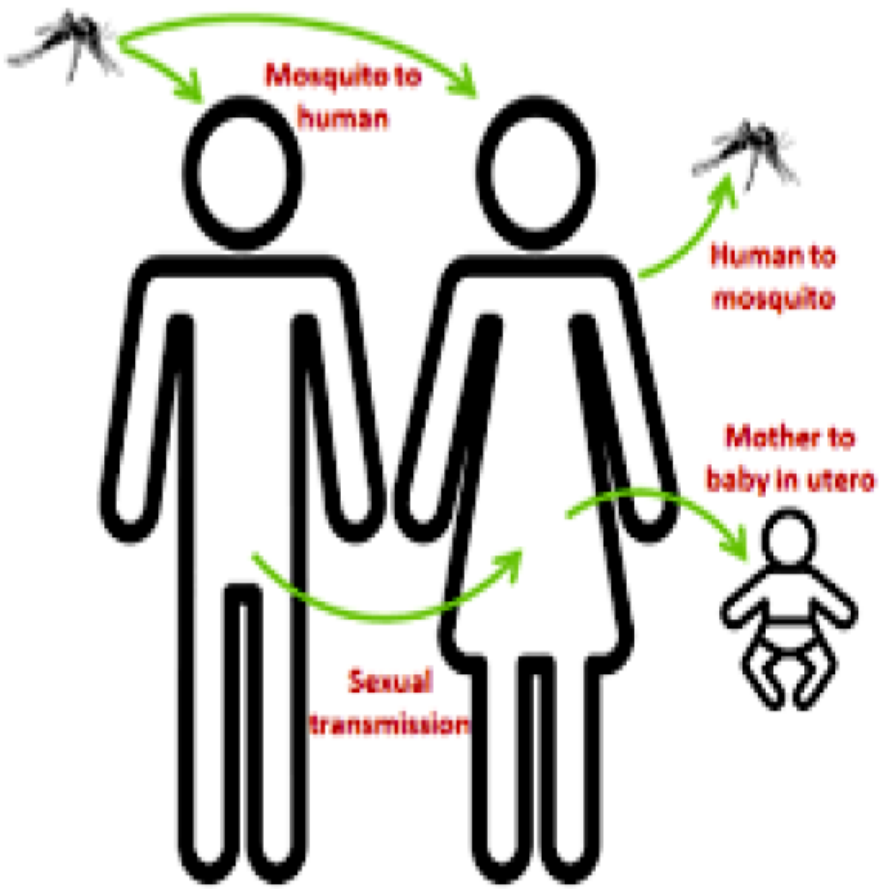


Figure 1. Areas in Which Zika Virus Infections in Humans Have Been Noted in the Past Decade (as of March 2016).
Only sporadic infections have occurred in Southeast Asia, the Philippines, and Indonesia.


Mosquito
Aedes (subgenus stegomyia)
Aedes (subgenus dicerormyia)
Sylvatic Transmission Cycle
Nonhuman primate
Nonhuman primate
Mosquito
Aedes (subgenus stegomyia)
Aedes (subgenus dicerormyia)
Human
Mosquito
A. aegypti
A. albopictus
A. hensilli
A. polynesiensis
Suburban–Urban Transmission Cycle
Human
Human
Mosquito
A. aegypti
A. albopictus
A. hensilli
A. polynesiensis

Zika Virus: Transmission Routes

- Zika virus infection only recently detected in the Americas
  - Same mosquitoes that spread dengue and chikungunya
- Three patterns of spread
  - Direct bites by infected mosquitoes
    - Active transmission
    - Sporadic transmission
  - Trans-placental
  - Sexual



We Have Learned and Done Much but Need to Learn and Do Even More

Some key things we've learned

- Mounting evidence of link w/ Guillain-Barré & microcephaly
  - Neurotropic virus
- Range of adverse pregnancy outcomes
- Sexual transmission more common than expected
- Pregnant women urgently want to take action to protect themselves against Zika
- **There is much more to be learned and done**

A few of the key things we're doing

- Travel and testing guidance
- Guidelines for pregnant women, babies and children w/ possible Zika infection and for couples interested in conceiving
- Clinical guidelines to prevent sexual transmission
- Laboratory tests to states and international partners (MAC-ELISA and Trioplex rRT-PCR)
- Studying how long Zika virus stays in semen, urine & breast-milk
- Vector control, support to pregnant women, and safe blood in Puerto Rico

Case Counts and Outcomes of Zika virus

US States*

- **312** travel-associated cases†
- **0** locally transmitted cases‡

- **27** pregnant women
- **1** case of Guillain-Barre syndrome
- **6** sexually transmitted cases

US Territories

- **3** travel-associated cases†
- **349** locally transmitted cases‡

- **37** pregnant women
- **1** case of Guillain-Barre syndrome
- **0** sexually transmitted cases

*40 states and District of Columbia
†Includes cases in travelers and their contacts with presumed sexual or in utero transmission
‡Presumed local mosquito-borne transmission

as of March 30, 2016