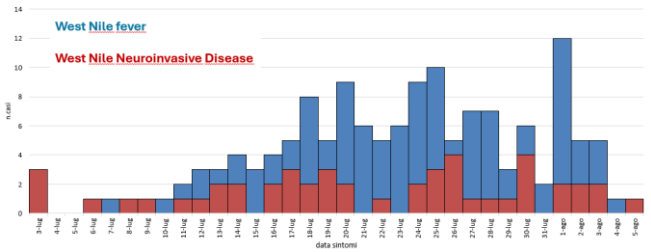
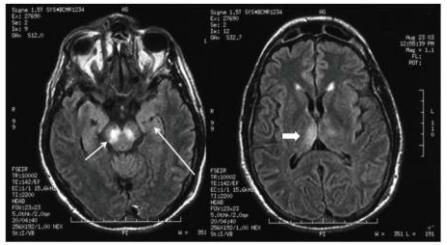
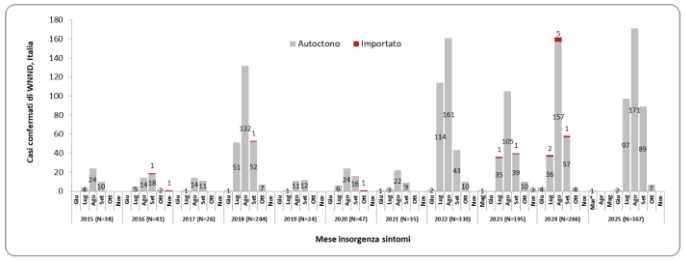






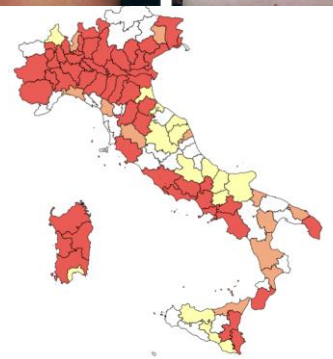
State of the art in WNV case management lesson from the field in Italy

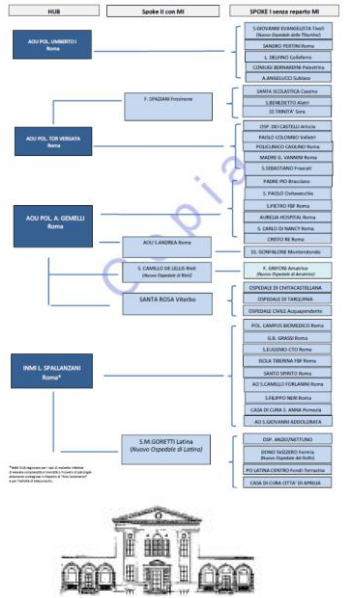
Emanuele Nicastri

Istanbul, March , 2026

National Institute for Infectious Diseases, Lazzaro Spallanzani, IRCCS

emanuele.nicastri@inmi.it

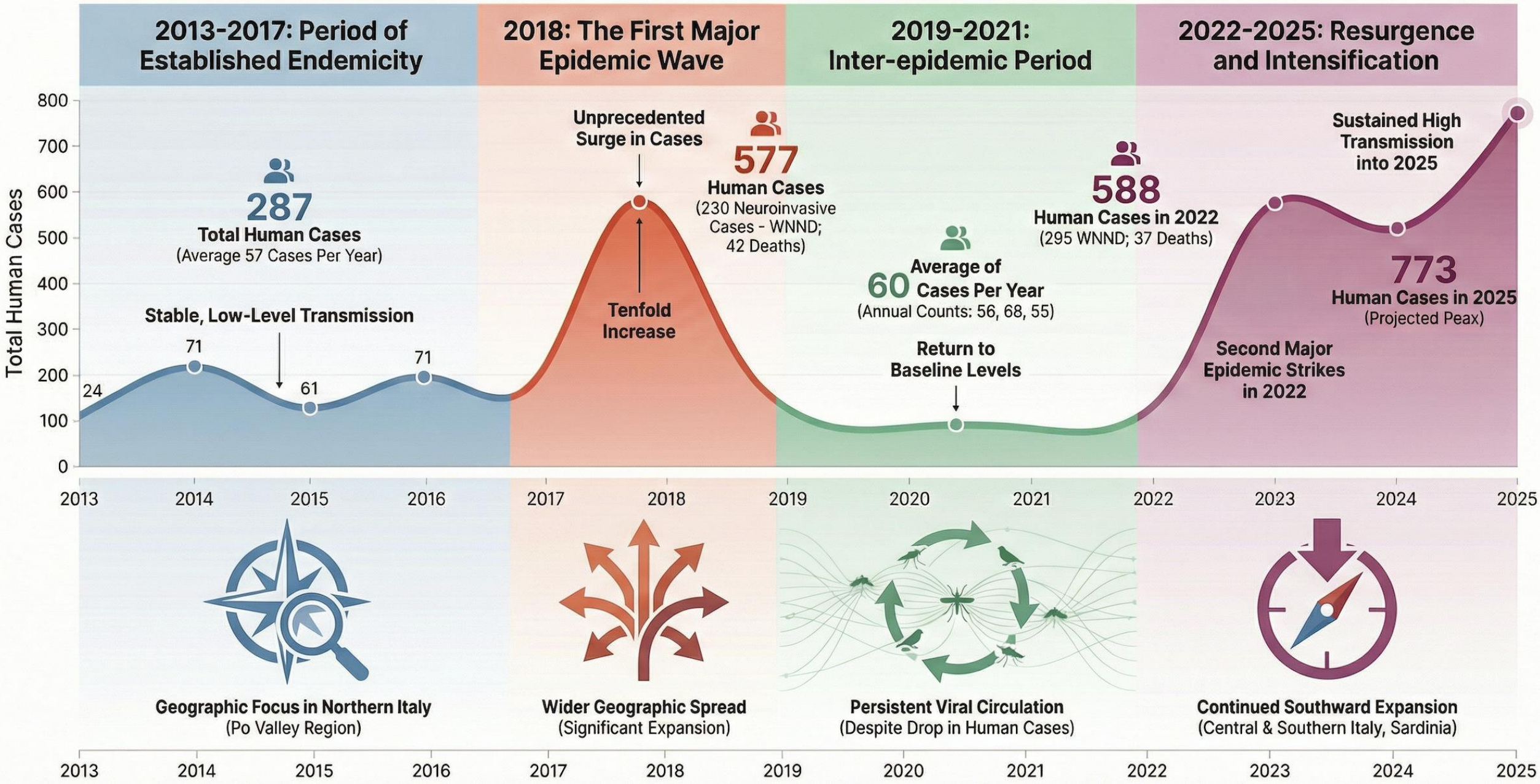




Training workshop on emerging infectious diseases

Istituto Nazionale per le Malattie Infettive
"Lazzaro Spallanzani"
Istituto di Ricovero e Cura a Carattere Scientifico

The Shifting Epidemiology of West Nile Virus in Italy: A 2013-2025 Overview



Main arbovirosis in Italy and Europe

- Chikungunya – single strand RNA alpha virus – transmitted by *Aedes* mosquitoes
- Dengue – single strand RNA flavi virus – transmitted by *Aedes* mosquitoes
- Tick Borne Virus TBE – single strand RNA flavi virus – transmitted by ticks (I*xodes ricinus* e *persulcatus*)
- Toscana Virus –single strand RNA flebo virus transmitted by *plebotomous*
- West Nile Virus single strand RNA flavi virus – transmitted by *Culex* mosquitoes

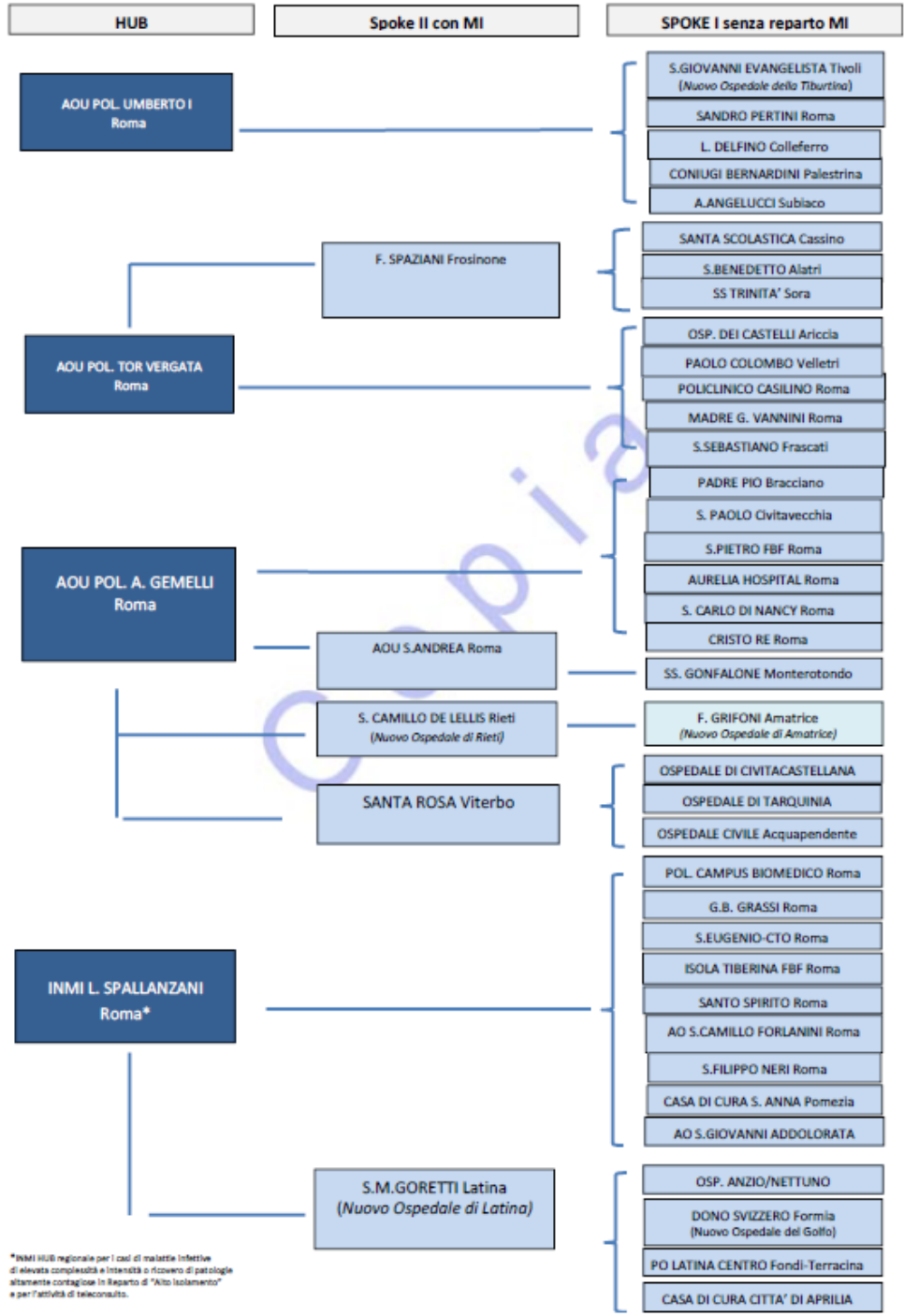
One Health – Italian Arbovirosis National Plan 2020-25

- The Italian Arbovirosis National Plan (PNA) adopts a **One Health** framework integrating **human, animal, and environmental health, all part of Italian MoH**
- Drivers include climate change, globalization, mobility, and increasing risk of autochthonous arbovirus transmission.
- **Surveillance** is jointly conducted across **human, veterinary, and entomological sectors** with early detection and vector monitoring (IIZZSS, CESME).
- **Capacity building** includes training for first-line HCWs, GP, and ID specialists, veterinary, entomology, and municipal staff with shared procedures and technical language.
- **Risk communication** focuses on public awareness, infodemic management, and coordinated multi-sector messaging.
- **Environmental and vector control** includes urban mosquito management, breeding site reduction, and municipal coordination.
- **Regional plans** (e.g., Lazio, Tuscany) operationalize and reinforce PNA One Health principles.

https://www.salute.gov.it/imgs/C_17_pubblicazioni_2947_allegato.pdf

One Health – Italian Arbovirosis Plan at regional level

- Lazio region has a **ID regional network wit Hub and Spoke** interconnection **between ID units and EDs**: a **teleconsultation platform** serve as remote ID consultation within the network: about **6.000 teleconsultation per year**
  - **Hub** (***3 UnivHospitals and INMI*** Spallanzani) a **24hr/7d ID/ DX call** ,
  - 2nd Spoke (5 units) 12hr/6D ID and Dx call,
  - 1st Spoke (37 EDs) no ID call.
- On 1st week of July, a **working group integrating Lazio regional authorities, epidemiologic services, the ID clinical** units in Latina and Rome, **Veterinary and Entomological** service was given
- **Three main webinars** on West Nile for 1st line HCWs, ID and GPs: more 1.000 contact per webinar
- **Three additional outpatient services for WNF fever cases** apart from ED were established in Latina and south Rome for diagnosing, counseling and notification. **Only 1 lab** for case confrmatior at INMI
- Several meeeting with main municipality



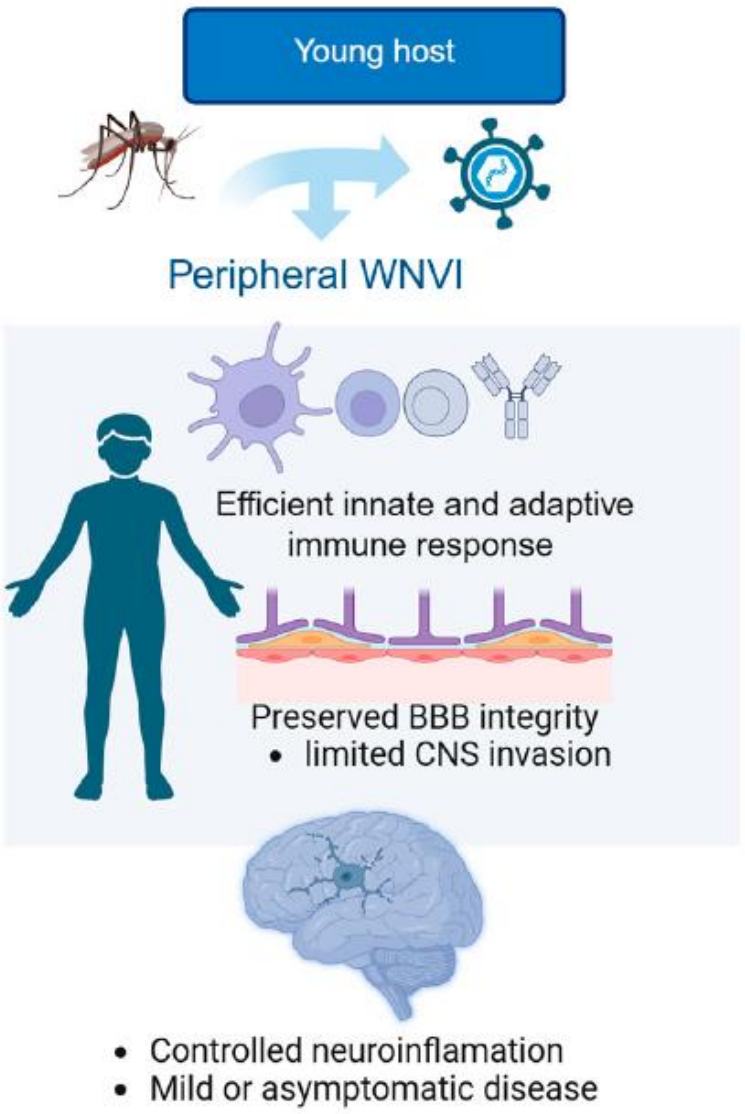
Classification WNV cases in the Lazio Region

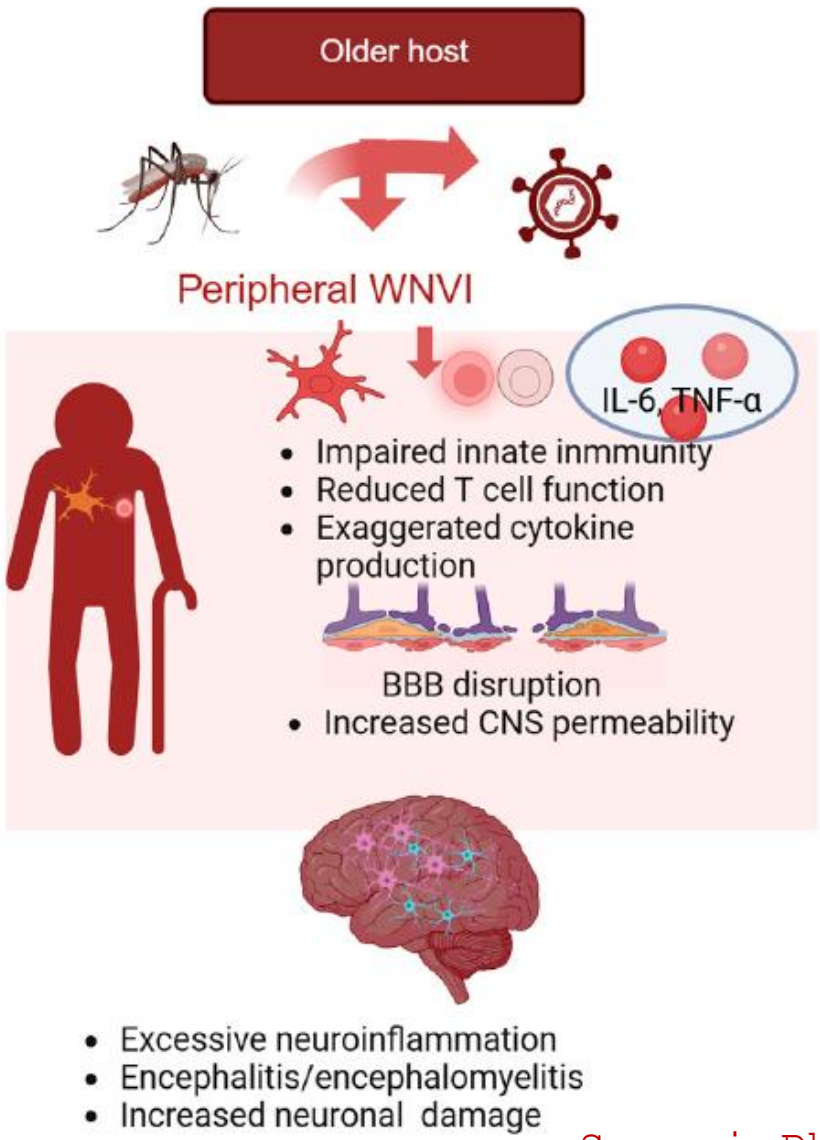
Parameters	WNV Clinical syndrome			
	Neuroinvasive n=88	WNV Fever N=174	Blood donors N_11	Total N=273
Age years, median (IIQR)	76, 69-82	54, 43-66	55, 41-60	60, 48-74
Gender, F	35, 40%	93, 53%	-	128, 47%
Clinical setting • Home • Clinical units (ICU)	2, 2% 86, 98% (14, 16%)	121, 70% 53, 30%	11, 100%	134, 49% 139, 51%
Death	17, 19%	2, 1.1%	0	19 (7%)

