Encéphalites

Romain Sonneville

Médecine Intensive Réanimation

APHP.Nord, Hôpital Bichat Claude Bernard, Paris

Université Paris Cité, INSERM UMR1137

 romain.sonneville@aphp.fr  @romsonnevil

Conflicts of interest

Grants:

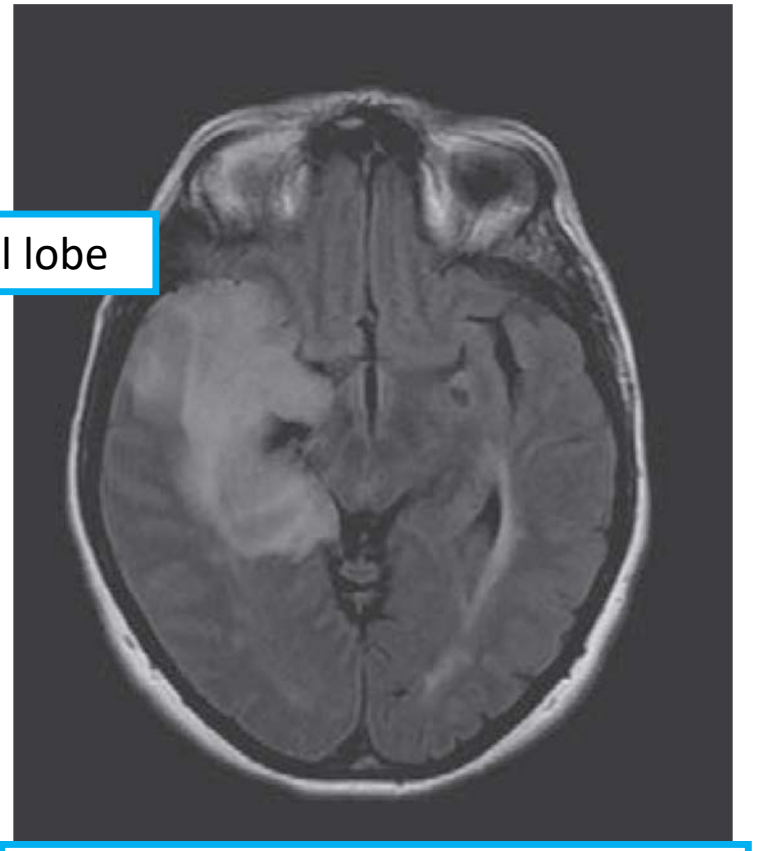
- French Ministry of Health (2015) : PHRC-IR EncephalitiCa
- ESICM (2017) : Research grant, EURECA
- LFB (2022) : Research grant, Immuno-EURECA

Encéphalites

- Epidémiologie
- Démarche diagnostique
- Corticostéroïdes ?
- Encéphalite auto-immune ?
- Pronostic

Encephalitis

Inflammation	**Brain parenchyma**
Causes	**Viral** Immune-mediated
Altered mental status	**+**
Fever	**+**
Meningism	+/-
Focal signs	+/-
Seizures	+/-



Herpes simplex encephalitis

	Encephalitis	Meningitis
Inflammation	**Brain parenchyma**	**Subarachnoid space**
Causes	**Viral** Immune-mediated	**Bacterial** Viral
Altered mental status	**+**	+/-
Fever	**+**	**+**
Meningism	+/-	**+**
Focal signs	+/-	+/-
Seizures	+/-	+/-

Diagnosis of encephalitis

MAJOR CRITERIA

- **Decreased level of consciousness, lethargy, personality change ≥24 h**

(+/- short-term memory deficits or psychiatric symptoms)

- No alternative diagnosis to explain presentation

MINOR CRITERIA (at least 3 for probable/confirmed encephalitis)

- **Fever** ≥ 38°C (within 72H before or after presentation)

- New-onset **seizure(s)**

- New **focal neurologic findings**