reasons, one in hearth transplantation and one on treatment

Vairo, regional report by

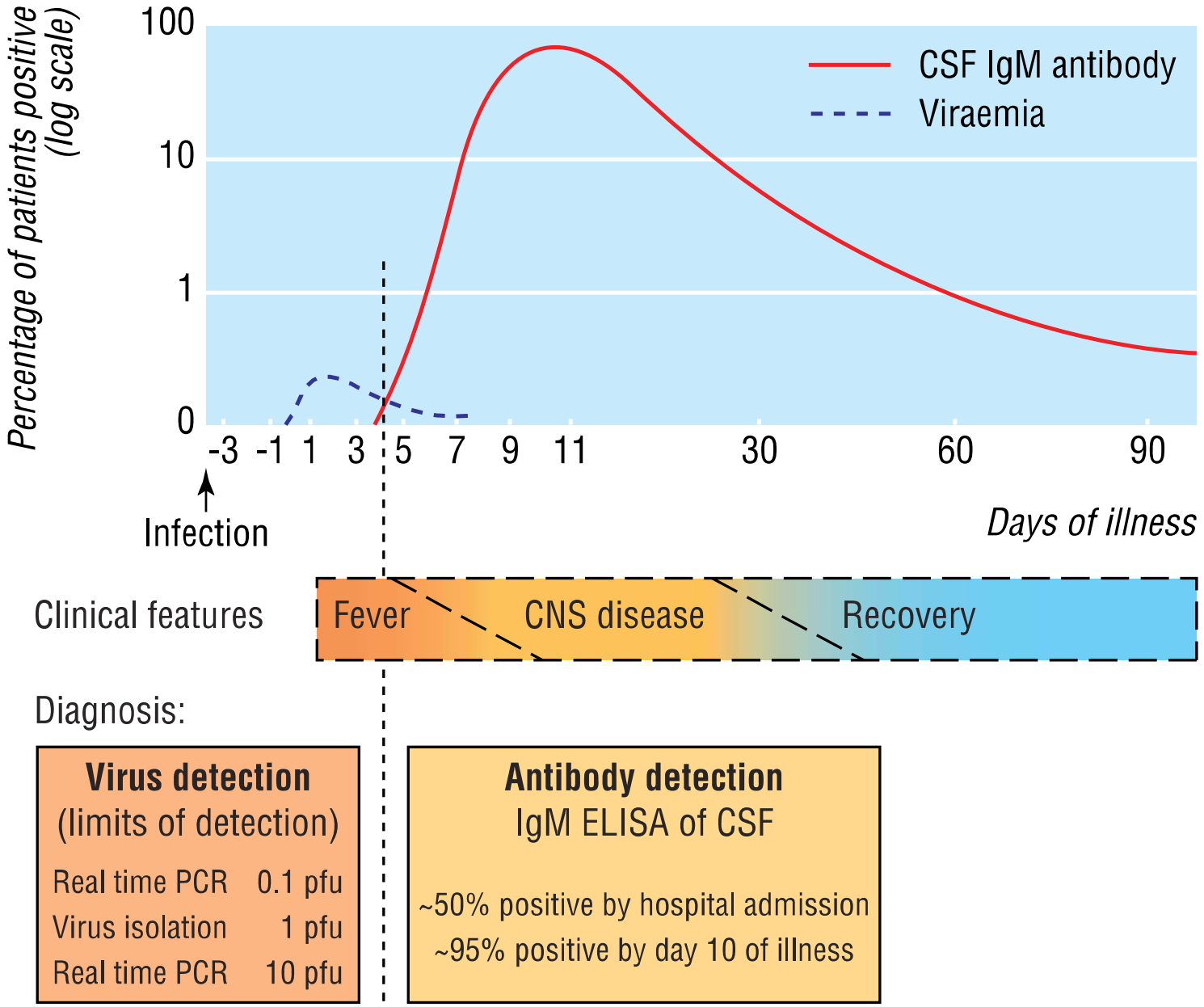
Pathogenesis of different WNV clinical manifestation

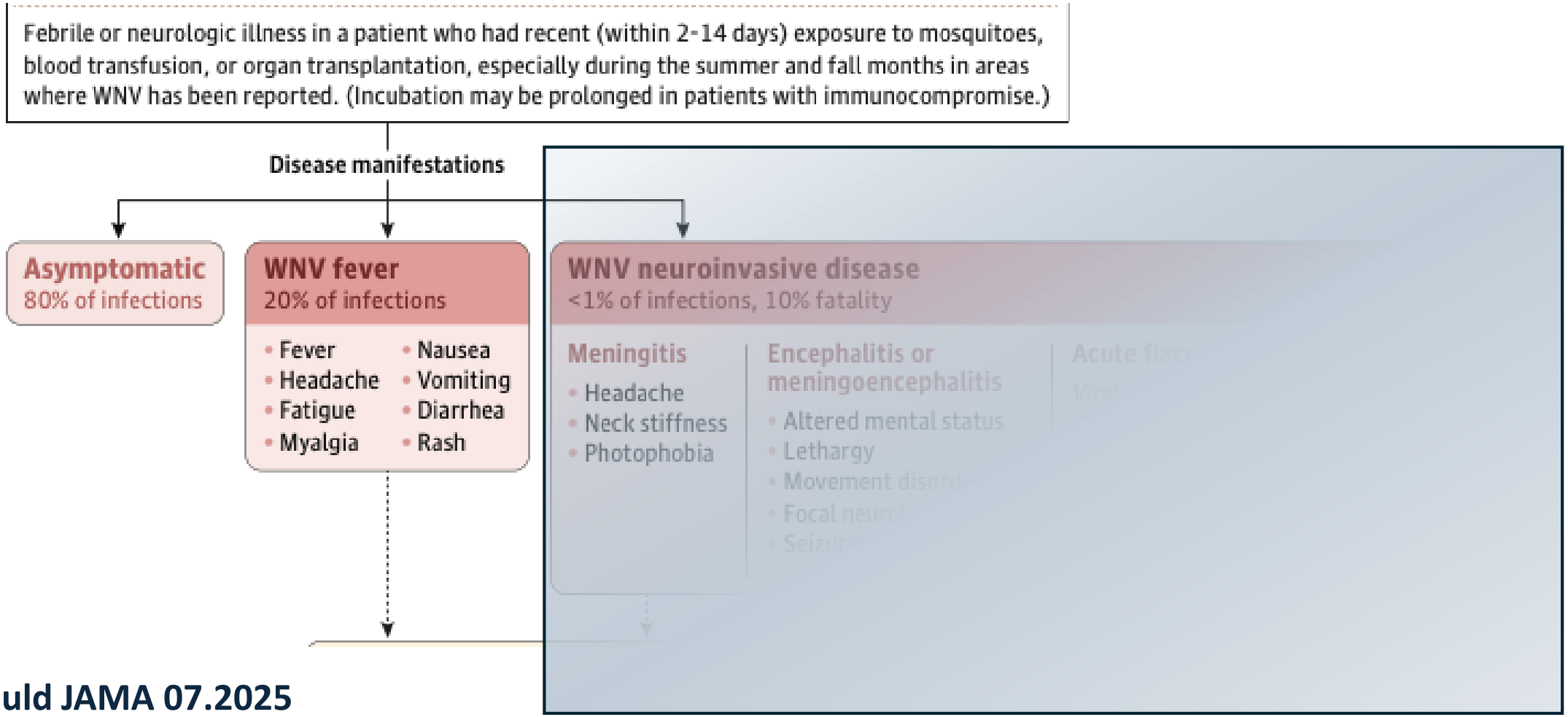




West Nile virus diagnosis

- ***WNV viremia occurs very early and is short-lived**, with viral loads close to the detection limits of PCR assays.*
- *Patients are often **hospitalized after 3–4 days of fever, when plasma viral load is already too low.***
- *The detection of **IgM in CSF fluid** represents a more robust diagnostic method.*
- ***IgG titer longitudinal assessment** is useful*
- ***WNV urine detection by PCR** is very useful even if delayed*





Gould JAMA 07.2025

West Nile Virus A Review

Clinical manifestation and outcome of WNV infection

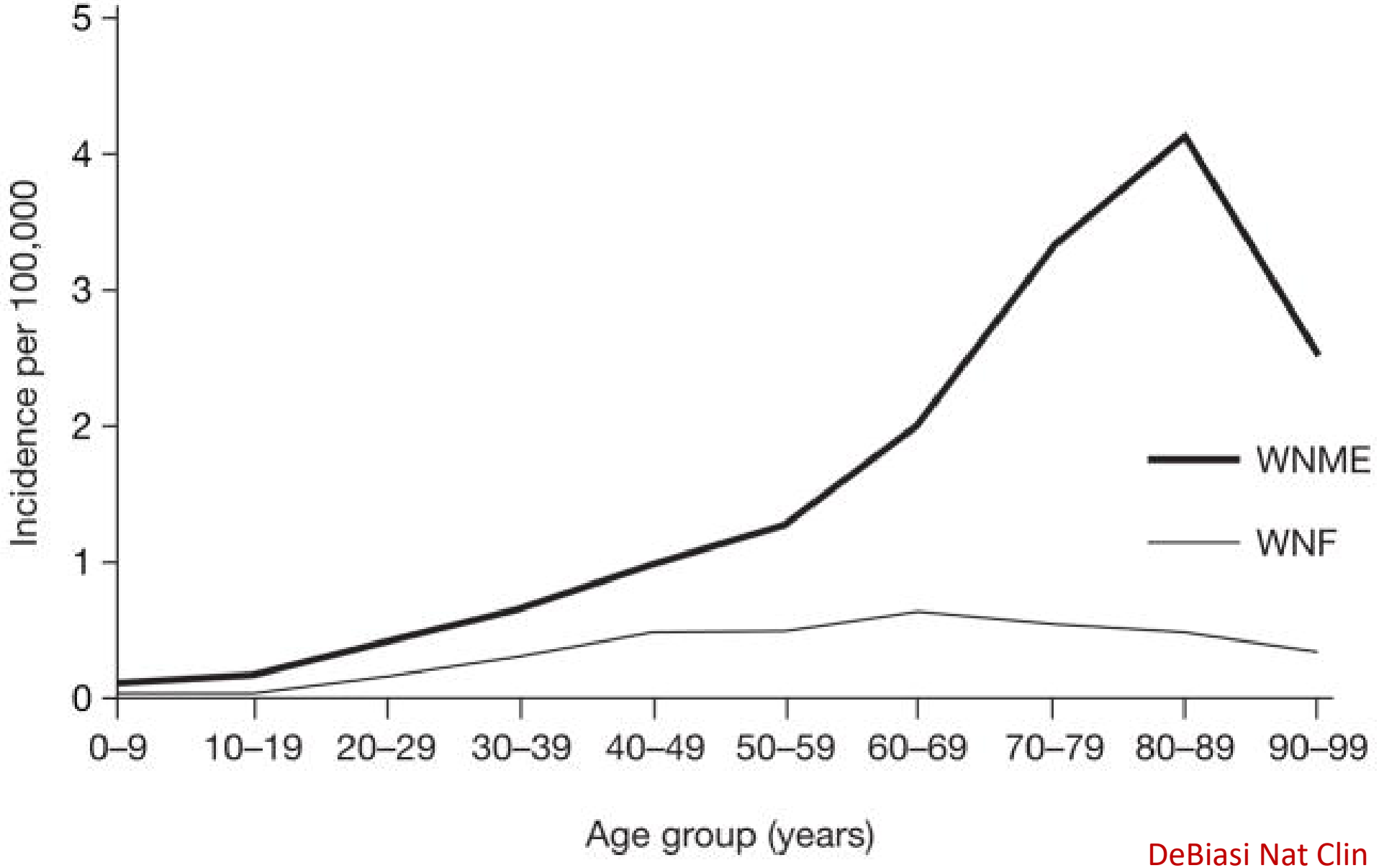
Figure 4. Diffuse Maculopapular Rash on Chest, Abdomen, and Arms of a Patient With West Nile Virus Disease

Rash, morbilliform, maculopapular and non-pruritic and predominates over the torso and extremities, sparing the palms and soles, may be transient, lasting less than 24 hr.

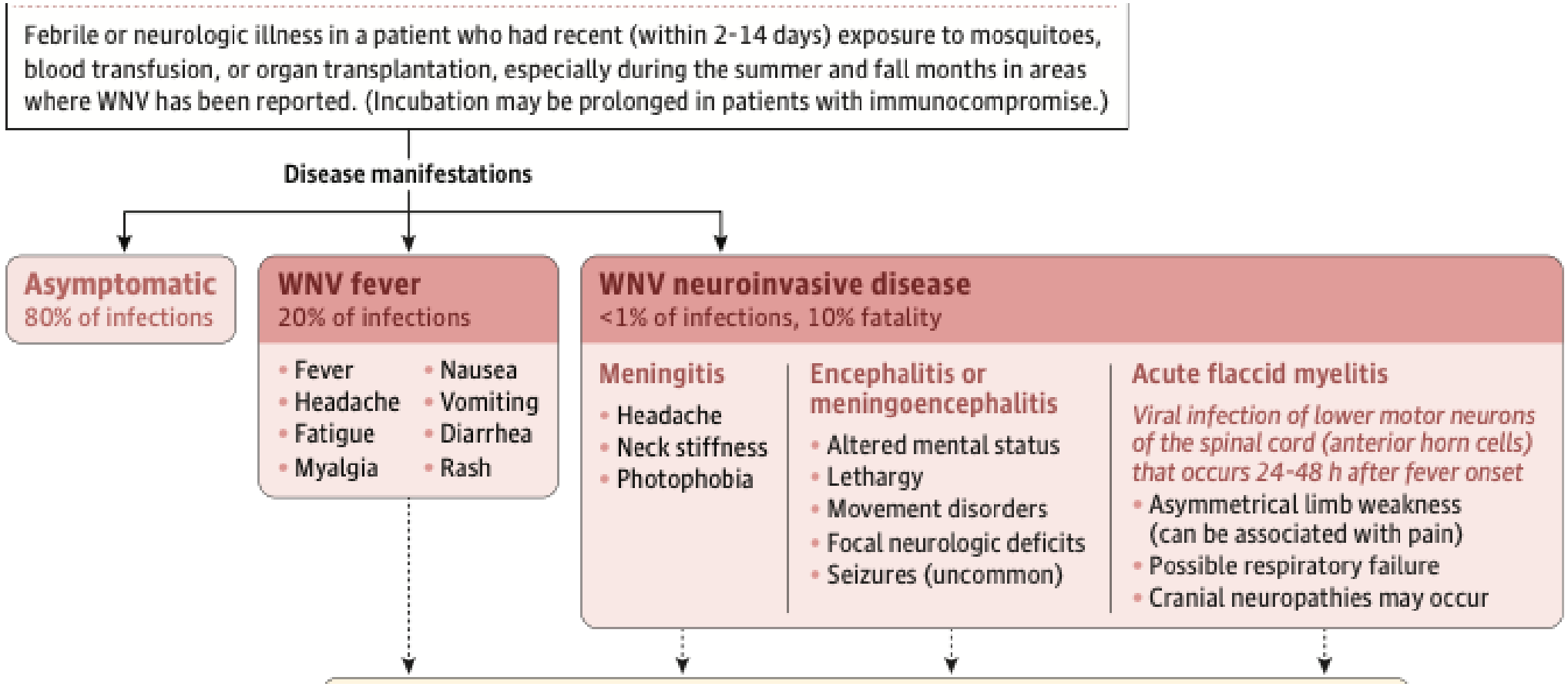
It is more frequent in WN fever than in more severe manifestations, rash is more frequently observed among youngers. These findings raise the question as

Sejvar Viruses 2004

Incidence of WNV infection vs neuroinvasion



DeBiasi Nat Clin Pract Neurol. ;2013



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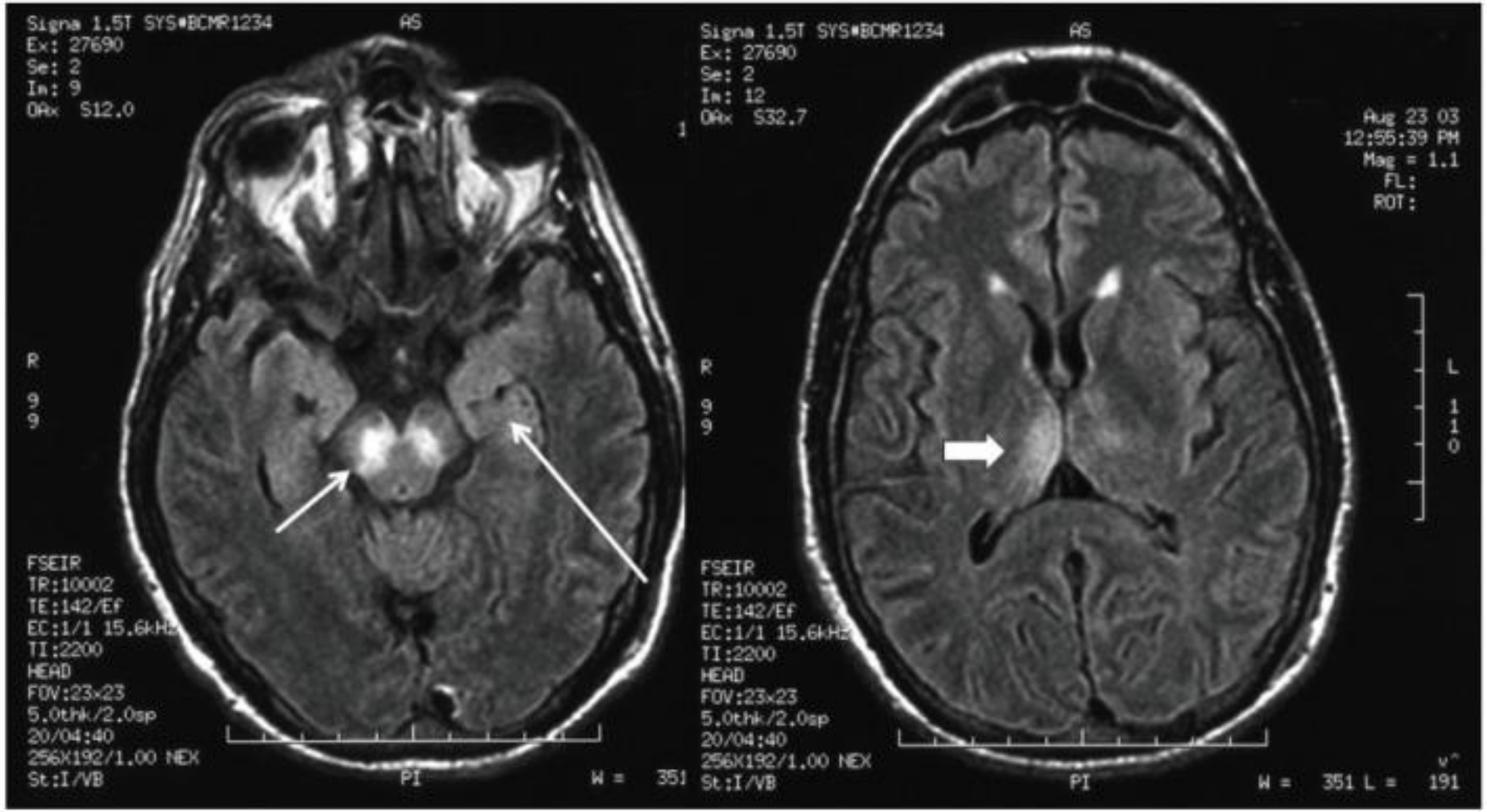
West Nile Virus A Review

Clinical manifestation and outcome of WNV infection



West Nile virus encephalitis with associated parkinsonism and tremor, displaying signal abnormality in the **substantia nigra (short arrow), the mesial temporal lobe (long arrow) and right**

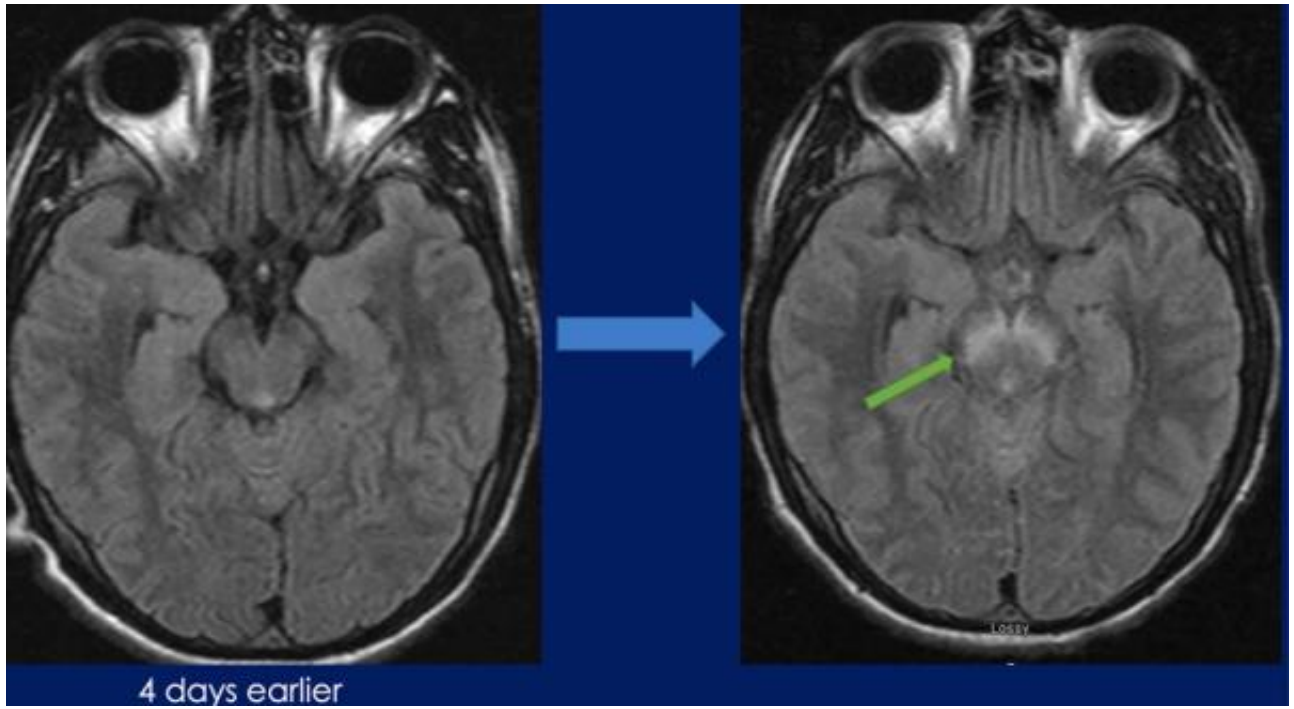
Sejvar Viruses 2004

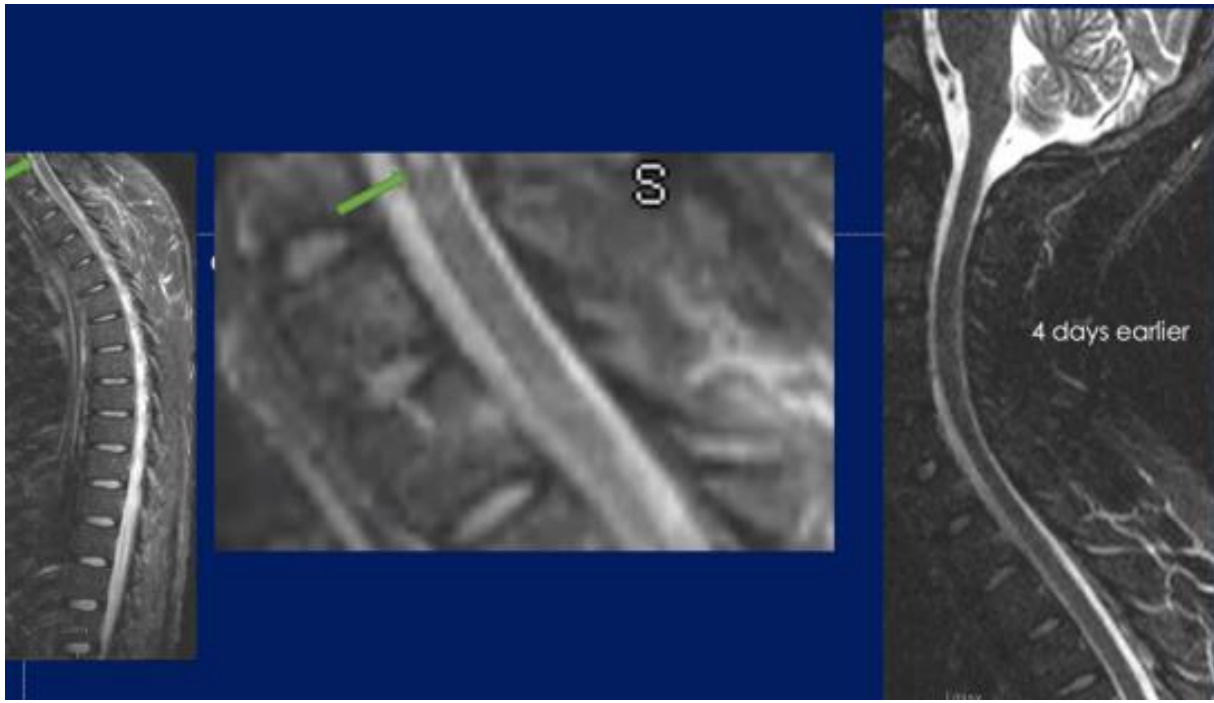
Clinical manifestation and outcome of WNV infection

Sagittal (A) and axial (B) T2 MR imaging of the cervical spinal cord of a patient with bilateral upper extremity paralysis and respiratory failure from West Nile poliomyelitis, displaying the increased signal

Sejvar Viruses 2004

Catastrophic WNV Rhombencephalitis in AIDS

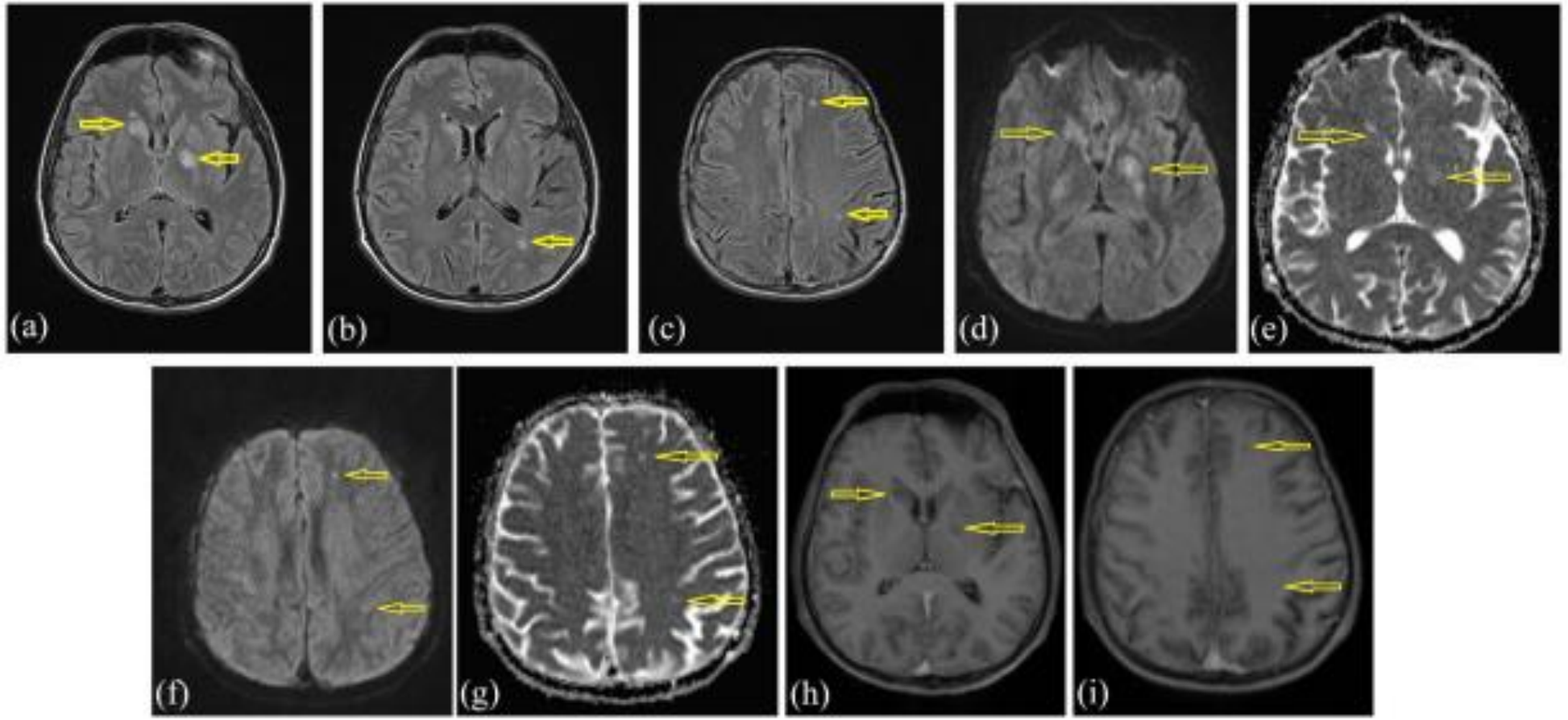




A 61-yo male presented with fatigue, ataxia, dysarthria (Opsoclonus-Myoclonus syndrome), and fever after a recent cabin visit in the summer. The initial workup ruled out meningitis and stroke. The patient's condition deteriorated despite empiric treatment. MRI revealed patchy FLAIR hyperintensities in the cerebellar hemispheres. Further evaluation confirmed WNV infection through positive IgM&IgG Ab

Sharma J Inv Med HI Case R

Disseminated cerebral cryptococcosis after silent WNV infection in a patient with polycythemia vera



In 2018, a 43-yo man with **polycythemia vera on Tx** experienced an unknown-cause fever and headache.

Brain MRI **indicated meningeal and gyral-leptomeningeal thickening and several localized T2 hyperintense lesions** measuring up to 10×14mm in diameter.

Cryptococcus neoformans was then cultivated from CSF

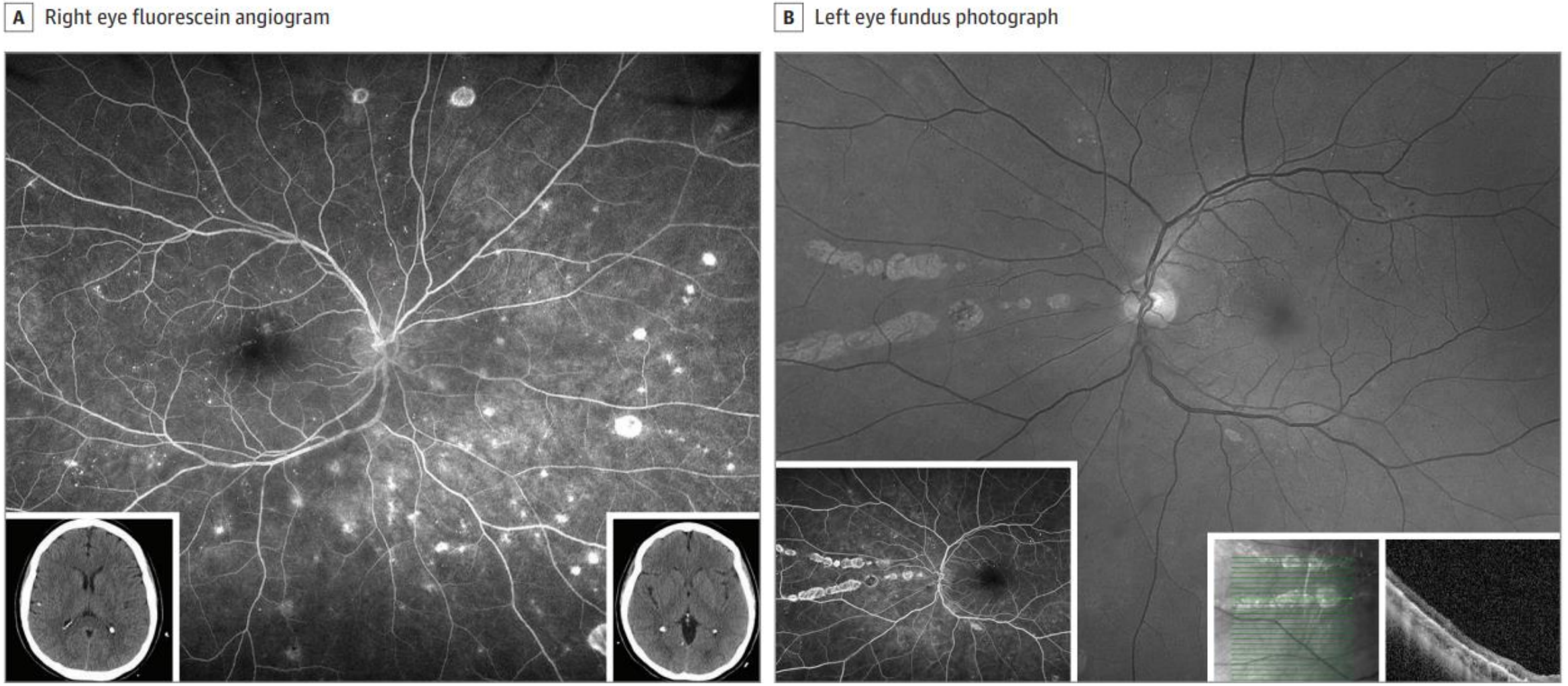
Serum IgM ab against WNV were positive.

After 8 weeks of treatment with amphotericin B and fluconazole, the overall condition improved, and the cerebrospinal fluid control culture became negative.

The symptoms returned shortly after discontinuing antifungal therapy, necessitating the

Colović SAGE Open Medical Case Rep

Fever and Floaters in a 56-Year-Old Woman with **type 2 diabetes,** in **Ohio River Valley** with 3-day neurological acute syndrome, 7-d after admission floaters in her right eye with normal vision



Ophthalmoscopic examination showed **moderate non-proliferative diabetic retinopathy and scattered and linear formations of chorioretinal lesions with mild patchy venular staining,** but no substantial leakage was observed on fluorescein angiography

Firn JAMA Ophthalmology

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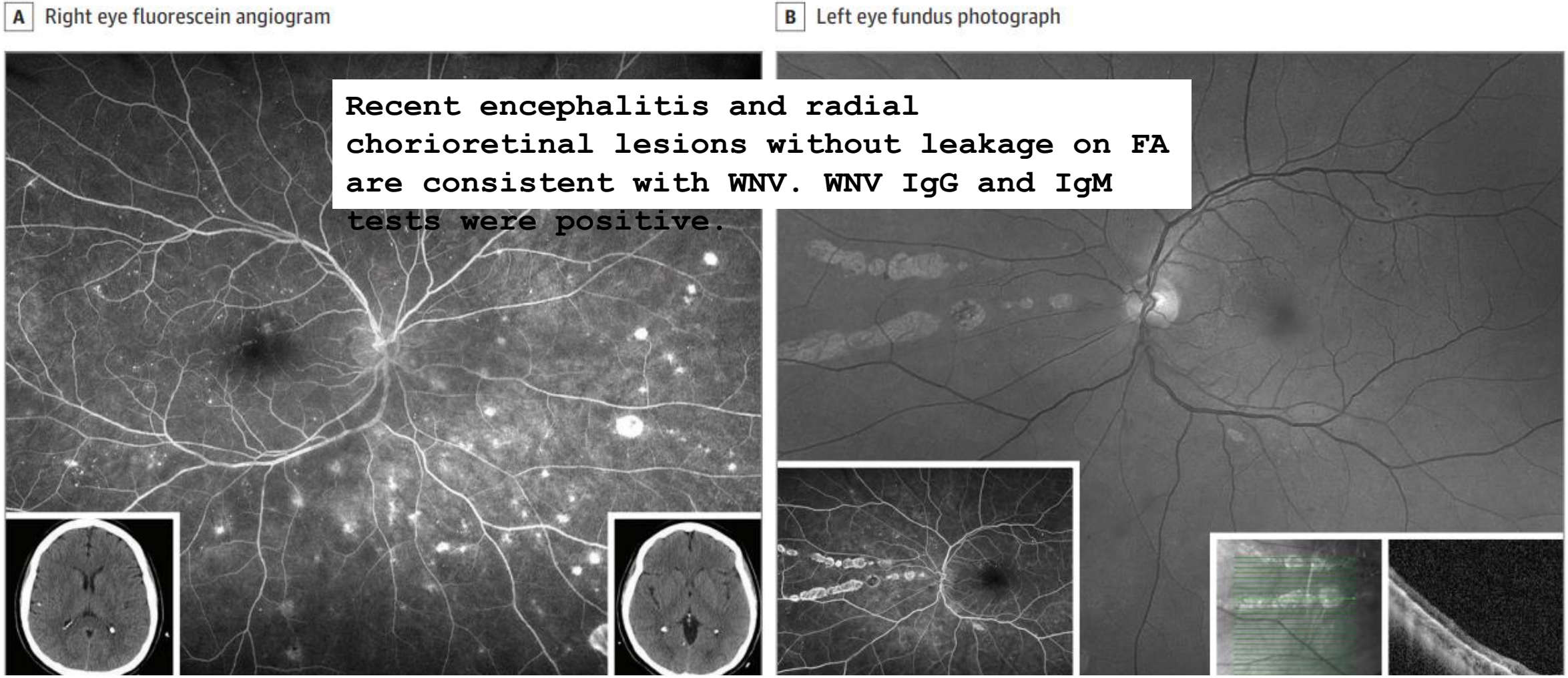

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Firn JAMA Ophthalmology

Ocular involvement in West Nile virus infection

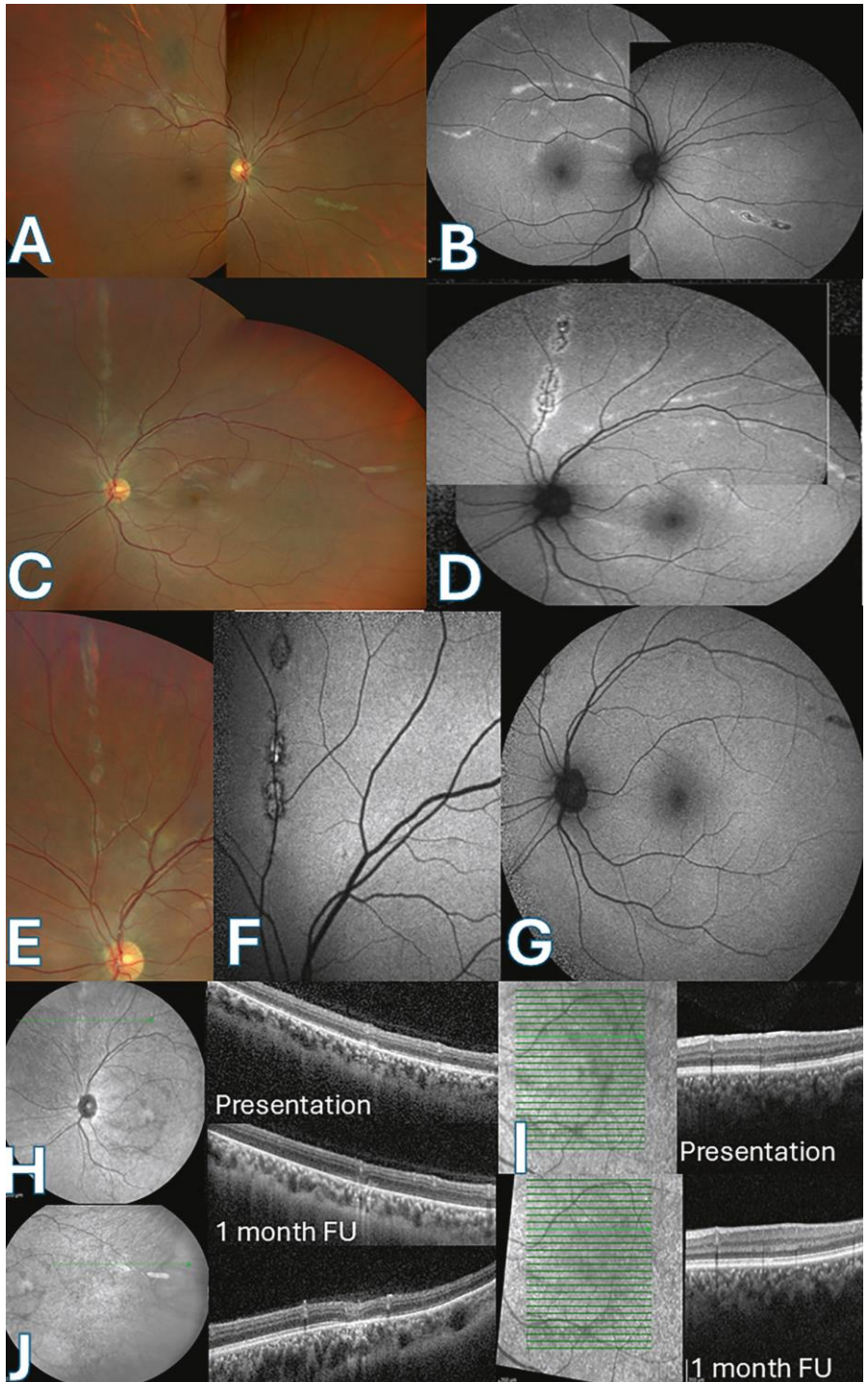
Table 1. Demographic, clinical, and laboratory parameters in West Nile virus patients with and without ocular manifestations.

Variable	Total cohort ($n = 37$)	Ocular involvement ($n = 17$)	No ocular involvement ($n = 20$)	*P*-Value
Age, mean ± SD (range)	69.2 ± 15.8 (27-93)	66 ± 13.9 (36–83)	71.8 ± 17.2 (27–93)	0.27
Female, *n* (%)	18 (48.6%)	8 (47%)	10 (50%)	1
Symptom duration before diagnosis, days ±SD (range)	5.8 ± 4.8 (1–21)	6.7 ± 5.2 (1–21)	4.9 ± 4.2 (1–14)	0.24
Hypertension, *n* (%)	19 (51%)	8 (47.1%)	11 (55%)	0.75
Diabetes Mellitus, *n* (%)	14 (38%)	7 (41%)	7 (35%)	0.74
Malignancy, *n* (%)	5 (14%)	4 (24%)	1 (5%)	0.16
Autoimmune diseases, *n* (%)	7 (19%)	3 (18%)	4 (20%)	1.0
Neuroinvasive disease, *n* (%)	28 (76%)	16 (94%)	12 (60%)	**0.017**
Hospitalisation duration, days ±SD (range)	15 ± 15.8 (1–79)	12.8 ± 11.4 (1–42)	17 ± 18.9 (1–79)	0.45
LP performed, *n* (%)	24 (65%)	14 (82%)	10 (50%)	**0.045**
WBC in CSF (cells/μL), mean ± SD (range)	257.8 ± 132 (0–1100)	155 ± 298.4 (0–1100)	102.8 ± 205 (0–675)	0.43
Protein in CSF (mg/dL), mean ± SD (range)	112 ± 92.0 (3.3–469)	134 ± 105.7 (55.8–469)	82 ± 62.1 (3.3–220.3)	**0.043**
Glucose in CSF (mg/dL), mean ± SD (range)	67.7 ± 24.6 (39–143)	70.1 ± 26.0 (39–143)	65.8 ± 19.6 (42–102)	0.42
Intubation, *n* (%)	7 (19%)	6 (35%)	1 (5%)	**0.024**
Days from diagnosis to exam, mean ± SD (range)	15.6 ± 18.4 (4–66)	16.3 ± 4 (3–49)	19.5 ± 16.8 (4–66)	0.69
Visual acuity at presentation (logMAR), mean ± SD (range)	0.41 ± 0.52 (0.00–2.70)	0.47 ± 0.58 (0.00–2.70)	0.31 ± 0.45 (0.00–1.78)	0.08
Blood WNV PCR, mean ± SD (range)	31.1 ± 2.9 (23.4–36. 6)	31.8 ± 1.6 (29.3–35.5)	30.7 ± 3.4 (23.4–35.6)	0.46
Positive WNV IgM in CSF results (%)	19/24(79.2%)	11/14 (78.6%)	8/10 (80%)	1

SD standard deviation, *LP* lumbar puncture, *WBC* white blood cells, *CSF* cerebrospinal fluid, *WNV* West Nile virus.
Bold indicates $p < 0.05$ for comparisons between patients with and without ocular involvement.

Fried Eye 2

WNV ocular involvement



A 36-year-old man with diffuse large B-cell lymphoma, treated with Rituximab, presented with fever, headache, and decreased consciousness.

He was intubated during hospitalisation and showed significant improvement after two months of rehabilitation. Multimodal imaging was performed during hospitalisation at baseline and in one month follow up:

A–D. Colour fundus photography (CFP) montage and Heidelberg fundus autofluorescence (FAF) at baseline of both eyes demonstrate **white linear clustering of chorioretinal lesions in the temporal, nasal, and superior retina**. These lesions are better visualised on FAF, which reveals hyperautofluorescent streaks forming a curvilinear pattern temporally and a radial linear pattern nasally and superiorly—some of which are not apparent on the corresponding CFP images. Some lesions show a combination **of hyper- and hypo autofluorescence** on FAF, resembling a target-like pattern.

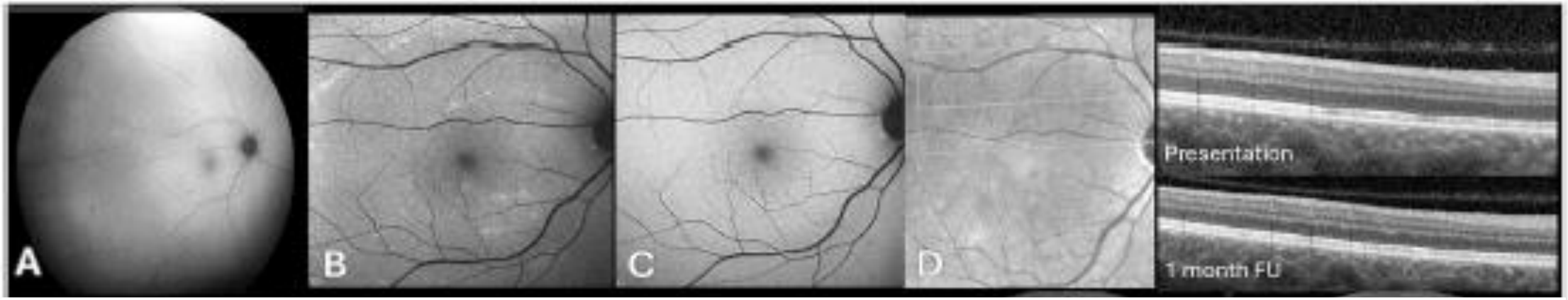
E. Colour fundus photograph of the left eye **1 month later**, shows the development of **pigmentation in association with the yellow lesions.**

F-G. FAF of the left eye, illustrates marked **resolution of the hyper AF** streaks and decrease in hyperAF of the superior lesions.

H. OCT B scans through the superior lesion at baseline and at one month, show **initial thickening of the retinal pigment epithelium (RPE),** followed by photoreceptor and RPE atrophy.

I. OCT B scan at presentation and 1 month later through the **hyperAF curvilinear streak, shows photoreceptor and ellipsoid zone loss with intact RPE and then complete resolution of the outer retinal alterations.**

WNV ocular involvement

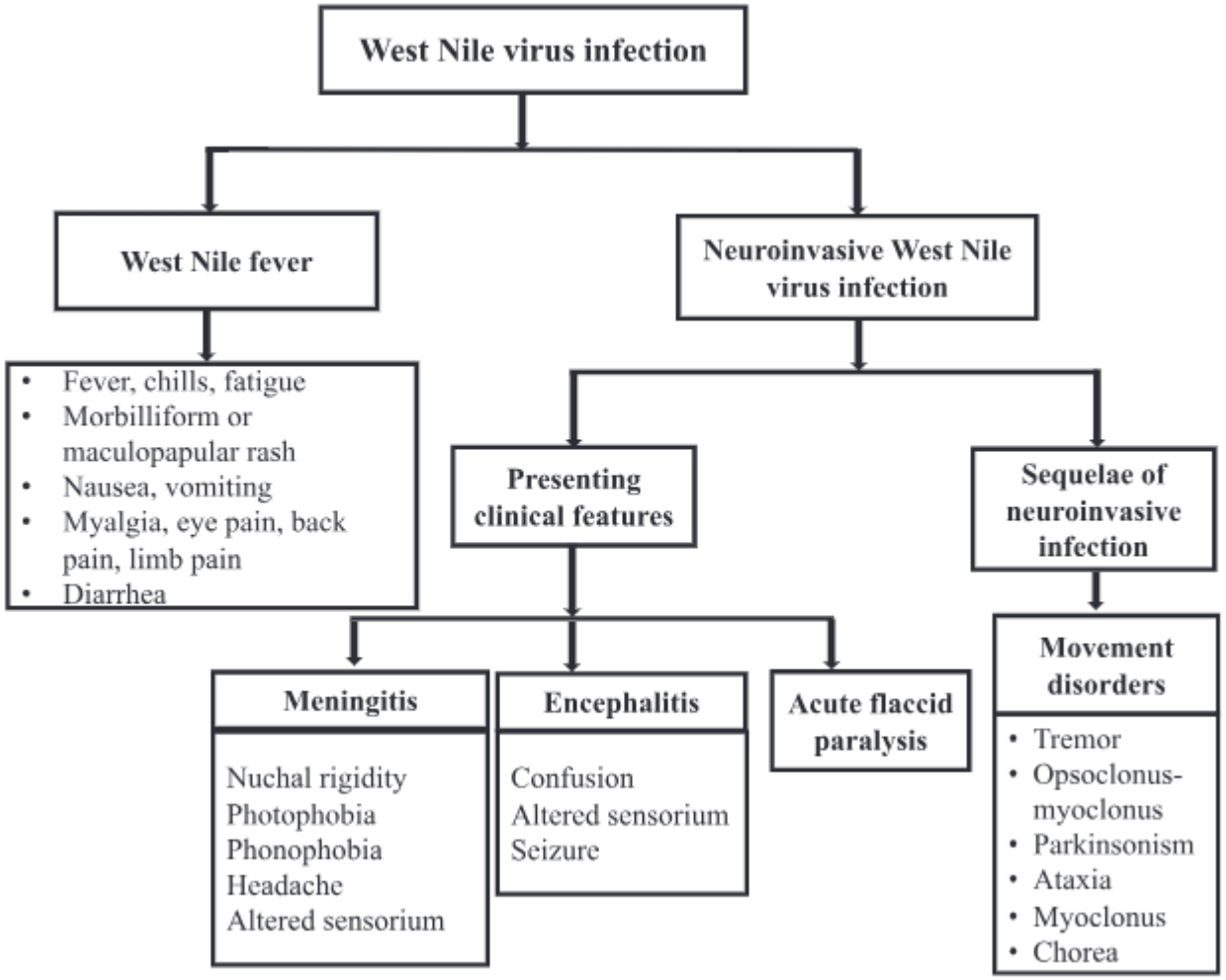


Multimodal imaging of three patients with chorioretinal lesions, shown at various intervals after detection.

A–D Imaging of **a 43- year-old female,** examined 3 days after WNV detection: **A** Clarus Blue fundus autofluorescence (FAF) image. **B, C** Heidelberg FAF at presentation and one month later of the right eye, demonstrate **gradual resolution of the hyperautofluorescent (hyperAF) curvilinear streaks. D** Near-infrared reflectance (NIR) image with a **corresponding OCT B scan at presentation and 1 month later through the superior curvilinear lesion,** shows photoreceptor and ellipsoid zone loss at presentation and subsequent resolution of the outer retinal alterations.

Fried Eye 2

Spectrum of Movement Disorders in Patients With Neuroinvasive WestNile Virus Infection



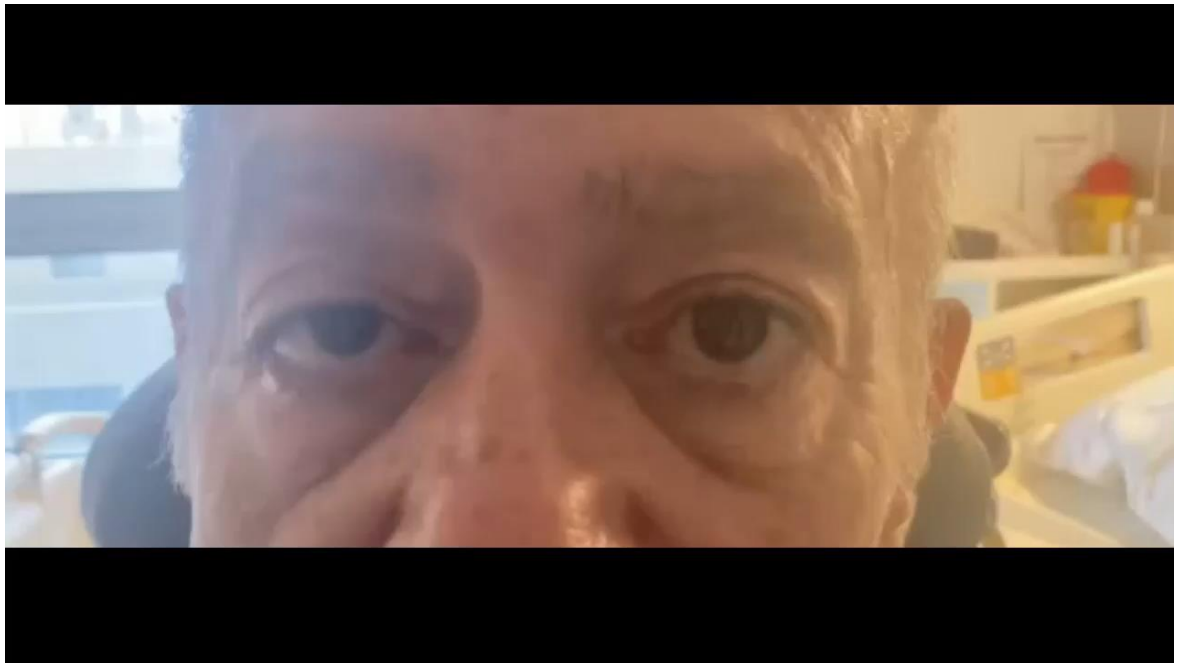
Movement disorders during WNV infections include **tremor, opsoclonus–myoclonus, parkinsonism, myoclonus, ataxia, and chorea.** Most resolve **within a few weeks** to months with an indolent course.

The commonly observed tremor phenotypes include action **tremor of the upper extremities (bilateral > unilateral) earlier phenotype** with WNV meningitis than with encephalitis/acute flaccid paralysis.

Opsoclonus–myoclonus in WNV infections **responds well** to IV IgG /plasmapheresis / steroids.

Leńka Mov Dis Clin Pract 2019

Opsoclonus-myoclonus following WNV encephalitis: when the virus enters the equation



64 male healthy yo, French teacher living in Algerian Sahara presented with fever, headache, confusion, and rapidly progressed to coma. CSF 83 cells (83% lymp). MRI revealed diffuse white-matter involvement, asymmetric basal-ganglia signal, and subtle hyperintensities in the brainstem and oculomotor nerves. EEG negative

CSF HSV PCR and cultures were repeatedly negative, as were neuronal/neuropil antibodies. **WNV IgM/IgG were strongly positive in serum and CSF**. WNV PCR—performed on blood and urine eight days after onset, negative.

After three weeks of coma, he developed opsoclonus, jaw clonus, and a paucireactive state. No improve with high-dose steroids and IVIG. Two cycles of five plasma exchanges led to resolution of abnormal movements and recovery to speak and solve simple equations

MRI Findings in Opsoclonus-Myoclonus Syndrome Secondary to the WNV

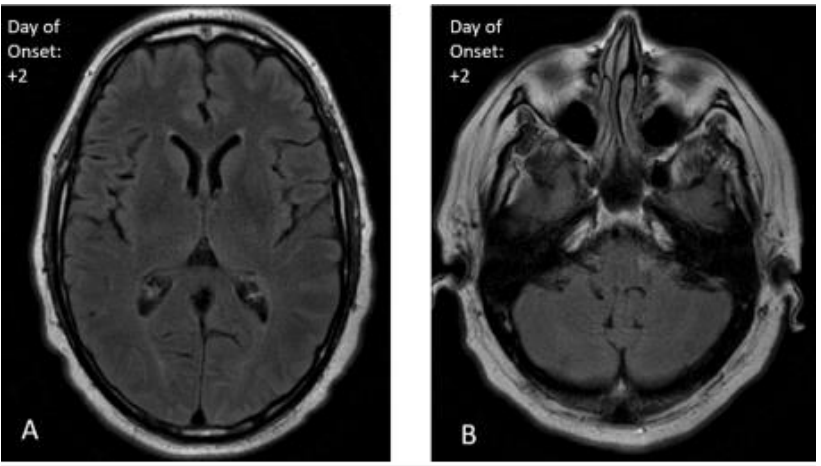


FIGURE 1: Baseline axial T2 FLAIR MRI. Day two after the onset of symptoms shows normal brain morphology in the cerebrum (A) and the cerebellum (B). There is no evidence of acute ischemia, hemorrhage, edema, or an abnormal mass effect. The brain volume and ventricular system are within normal limits for the patient's age.

FLAIR: fluid-attenuated inversion recovery.

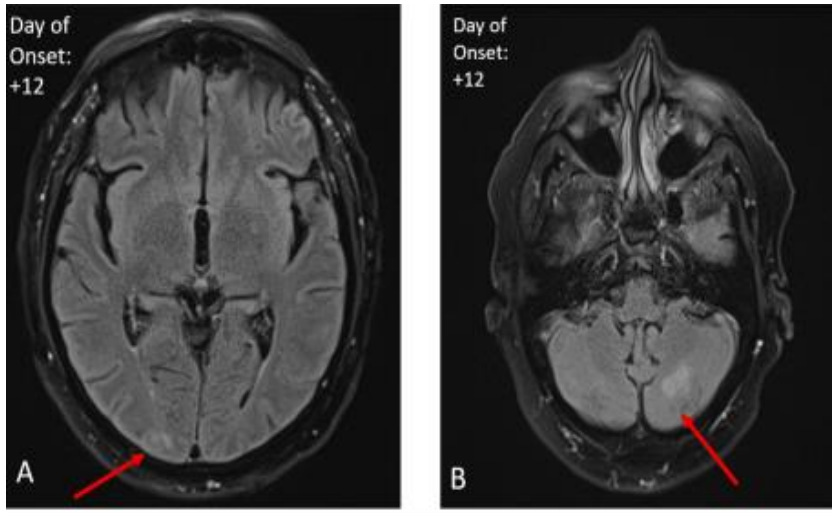


FIGURE 2: Follow-up axial fat-suppressed T2 FLAIR MRI. Day 12 after the onset of symptoms demonstrating mild sulcal FLAIR hyperintensity in the right occipital lobe (A) and patchy FLAIR hyperintensity in the left cerebellar hemisphere (red arrows) (B).

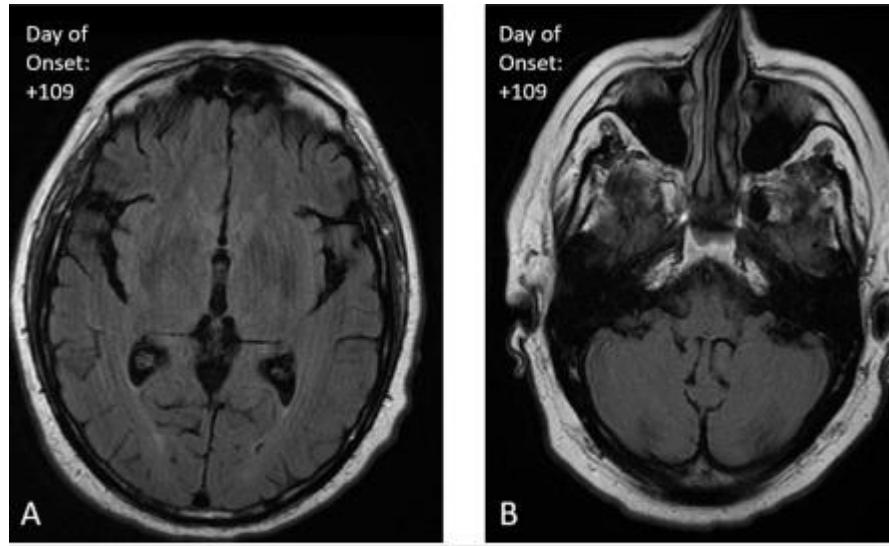


FIGURE 3: Post-treatment axial T2 FLAIR MRI. Day 109 after the onset o symptoms showing complete resolution of the previously observed right occipital (A) and left cerebellar abnormalities (B).

A 61-yo male presented with fatigue, ataxia, dysarthria (Opsoclonus-Myoclonus syndrome), and fever after a recent cabin visit in the summer. The initial workup ruled out meningitis and stroke. The patient's condition deteriorated despite empiric treatment. MRI revealed patchy FLAIR hyperintensities in the cerebellar hemispheres. Further evaluation confirmed WNV infection through positive IgM&IgG Ab

Yang Cureus 2

The importance of haematological and biochemical findings in patients with WNV neuroinvasive disease

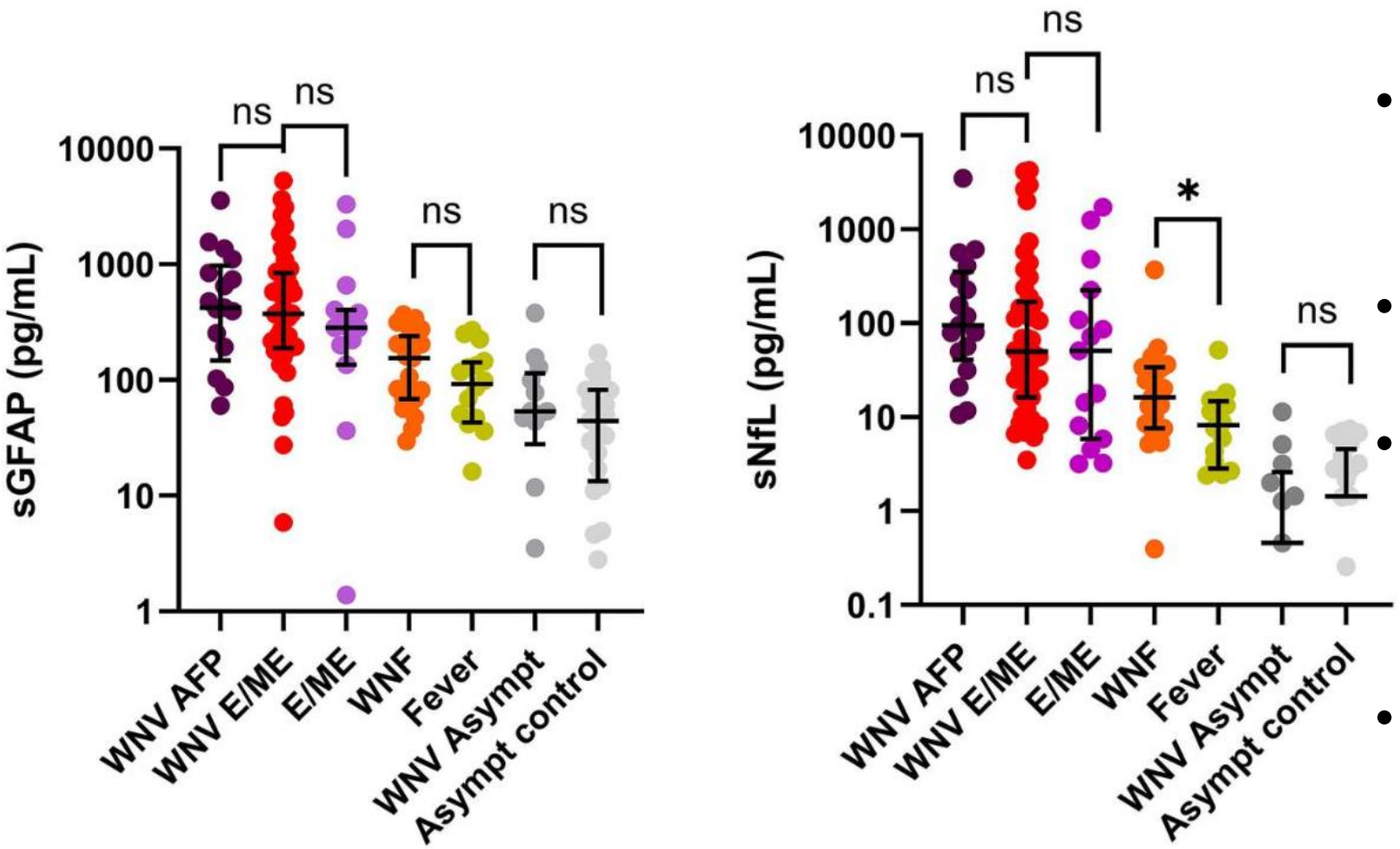
Table III Haematological and biochemical parameters as risk factors for fatal outcome in patients with West Nile virus neuroinvasive disease (n=161).

Urosevic J Med Chem 2016

	Survived (n=133)	Died (n=28)	p-value	Multivariate analysis odds ratio (95% CI)
Blood				
Leukocytosis (%)	58 (43.6)	16 (57.1)	0.192	/
Anaemia (%)	57 (42.8)	11 (39.3)	0.728	/
Thrombocytopenia (%)	36 (27.1)	10 (35.7)	0.357	/
CRP > 100 mg/L (%)	8 (6.0)	10 (35.7)	<0.001	7.21 (1.56–33.28)
Cerebrospinal fluid				
WBC < 5×10^6/L (%)	2 (1.5)	2 (7.1)	0.081	/
WBC > 500×10^6/L (%)	7 (5.2)	2 (7.1)	0.694	/
Neutrophils > 50 (%)	59 (44.3)	10 (35.7)	0.401	/
Hypoglycorrhachia (%)	13 (9.8)	2 (7.1)	0.663	/
Proteins > 1 g/L (%)	49 (36.8)	25 (89.3)	<0.001	12.07 (2.43–60.02)

161 WNVD treated during 2012-3 Infectious Diseases Clinical Centre of Serbia, Belgrade.

Serum Neurofilament Light Chain (NfL) and Glial Fibrillary Acidic Protein (GFAP) and WNV disease severity

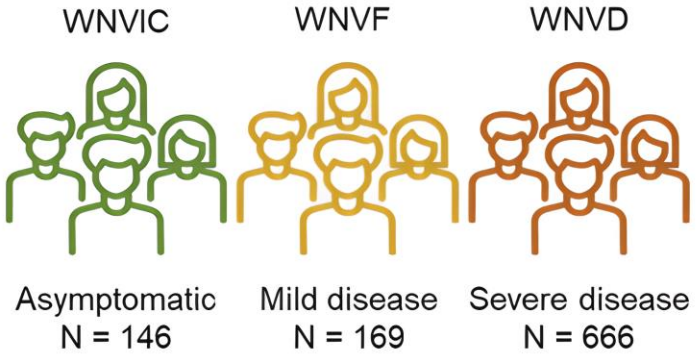


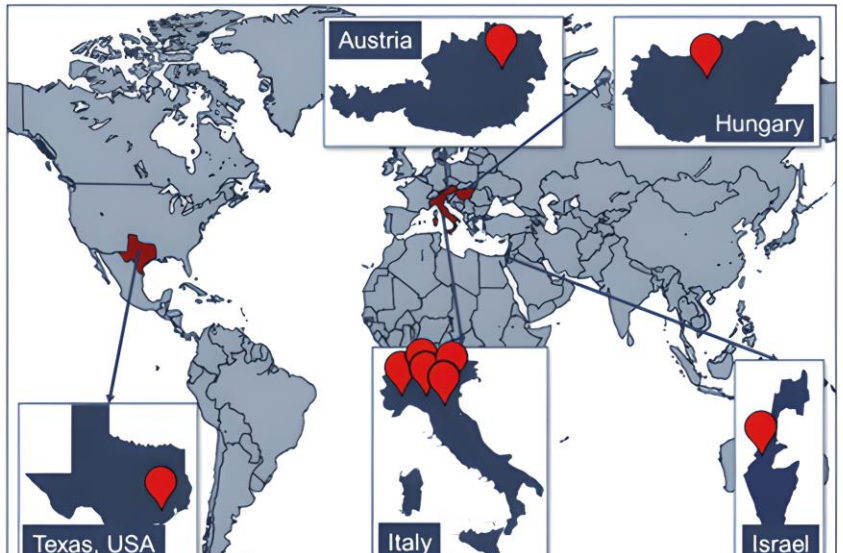
Serum levels of age-adjusted GFAP and NfL according to WNV infection and clinical presentation.

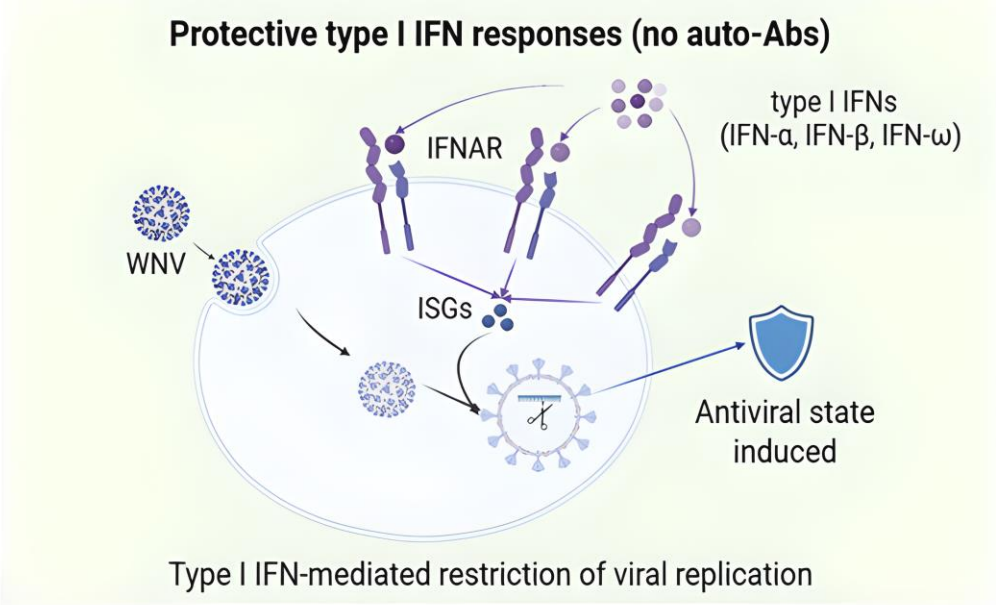
- sNfL and sGFAP are biomarkers of neuroaxonal and astrocyte damage even in WNV infection
- Both were significantly higher in WNND than in WNF
- Combined analysis allowed to discriminate between WNF and WNND with 67.2% sensitivity and 91.3% specificity.
- Elevated levels of sNfL and sGFAP predicted ICU admission, prolonged hospital stay, and death or sequelae

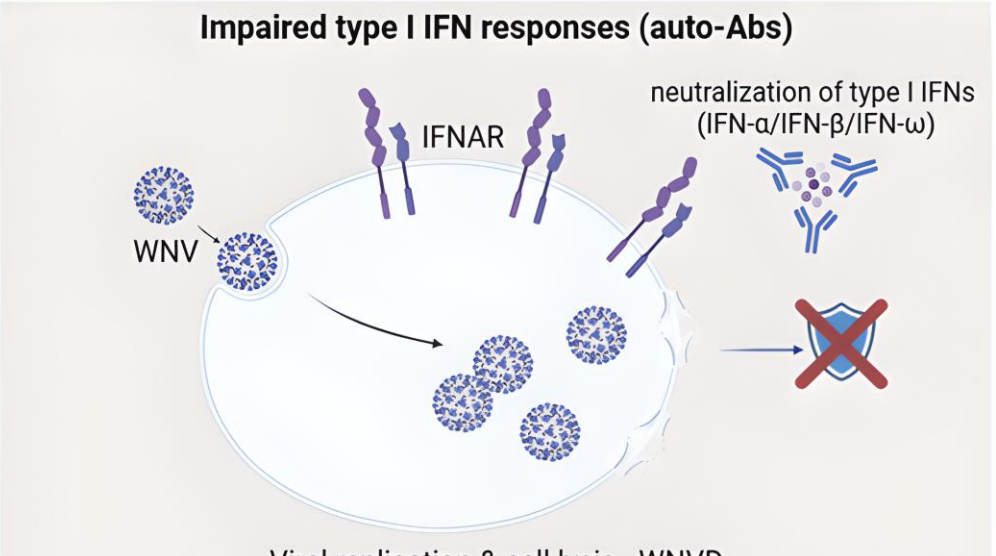
Autoantibodies neutralizing type I IFNs in 40% WNV encephalitis patients in 7 new cohorts

981 individuals (aged 9-99) from 13 cohorts from 5 countries in 3 continents







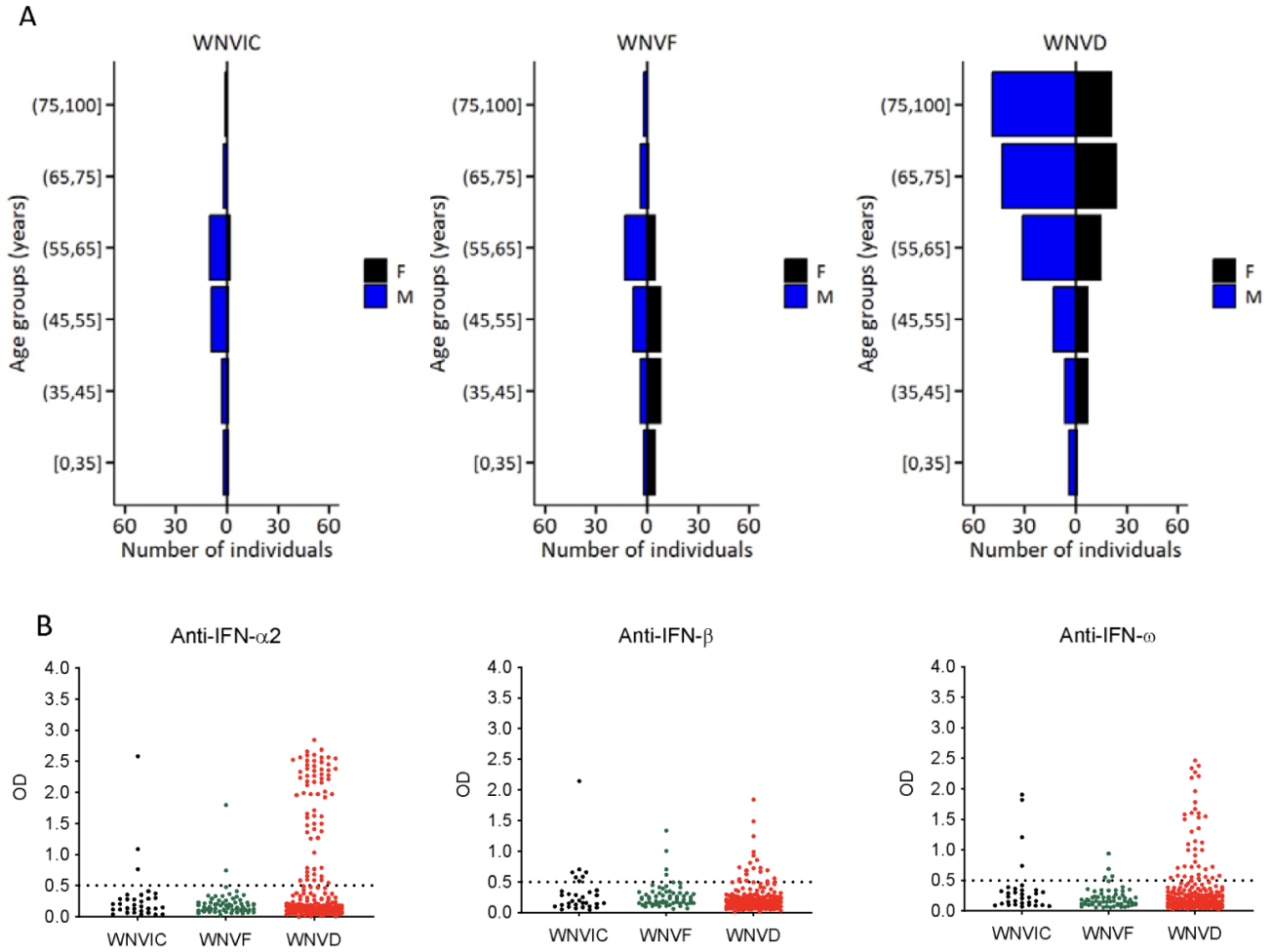


Gervais B J Human Immun 03.26

Autoantibodies neutralizing type I IFNs in 40% WNV encephalitis patients in 7 new cohorts

Table 2. Type I IFN-neutralizing auto-Abs in the study population

Characteristic	Auto-Ab+, *n* = 82[a]	No auto-Ab, *n* = 236[a]
Age (y)	69.52 [15.27]	60.88 [15.32]
≤40	3/29 (10%)	26/29 (90%)
(40–65]	20/137 (15%)	117/137 (85%)
>65	57/148 (39%)	91/148 (61%)
Unknown	0/4 (0%)	4/4 (100%)
Sex		
F	19/107 (18%)	88/107 (82%)
M	62/207 (30%)	145/207 (70%)
Unknown	1/4 (25%)	3/4 (75%)
WNV groups		
WNVD	81/225 (36%)	144/225 (64%)
WNVF	1/61 (2%)	60/61 (98%)
WNVIC	1/32 (3%)	31/32 (97%)
Subgroups of WNVD		
Non-neuroinvasive WNVD	9/25 (36%)	16/25 (64%)
Neuroinvasive WNVD		
All	71/200 (36%)	129/200 (64%)
WNE	59/154 (38%)	95/154 (62%)
WNM	8/32 (25%)	24/32 (75%)
AFP	2/7 (29%)	5/7 (71%)
UNS	2/7 (29%)	5/7 (71%)



Gervais B J Human Immun 03.26

Neuroinvasive WN virus infections after solid organ transplantation: Nebraska single center experience and systematic review

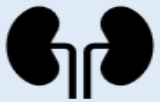
@TheTxIDJournal @AnumAbbasMD

Abbas *et al.* ***Transplant Infectious Diseases.*** 2022.

Retrospective, single-center review

8 SOT recipients with neuroinvasive WNv infection

5 kidney
1 kidney-pancreas



1 liver

1 lung

Median time from transplant to infection: 49.8 months

3 meningitis
1 encephalitis
4 meningo-encephalitis

Systematic review:
29 studies

Abnormal movements:
myoclonus, tremors, seizures

69%

Mortality of neuroinvasive WNv in SOT:

46%

Conclusions:

1. Neuroinvasive WNv infections in SOT recipients can be severe and cause death.
2. Infections can be donor-derived or community acquired and require a high index of suspicion.

5 (62.5%) pts on IV Ig. None received IFN. All apart 1 decreased immunosuppression. 5 had an abnormal EEG. Two patients had neurologic sequalae, one had foot drop, and the other had chronic dizziness.
Two patients had WNV- related death

53 cases; most kidney trasnplant

Abbas , Transp ID 2022

Incubation Periods of Mosquito-Borne Viral Infections: A Systematic Review

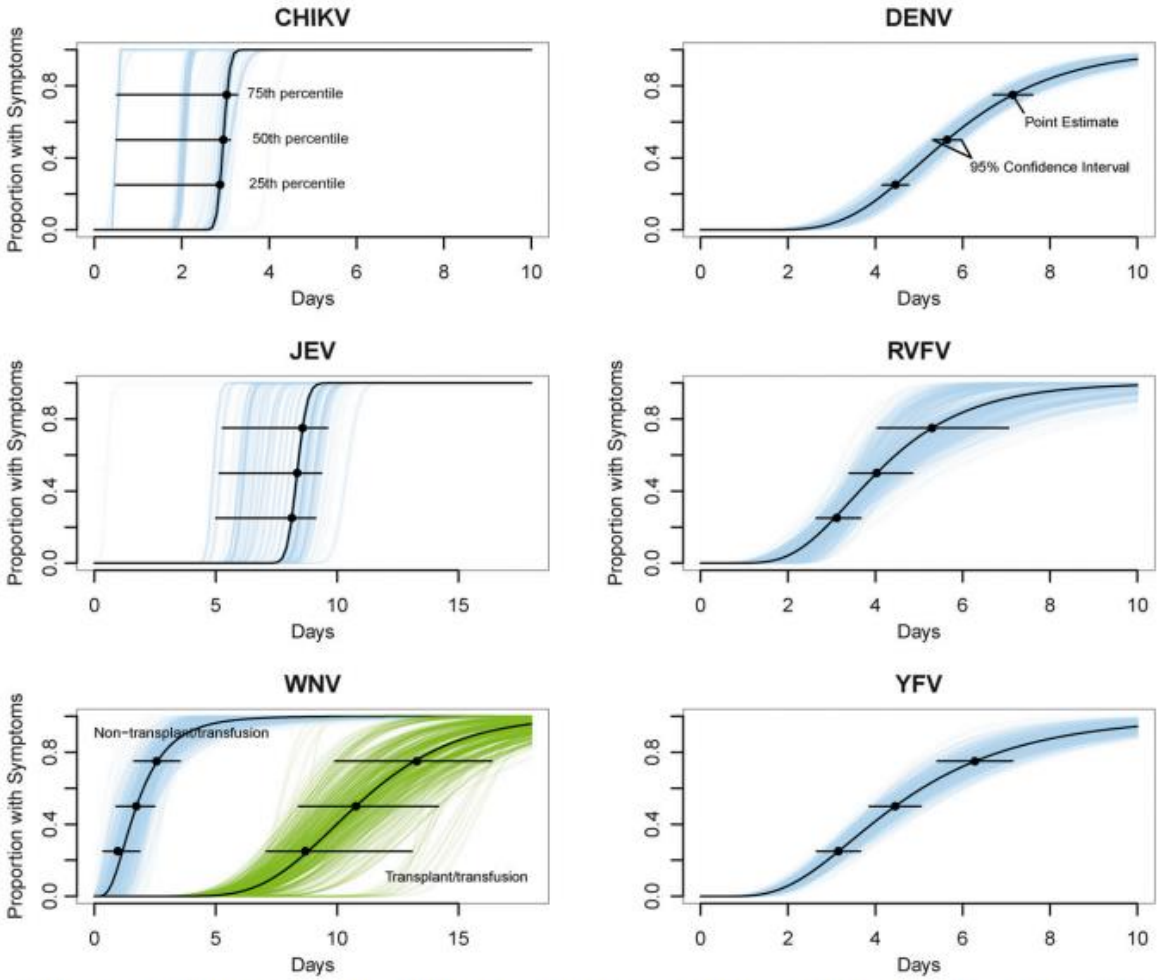
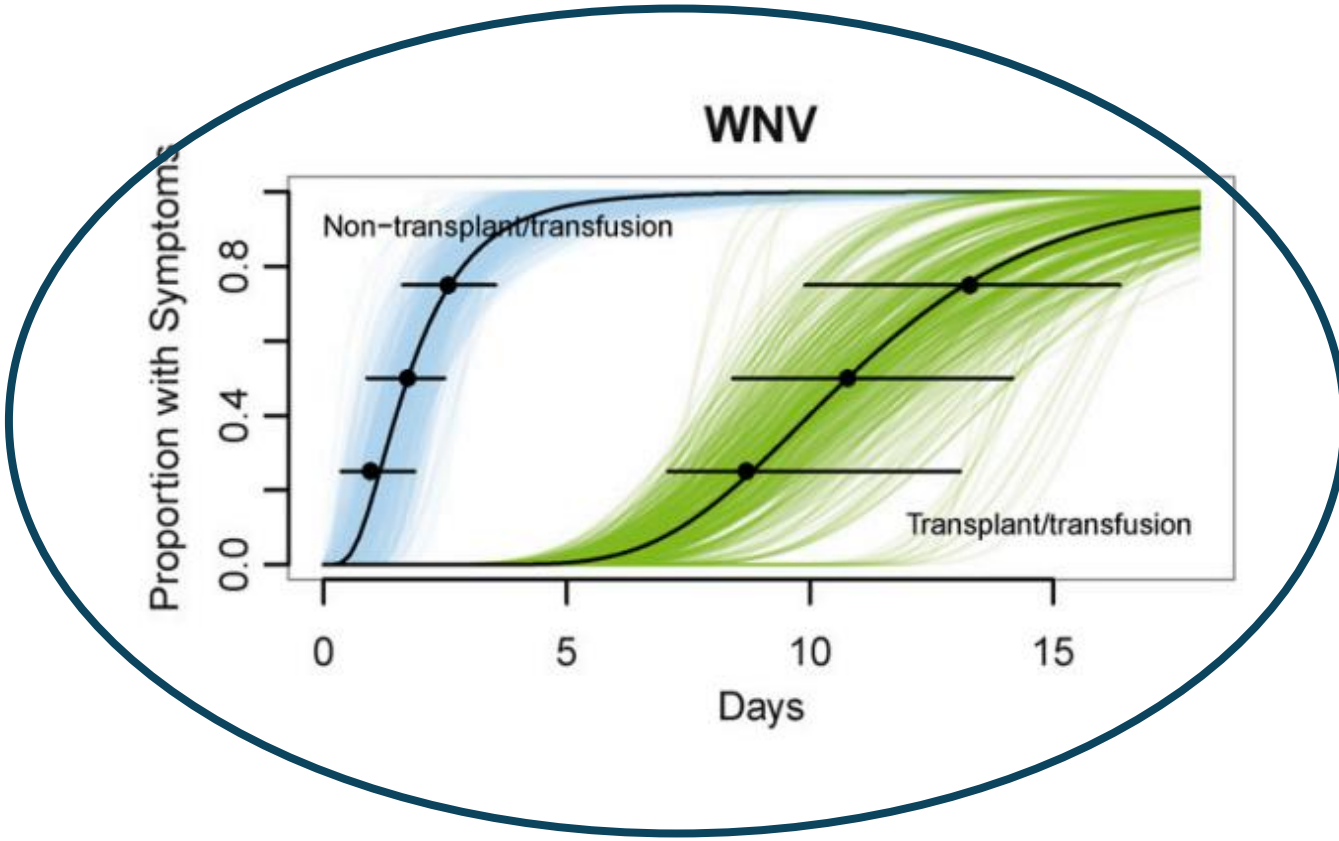


FIGURE 2. Estimated cumulative distributions of the incubation periods. Horizontal bars show the 95% confidence intervals at the 25th, 50th, and 75th percentiles. Individual lines represent bootstrap samples.



Rudolph AJTMH 2014

Correlation Between WNV and Pregnancy: A Systematic Review

Included Studies	Study Design	Parameters Assessed	Clinical Manifestations	Diagnosis/Serology	Outcomes/Conclusions
Study of frequencies of WNV infections during pregnancy and intrauterine WNV infections					
Paisley J. E. et al., 2005 (U.S.A.) [29]	Cross-sectional study, 566 women presenting for delivery and 549 newborns	Demographic characteristics, clinical symptoms (fever and timing of fever, WNV infection, congenital infection) and maternal IgG, IgM testing and growth, IgG testing, IgM audiogram, and newborn Apgar scale	Maternal: fever Newborn: 15% Apgar score < 7 5.3% low birth weight, 2.4% short stature, 4.9% smaller head, retinal hemorrhage, Roth spots	22/547 (4%) IgG (+), 0/547 IgM (+) in cord samples in newborns 5/184 Maternal serum IgM (+)/IgG (+) & IgG cord blood (+) but IgM cord blood (−)	- There were no statistically significant differences in neonates according to maternal disease. - Intrauterine WNV infections seemed to be infrequent.
Study of effects during pregnancy					
Chapa J. B. et al., 2003 (U.S.A.) [31]	Case study, 1 African-American woman affected by the virus, in the second trimester of pregnancy	Demographic characteristics, clinical symptoms and maternal IgG, IgM control and growth, IgG, IgM control, and newborn Apgar score	Maternal: fever, headache, nausea, vomiting, sore throat, neck stiffness, diplopia, reduced joint movement, preeclampsia	IgM maternal CSF Positive–Serology on newborn not performed	- Pregnant women are at high risk of developing serious complications such as encephalitis. - Data on the effect of WNV on the fetus are limited.
Pridjian G. et al., 2016 (U.S.A.) [26]	Prospective longitudinal cohort study, 28 pregnant serologically confirmed WNV women, matched on maternal age and enrollment month with 25 controls, and their newborns	Pregnancy and newborn data were collected; cord blood WNV serology was obtained. Pediatric exams and the Bayley Scales of Infant and Toddler Development-Third Edition (Bayley-III) were performed	Maternal: fever, rash, low concentration, weakness, meningitis, encephalitis	Maternal IgG 28 (+)/IgM (−)	- No differences in pregnancy and delivery characteristics. - Mothers with infection were more likely to have a fever and used a greater amount of medication. - Birth weight, length, head circumference, and rate of congenital malformations were similar in babies born to WNV-infected and -uninfected mothers. - Follow-up physical exams were generally normal. - The Bayley-III assessments, available for 17 children born to mothers with WNV illness, showed performance at or above age level across domains. - The risk for adverse pregnancy and newborn outcomes in WNV pregnant women appears to be low.
O'Leary D. R. et al., 2015 (U.S.A.) [30]	Cross-sectional study, 71 women with WNV and 72 of their newborns	Demographic characteristics, clinical symptoms and maternal IgG, IgM control and growth, IgG, IgM control, and newborn Apgar score	77 pregnant women with WNV were monitored: 71 delivered 72 live infants, while 4 had miscarriages, and 2 had elective abortions. Most infants were born at term Newborn: 5.6% preterm, 4.8% low birth weight, 10.6% some major birth defect (aortic coarctation, cleft palate, Down syndrome, lissencephaly, microcephaly, and polydactyly)	1/55 (cord serum) infants IgM (+)	- Three infants had a WNV infection that could have been congenitally acquired. - Seven infants had major malformations, but only three of these had defects that could have been caused by maternal WNV infection based on the timing of the infections and the sensitive developmental period for the specific malformations, and none had any conclusive evidence of WNV etiology.

Correlation Between WNV and Pregnancy: A Systematic Review

Included Studies	Study Design	Parameters Assessed	Clinical Manifestations	Diagnosis/Serology		Outcomes/Conclusions
Stewart R. D. et al., 2013 (U.S.A.) [32]	Case study, 3 women with WNV and 1 newborn	Demographic characteristics, clinical symptoms and maternal IgG, IgM control and growth, IgG, IgM control, and newborn Apgar score	Maternal: fever (66.6%), Nausea/vomiting (66.6%), headache (33.3%), neurologic symptoms (33.3%)	3 Maternal IgG (+)/3 IgM (+) – 1/1 newborn IgG (+)/IgM (–)	-	The effect of pregnancy on WNV infection and the effect of maternal WNV infection on the fetus both require further investigation.
Study of effects during lactation						
Hinckley A. F. et al., 2015 (U.S.A.) [28]	Cross-sectional study, 6 WNV mothers while breastfeeding their infants	IgA, IgM, IgG, WNV Neutralizing Antibody Titer, and SLEV Neutralizing Antibody Titer were studied in breast milk, maternal and child plasma	Newborn: transient papular rash, aortic isthmus stenosis, aortic dissection	Constituents in Milk 1/6 (+) in WNV Neutralizing $Antibody Titer, Constituents in Maternal Serum 5/6 (+) in WNV Neutralizing Antibody Titer, 6/6 IgM(+)/IgG(+) Constituents in Child Serum 0/6 IgM(+)/IgG(+)	- -	Six infants breastfed from mothers with WNV: five remained healthy, and one developed a rash. Two fell ill during breastfeeding, and two had congenital antibodies.
Study of effects on development						
Sirois P. A. et al., 2014 (U.S.A.) [27]	Cross-sectional study, 11 neonates and infants born to mothers with WNV	Demographic characteristics, growth screening, Bayley scale III, and eye examination of newborns	No significant clinical events were reported 1/11 newborns were born prematurely. While completing the questionnaire, 1/11 children had a moderate developmental delay	Infant and neonate IgG n/IgM not measured	-	Maternal WNV infection does not appear to be associated with global developmental delays in young children.

Pregnant women's symptoms and prognosis match those of the general population. A noteworthy difference is that there was a zero percent mortality following neuroinvasive disease compared to the average 10% of the general population, a finding that needs further investigation to be elucidated

Marnezi Pathogens 2024

West Nile virus: a risk for maternal-fetal medicine in Europe?

Vertical transmission during pregnancy, although rare, is possible.

- The **first recognized congenital infection, reported in 2002**, followed maternal infection at 27 weeks' gestation and was associated with neonatal encephalitis, cortical atrophy, and cystic destruction of the white matter and chorioretinitis
- In the US CDC a registry of 77 pregnancies (2003-04), **three (4%) infants had WNV infection** believed to have been acquired congenitally.
  - One infant, born to a mother who developed symptoms of WNV 6 days postpartum, presented with **WNV meningitis at age 10 days**.
  - Another infant, whose mother's illness began 3 weeks before delivery, developed WNV encephalitis with **lissencephaly and ultimately died** in early infancy.
  - Among the 72 live-born infants, **two cases of microcephaly were also reported**. Although the range of fetal neurological

Leo Pomar The Lancet 10.25

Data on 57 confirmed WNV inpatients in the Lazio region

Age Disparity in Infection Severity

- Patients with **neuroinvasive disease had a median age of 74,** higher than **58 in non-neuroinvasive cases.**

Comorbidity Index Difference

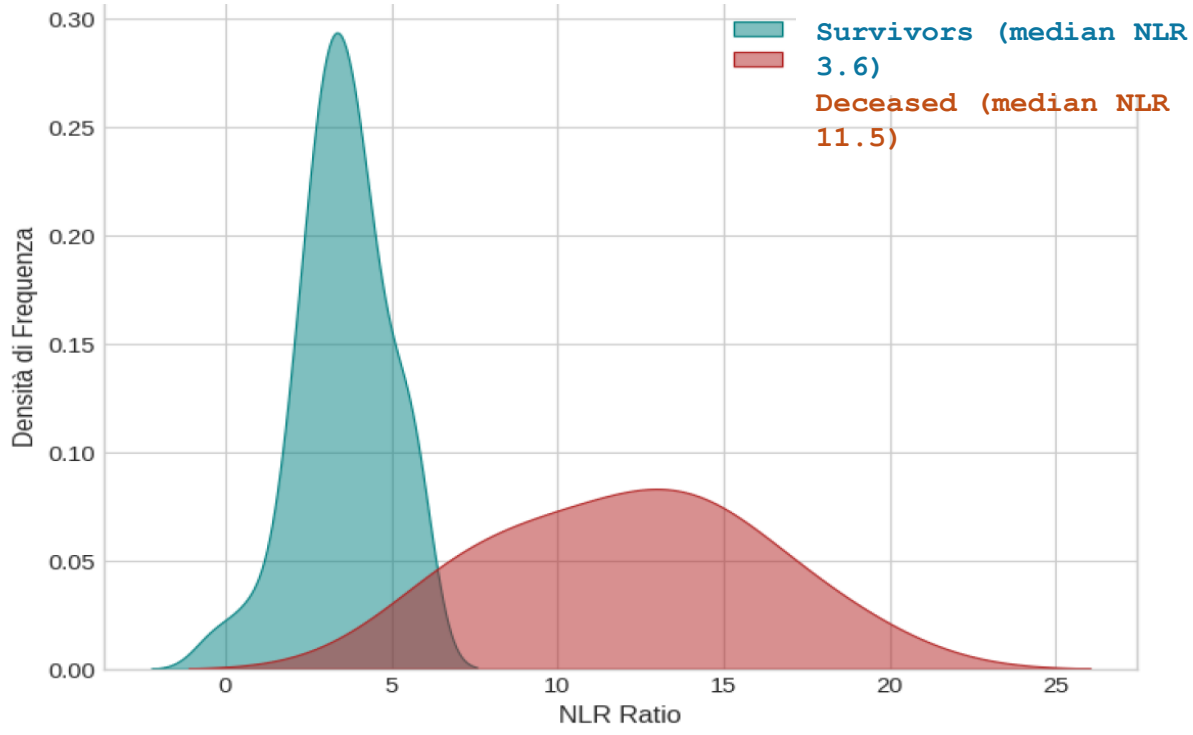
- **Higher median Charlson Comorbidity Index (7) in neuroinvasive WNV** than in fabrile WNV only **(3),** suggest a significantly indicating greater comorbidity burden.

Glasgow Come score

- **GCS 8 in neuroinvasive diseases versus**15.0 in febrile only WNV

Inflammatory profile in peripheral BD and CSF

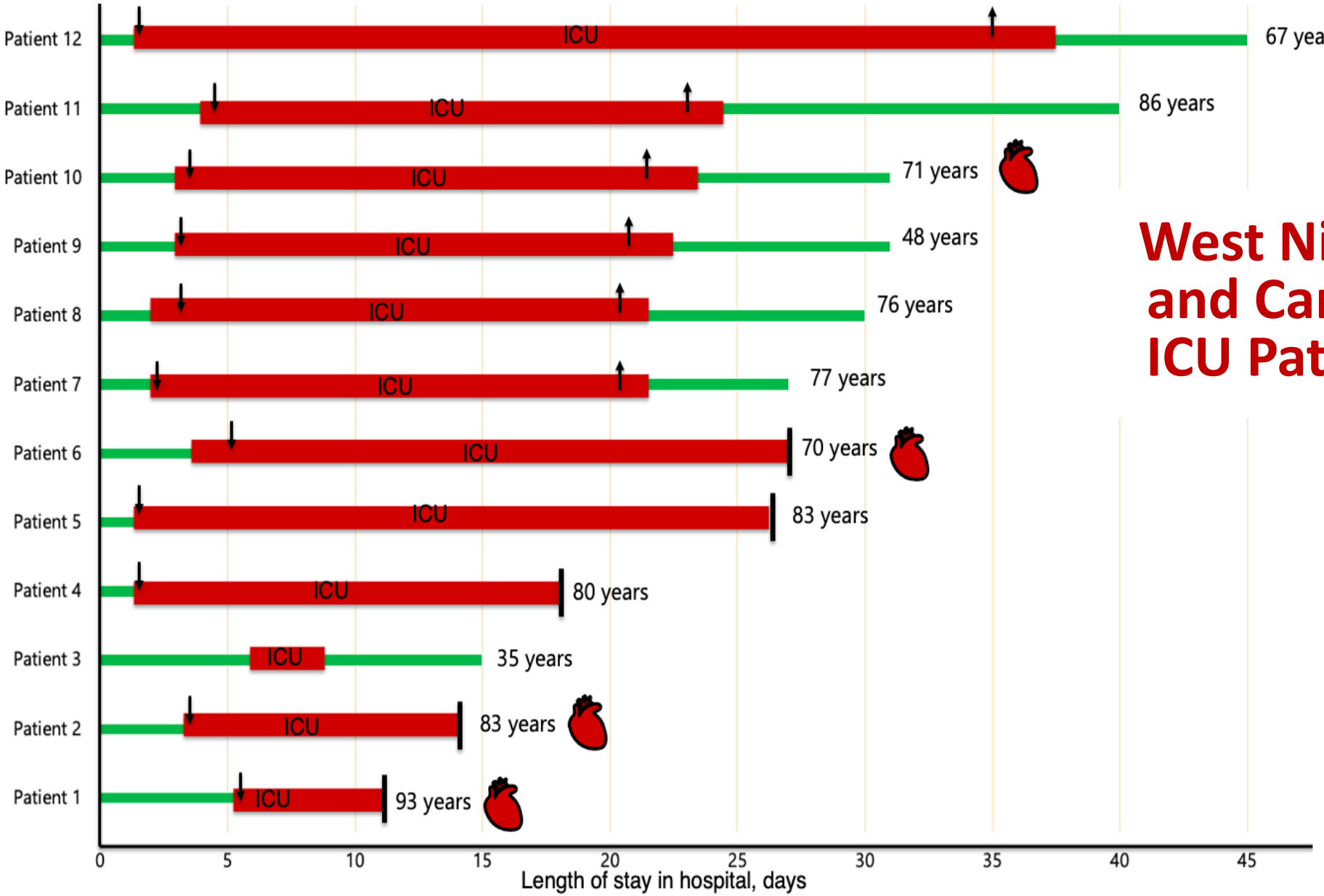
- **Neutrophyle-Lymphocyte-Ratio - NLR**
- Elevated **protein in CSF > 1 gr/L**



West Nile Virus Encephalitis and Cardiac Involvement in ICU Patients in Central Italy

	Total	Survivor group	Non-survivor group
Number of patients	**12**	**7 (58%)**	**5 (42%)**
CSF profile			
CSF Leukocyte count (cells/mm^3)	135 (79-192)	**90 (79 -190)**	**240 (130-430)**
CSF Protein (mg/dl)	126 (84-145)	**99 (83.8-145)**	**163 (136-247)**
CSF Glucose (mg/dl)	61 (52-71)	60 (52-71)	62 (59-67)
Blood Test at admission, Median (IQR)			
White blood cell count (x10^3 cells/mm^3)	10.6 (8.7-12.9)	11.5 (8.2-12.4)	9.5 (8.7-13.5)
Lymphocytes (x10^3 cells/mm^3)	0.79 (0.56-0.98)	0.86 (0.64-0.98)	0.75 (0.42-0.94)
Hemoglobin (g/dL)	12.6 (12-13.2)	13 (12.3-13.85)	12.4 (11.8-12.7)
Platelets (x10^3 cells/mm^3)	190 (162-263)	185 (151-226)	225 (170-285)
Creatinine (mg/dL)	1.07 (0.73-1.31)	1.04 (0.6-1.18)	1.18 (0.9-1.46)
AST (UI/L)	36 (25-64)	28 (24-46)	47 (32-613)
ALT (UI/L)	31 (23-72)	28 (19.5-35)	67 (25-89)
Total bilirubin (mg/dl)	1.16 (0.96-1.4)	1.22 (0.8-1.5)	1.03 (0.96-1.13)
INR	1.03 (1-1.2)	1.12 (1.01-1.3)	1 (0.98-1.03)
D-Dimer (ng/mL)	880 (780-1191)	895 (351-1391)	865 (795-1170)
C-Reactive Protein (mg/dL)	3.78 (1.17-8.9)	7.04 (2.8-9.3)	2.5 (0.76-3.06)
Procalcitonin (ng/mL)	0.09 (0.05-0.17)	0.125 (0.06-0.17)	0.09 (0.04-0.1)
Diagnostic tests, %			
WNV-specific IgM serum antibodies +	7 (58.3%)	4 (57.1%)	3 (60%)
WNV PCR of CSF +	6 (50%)	4 (57.1%)	2 (40%)

West Nile Virus Encephalitis and Cardiac Involvement in ICU Patients in Central Italy



Timeline of patients with neuroinvasive WNV during hospitalization

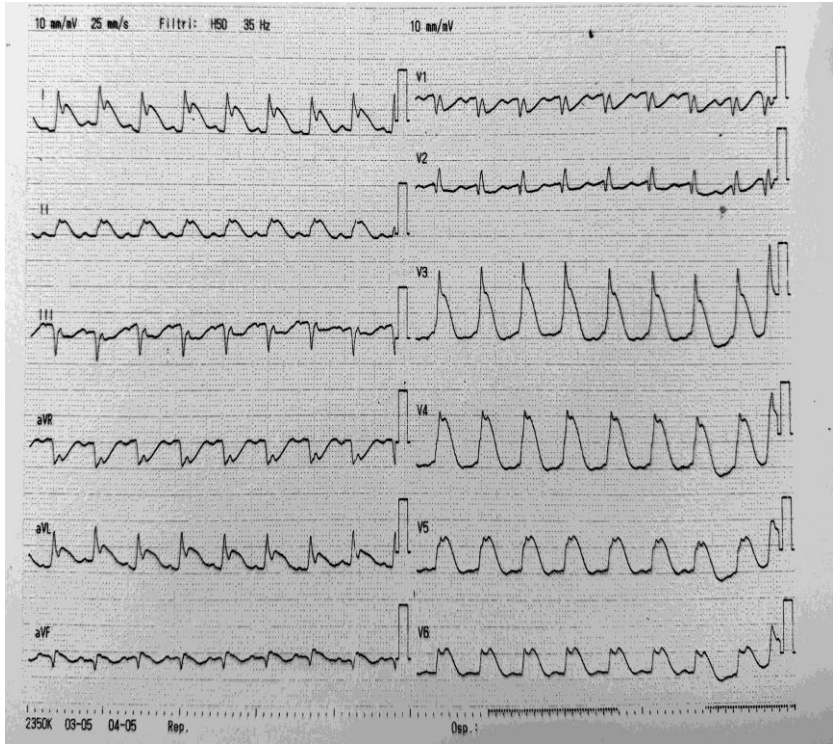
Green line, ward stay; Red line, ICU stay; Downward arrow, orotracheal intubation; Upward arrow, extubation; Vertical bar, exitus; Red heart symbol indicates a cardiac involvement with suspected WNV myocarditis

West Nile Virus Encephalitis and Cardiac Involvement in ICU Patients in Central Italy

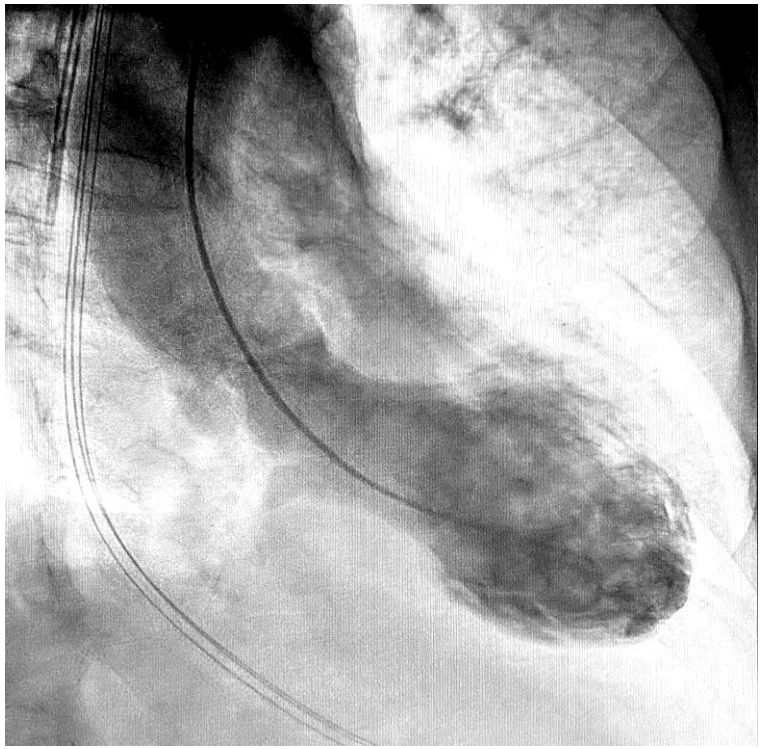
Clinical, laboratory, electrocardiographic, and echocardiographic features of the four patients with WNV neuroinvasive disease and acute cardiac involvement compatible with myocarditis.

Patient	Gender/age	Troponin peak	NTproBNP	Echocardiography findings	ECG alterations	Cardiac involvement
1	F/93y	109->345->765	2360	LV dysfunction with EF 40%	New onset T-waves inversion in V4-V6	Type II AMI
2	F/83y	100->300	1298	LV EF (30-35%), diffuse hypokinesia	New onset T-wave inversion in the precordial leads	Sustained ventricular tachycardia, ROSC after ALS
6	M/70y	25->100->350	4000	Reduced LV EF (35%), diffuse hypokinesia, more pronounced in the latero-apical segments	ECG showed new onset biphasic T waves in V3-V6	Suspected myocarditis
		25-		LVEF 30%,	ST-segment elevation	Takotsubo Syndrome, ACS-STEMI

Takotsubo Cardiomyopathy Triggered During Weaning from Mechanical Ventilation in a WNV Encephalitis Case



ST-segment elevation in leads V4–V6, DI, DII, and aVL during sedation weaning.



Left ventricular angiography with apical ballooning with preserved basal contraction

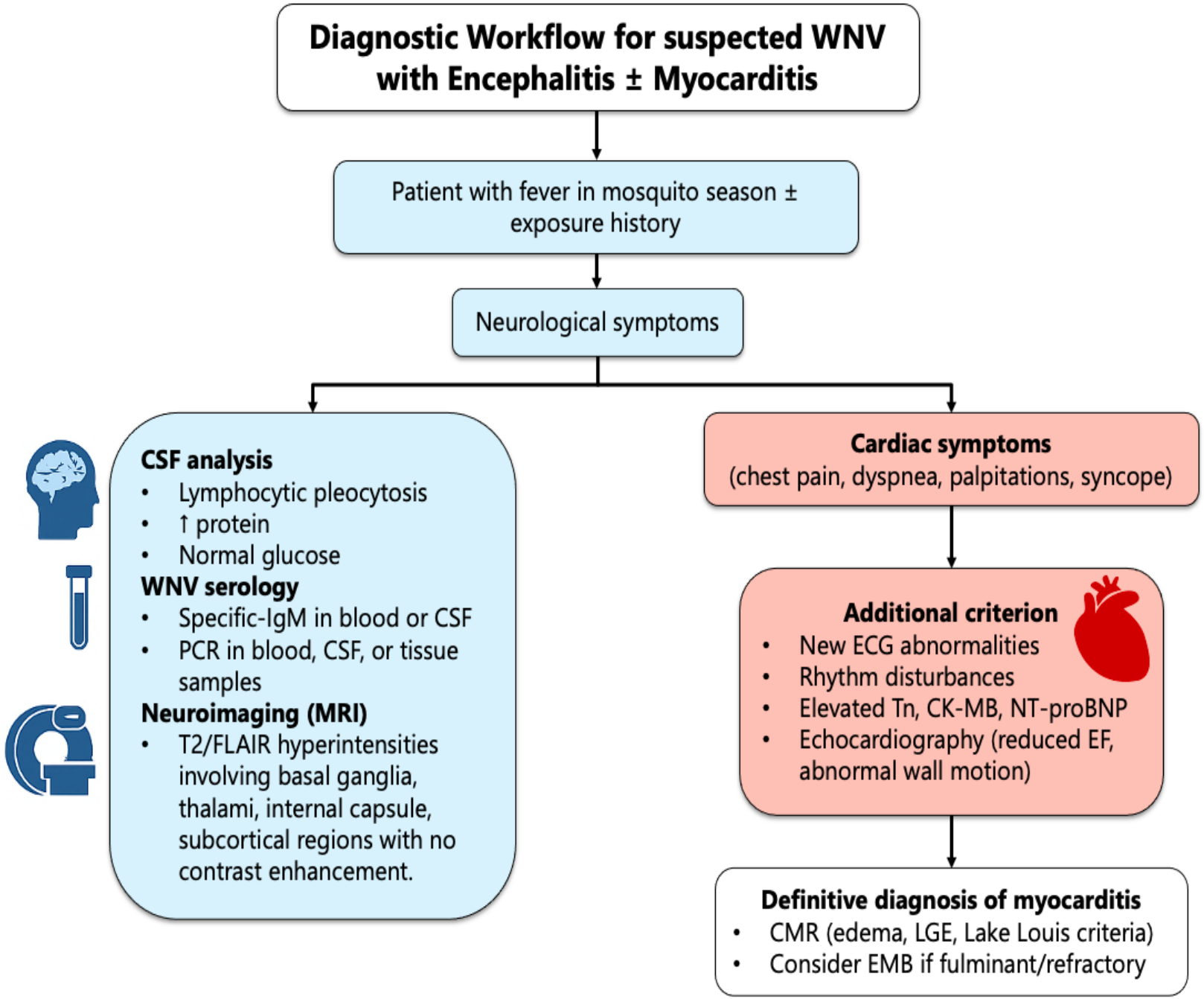
TTE (apical 4 chamber view, in the telesistolic phase) revealing apical and para-apical akinesia with basal hyperkinesis (EF ≈30%)

Submitted 3.2

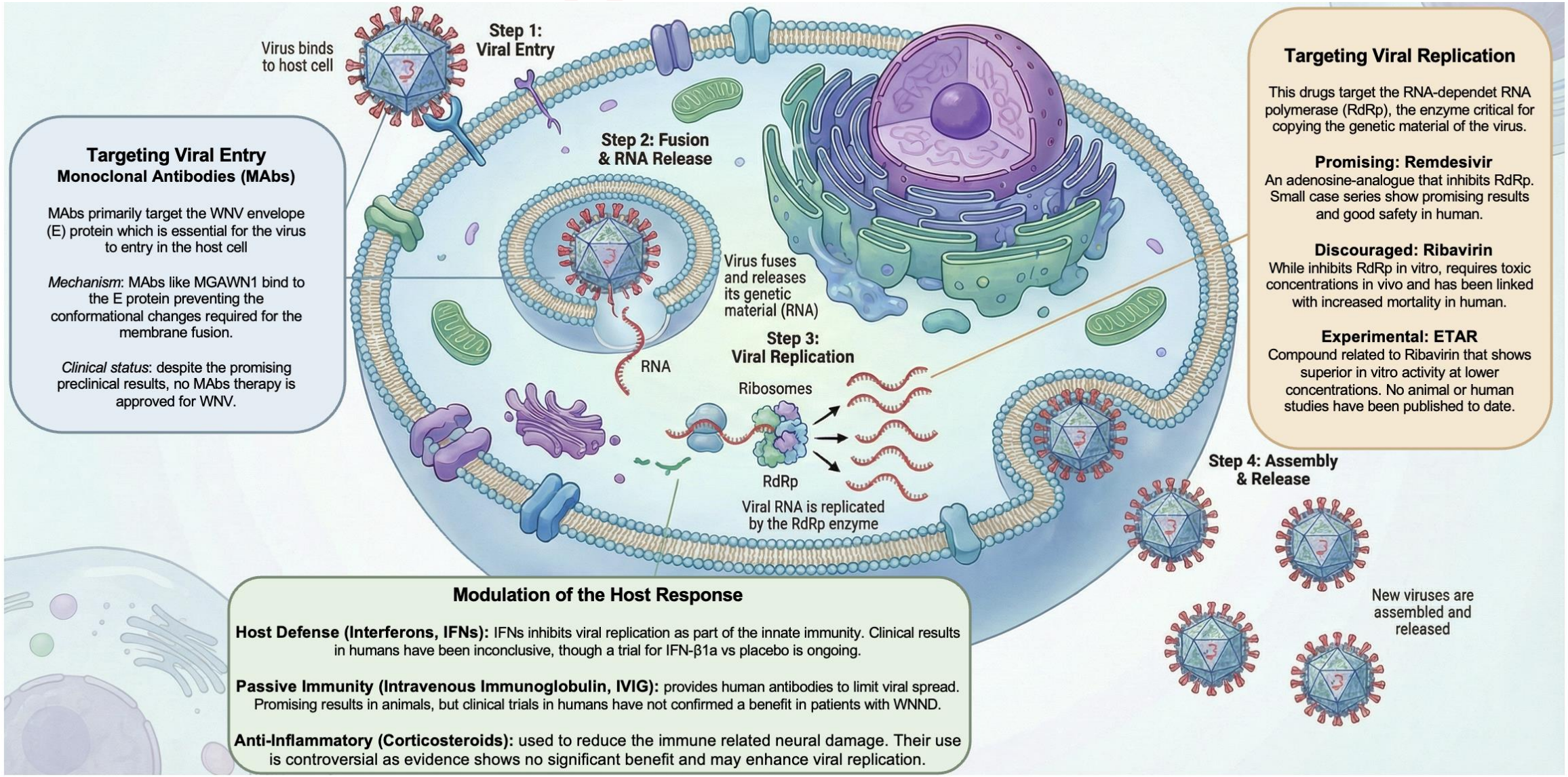
Diagnostic clinical management for suspected WNC with organ involvement

A diagram showing the diagnostic workflow for WNV encephalitis with or without cardiac involvement.

Abbreviations: CK-MB, creatin kinase MB; NT-proBNP, N-terminal pro B-type natriuretic peptide; EF, ejection fraction; CMR, cardiac magnetic resonance; EMB, endomyocardial biopsy.



West Nile Virus target antiviral and host directed therapy



Curtolo submitted

Agent studied	Subjects	Study type	Clinical presentation	Endpoints	Results	Notes
INFα2b (Sayaho 2004)	7 patients (only 3 treated with INFα2b) #1 73 years-old woman with hypertension, DM II; #2 71 years-old man with DM II, cardiac bypass, AF; #3 50 years-old man with no chronic diseases	Case series	Mild to severe disease	Survival	All survived	INFα2b start in the first 10d No AD reported
INFα2b (Wehbeh 2004)	23 patients with WNV; 15 received IFNα-2b and 8 received BSC	Unblinded randomized clinical trial	Neuroinvasive diseases	Neurologic improvement	Preliminary results: greater neurologic improvement in INFα2b group	Final results never published AD: neutropenia and hepatitis (resolved after treatment discontinuation)
INFα2b (Chan-Tack 2005)	1 patient # 76 years-old man with hypertension, TURP	Case report	Neuroinvasive disease, ARDS	Survival	Died without improved neurological functions	IFNα2b given after 17 days
INFα2b	2 patients (#1: 43y,	Case	Neuroinvasive	Survival	Survived without	INFα2b after 6 and

INFα2b **(Lewis 2007)**	1 patient 83 years-old man	Case report	Neuroinvasive disease	Survival	Survived Last neurological sequala resolved after 3 months	INFα2b Administered after 3weeks from onset
INFα2b **(Winston 2014)**	3 patients with SOT	Case series	Neuroinvasive disease	Survival	2 survived, 1 died	INFα2b Administered with human IG
IFN-β1a **(NCT06510426)**	100 patients (estimated)	Double blind placebo-control trial Ongoing (expected results 2025.12.31)	Mild to severe confirmed disease (older than 18 years-old)	Therapeutic effects Prevalence of anti-type-I-IFN autoantibodies in patients with WNV	--	IFN-β1a administered every 48h for 3 doses. Preliminary data not already published
Ribavirin **(Chowers 2001)**	233 patients; 37 treated with ribavirin	Observational retrospective study	Mild to severe disease (57.9% encephalitis)	Survival	Ribavirin independent death factor (OR 6.7 CI 3-15.2; p 0.0001)	Patients treated with RBV: alive 22 vs dead 15
Ribavirin **(Spiegel 2002)**	1 patient # 4 years-old child with LH)	Case report	Neuroinvasive disease	Survival	Discharge after 28 days Complete recovery after 8 months	RBV 200mg every 6 hours for 14 days WNV infection during chemotherapy against LH
Remdesivir **(Esposito 2025)**	12 patients (4 treated with RDV vs 8 treated with BSC)	Case series	Neuroinvasive disease	Survival Neurological sequelae	Lower median hospitalization (12d IQR 8-12 vs 16d IQR 8-34) Lower in-hospital mortality (0% vs 25%) Reduced need of rehabilitation (12% vs	Only 5 confirmed cases No statistically significant differences No AD reported

Agent studied	Subjects	Study type	Clinical presentation	Endpoints	Results	Notes
Corticosteroids (Colaneri et al., 2023)	65 patients 32 no steroids 33 mean dose of dexamethasone 13.6 mg/day, mean age 68.1 y, 73% M	Multicentric retrospective observational study	Neuroinvasive disease	Primary: Survival, Secondary: reducing LOS, neurological sequelae	No benefit observed: CSI did not reduce mortality or neurologic sequelae, and patients without steroids had shorter hospital stays.	Within the steroid group: 21 dexamethasone (64%), 4 methylprednisolone (12%), and 8 prednisone (24%).
Corticosteroids (Kal et al., 2022)	M, 61 y no medical history	Case report	Neuroinvasive	Survival	Marked improvement: spontaneous eye opening by day 2, extubated by day 4, and speech returned after treatment completion.	Solumedrol 1 g IV daily for five days
Corticosteroids (Leis & Sinclair, 2019)	F, 71y no medical history	Case report	Neuroinvasive	Survival	Rapid recovery: increased movement by day 1, fully responsive by day 2, with continued improvement leading to transfer to standard care.	methylprednisolone 1 g IV daily × 5 days
Corticosteroids (Pyrgos & Younus, 2004)	M, 68 y no medical history	Case report	Neuroinvasive	Survival	Patient improved quickly: speech returned within 24 hours, and by 48 hours upper limb strength and continence were fully restored.	methylprednisone 500mg IV daily x 4 days
MGAWN1 (ClinicalTrials.gov: NCT00927953, unpublished	13 patients 7 placebo 6 single infusion of	Phase I/II randomized trial	Neuroinvasive	Survival	Outcomes were limited: two of six patients on MGAWN1 died versus one on placebo; the study ended early due to poor enrollment.	30 mg/kg single infusion IV of MGAWN1

IVIG (Gnann et al., 2019)	62 patients randomized3: 1:1 to receive Omr-IgG-am (37), standard IVIG (12), placebo (13); mean age 56.2 y, 66.1% M	Phase I/II randomized double-blind, placebo-controlled trial	Neuroinvasive and Mild to severe disease	Primary: safety and tolerability Secondary: survival, therapeutic effects	No safety issues, but no efficacy was shown. A non-significant trend suggested better clinical and survival in the placebo group.	Single dose 0.5g/kg of Omr-IgG-am (OMRIX Bio pharmaceuticals, Israel); single dose of standard IVIG (Polygam S/D; Baxter).
IVIG (Malone et al., 2022)	M, 63 y DM II, hyperlipidemia	Case report	Neuroinvasive	Survival	Improvement in respiratory function, mental status, and movement.	Plasma exchange and IVIG for 4 days
IVIG (Hamdan et al., 2002)	M, 42 y Lung transplantation 6 months before	Case report	Neuroinvasive	Survival	Rapid improvement: fully oriented by day 1, symptoms resolved within 48 hours, and discharged two days later without sequelae.	400mg/kg Omr-IgG-am
IVIG (Hébert et al., 2017)	F, 63 y no medical history	Case report	Neuroinvasive (opsoclonus-myoclonus syndrome)	Survival	No adverse effects. Within 24 h, myoclonus improved and opsoclonus nearly resolved. Full neurological remission by 8 weeks.	1 g/kg standard IVIG per day for 2 days
IVIG (Shimoni et al., 2001)	F, 70 y chronic lymphatic leukemia on follow-up	Case report	Neuroinvasive	Survival	Initial condition stable for 2 days, then gradual improvement. Within 5 more days, consciousness fully returned to normal.	400mg/kg Omr-IgG-am

The Impact of Corticosteroid Therapy on WNV Patients: A Retrospective Cohort Study

Table 3. Hospitalization Outcomes

Outcome	No Treatment N = 109	CS Treatment N = 41	HR (95% CI)	*P* Value
Hospital mortality				
Crude	8 (7.3)	8 (19.5)	2.94 (1.06–8.17)	.04
Adjusted[a]			3.64 (1.14–11.67)	.03
Adjusted with IPTW[a]			3.93 (1.14–13.51)	.03
ICU and mechanical ventilation[a]	8 (7.3)	6 (14.6)	4.6 (1.07–19.85)	.04
Rehabilitation or LTCF[a]	26 (25.7)	12 (36.4)	1.1 (0.5–2.36)	.83

IPTW, inverse probability of treatment weight; ICU, intensive care unit; LTCF, long-term care facility.

[a]Adjusted for age, sex, chronic renal failure, immunosuppression, history of stroke, and neuroinvasive disease.

- 150 WNV patients during all 2024 y admitted at Rabin Medical Center, of them 41 (27%) patients received steroids.
- Steroid treatment was found to significantly increase hospital mortality ([aHR 3.9, 95% CI 1.1–

Poran JID 12.

Expanded profiling of Remdesivir as a broad-spectrum antiviral and low potential for interaction

Scientific Reports 2023

Viral family	Virus (strain) [cells]	Antiviral activity EC_{50} (μM)[a]	CC_{50} (μM)	Selectivity index (SI)[b]	Previously reported activity EC_{50} (μM)
Corona-	OC43 [Huh-7]	0.067 ± 0.005	18.9 ± 1.8	282	0.096–0.15[16,17]
	229E [H1 HeLa]	0.093 ± 0.053	> 50	> 538	0.024[18]
Picorna-	Enterovirus 68D [RD]	0.050 (n = 1)	2.82	56	0.1–1[8]
	Enterovirus 71 [RD]	0.140 (n = 1)	3.31	24	NA
	Rhinovirus A2 [H1 HeLa]	0.450 (n = 1)	> 10	> 22	NA
	Rhinovirus 14 [H1 HeLa]	0.385 ± 0.318		> 26	
	Rhinovirus 16 [H1 HeLa]	0.750 (n = 1)		> 13	
Flavi-	Dengue 1 virus (Western Pacific) [Huh-7]	0.21 (n = 1)	33.4	159	NA
	Dengue 1 virus (Djibouti) [Huh-7]	0.31 ± 0.09		108	
	Dengue 2 virus (New Guinea C) [Huh-7]	0.23 (n = 1)		145	
	Dengue 2 virus (RL) [Huh-7]	0.29 ± 0.07		115	
	Dengue 3 virus (VN32) [Huh-7]	0.12 (n = 1)		278	
	Dengue 3 virus (H87) [Huh-7]	0.17 ± 0.07		196	
	Dengue 4 virus (MY01) [Huh-7]	0.18 (n = 1)		186	
	Dengue 4 virus (Dakar_HD_34460) [Huh-7]	0.19 ± 0.05		176	
	Zika virus (PRVABC59) [Huh-7]	0.26 (n = 1)	33.4	128	NA
	Zika virus (Dakar) [Huh-7]	0.37 (n = 1)		90	
	Zika virus (MR766) [Huh-7]	1.15 ± 0.03		29	
	Yellow fever virus (YFS11) [Huh-7]	1.06 (n = 1)	33.4	32	NA
	Yellow fever virus (17D) [Huh-7]	0.18 ± 0.03		186	
	Japanese encephalitis (14–14-2) [Huh-7]	0.34 (n = 1)	33.4	98	NA
	West Nile (NY99) [Huh-7]	0.05 (n = 1)	33.4	668	NA

Analysis of WNV proteins: an in silico drug repurposing aproach: Remdesivir, rilpivirine and doravirine

This study employs computational approaches to identify suitable druggable viral targets and evaluate the binding affinities of three antivirals

- ✓ **NS5 (RdRp)** – **Remdesivir** interacts with various residues at the targeted site, effectively coordinating the divalent cation. Notably, it showed high stability and promising thermodynamic values throughout the MD simulation.
- ✓ **NS5 (MTase)** – **Doravirine** demonstrates exceptional geometric stability at the SAH site and the KDKE motif, remaining firmly anchored to each site. **Rilpivirine** also yielded promising results in the SAH domain.
- ✗ **NS3 (Serine protease)** – None of the antiviral drugs was stabilized within the proteolytic site, showing high instability. Moreover, all three ligands did not show the necessary conditions for a covalent bond.
- ✓ **Core protein** – **Doravirine** is the only drug capable of remaining well anchored in the entrance of the RNA tunnel, with excellent thermodynamic values throughout the simulation. Regarding the hydrophobic membrane involved in the interaction with the membrane, all three antivirals dock firmly to the two α-helices, with Rilpivirine yielding the best results.

Doravirine's binding modes and overall **stability** highlight its potential as a **promising candidate** for WNV inhibition with a multitarget activity

Artese A, Quiros E et al Drug Des Devel Ther. 2025

Outbreak of human neuroinvasive infection in Campania, Italy, August to September 2024

Table 1 – Epidemiological and diagnostic features of WNV infection outbreak in the province of Benevento, Campania, Italy. WNND = West Nile virus neuroinvasive disease; NAD = not available; AFP = acute flaccid paralysis.

Cases	Case classification	Travel outside province	Type of disease	Clinical presentation	Age	WNV RNA serum	WNV RNA CSF	IgM index	IgG index
Case 1	Confirmed	NO	WNND	Encephalitis	50-60	detectable	NA	8.12	1.55
Case 2	Probable	NO	WNND	Encephalitis	80-90	undetectable	undetectable	8.421	0.379
Case 3	Probable	NO	WNND	Encephalitis	70-80	undetectable	undetectable	8.736	0.326
Case 4	Probable	NO	WNND	Meningitis	60-70	undetectable	undetectable	6	1,5
Case 5	Probable	NO	WNND	Encephalitis	80-90	undetectable	NA	7.2	1.4
Case 6	Confirmed	NO	WNND	AFP	40-50	undetectable	detectable	NAD	NAD
Case 7	Probable	NO	WNND	Encephalitis	60-70	undetectable	undetectable	6.94	2
Case 8	Confirmed	NO	Asymptomatic	Asymptomatic	60-70	detectable	NA	NAD	NAD
Case 9	Confirmed	NO	WNND	Encephalitis	80-90	detectable	NA	8	0
Case 10	Confirmed	NO	WNND	Encephalitis	80-90	detectable	NA	8	1.5
Case 11	Probable	NO	WNND	Encephalitis	80-90	undetectable	NA	6.7	0
Case 12	Probable	NO	WNND	Encephalitis	80-90	undetectable	NA	6	2

- Five confirmed and seven probable cases of WNV were identified from August to September 2024.
- Predominantly affecting elderly males with comorbidities, all but one patient developed West Nile neuroinvasive disease, presenting with fever and impaired consciousness.
- Remdesivir was administered off-label in four cases, potentially reducing hospitalization and improving outcomes.
- Mortality was limited to two cases, attributed to bacterial infections.

Vect Born Zoon Dis 07.2025

Proposal of a pospective Multicenter Observational Study on Arbovirus Infections Circulating in EUrope (MOSAIC-EU): clinical, epidemiological and genomic integration for the surveillance and management of autochthonous arboviral diseases

Primary objective

- **International multicenter prospective cohort of autochthonous arbovirus in Europe** to systematically define the clinical, epidemiological, and environmental profiles, with particular attention to **WNV, Toscana or CCHF**

Secondary objectives

- Identification of **determinants of severe disease** associated with the development of severe forms, including neuroinvasive manifestations and adverse outcomes.
- Definition of **clinical phenotypes** in autochthonous arboviral diseases, evaluating response to clinical management, and short- and medium-term outcomes.
- Optimization of **diagnostic and care pathways** in the various participating centers to identify areas for improvement and propose strategies for optimizing clinical management.
- Development of **predictive tools** for the early identification of patients most likely to develop severe diseases, which can be used in clinical practice and surveillance systems.
- **Support for public health and integrated surveillance**: provide evidence to strengthen epidemiological surveillance systems

Proposal of a prospective Multicenter Observational Study on Arbovirus Infections Circulating in EUrope (MOSAIC-EU): clinical, epidemiological and genomic integration for the surveillance and management of autochthonous arboviral diseases

Target population

- Adult patients diagnosed with **arbovirus infection acquired in Europe**, identified in hospitals or local healthcare facilities participating in the study.

Study design

- **European multicenter prospective observational study based on real-world data**
- M&M
- **Clinical, epidemiological, and lab routinely collected data** patients with indigenous arboviral disease enrolled in participating centers as part of routine clinical practice.
- The primary outcome measures include **disease severity** (with particular reference to invasive forms), mortality, **drug use** and **clinical outcome** at discharge. Secondary outcome measures include clinical and laboratory characteristics, length of hospital stay, diagnostic and care pathways, and short- and medium-term outcomes, when available.
- The data collected will allow for the evaluation of variability in clinical management between centers and the production of evidence useful for improving care pathways and epidemiological surveillance systems.
- **36 months** from approval by the Ethics Committee

Conclusions

- WNV is primarily an **asymptomatic zoonosis in >80%** patients
- In young adults is an **acute syndromic fever wih morbilliform rash**
- **Epidemiologic case definitions do not fit for clinical purpose**
- In **elderly or IC** patients can be **neuroinvasive i with unfavourable outcome (10%)** but other organs ie **hearth can be severely involved**
- **No primary or secondary prophylaxis or vaccine**
- **No effective antivirals** even if few anedoctical cases or case series are reported
- **Prevention is all**

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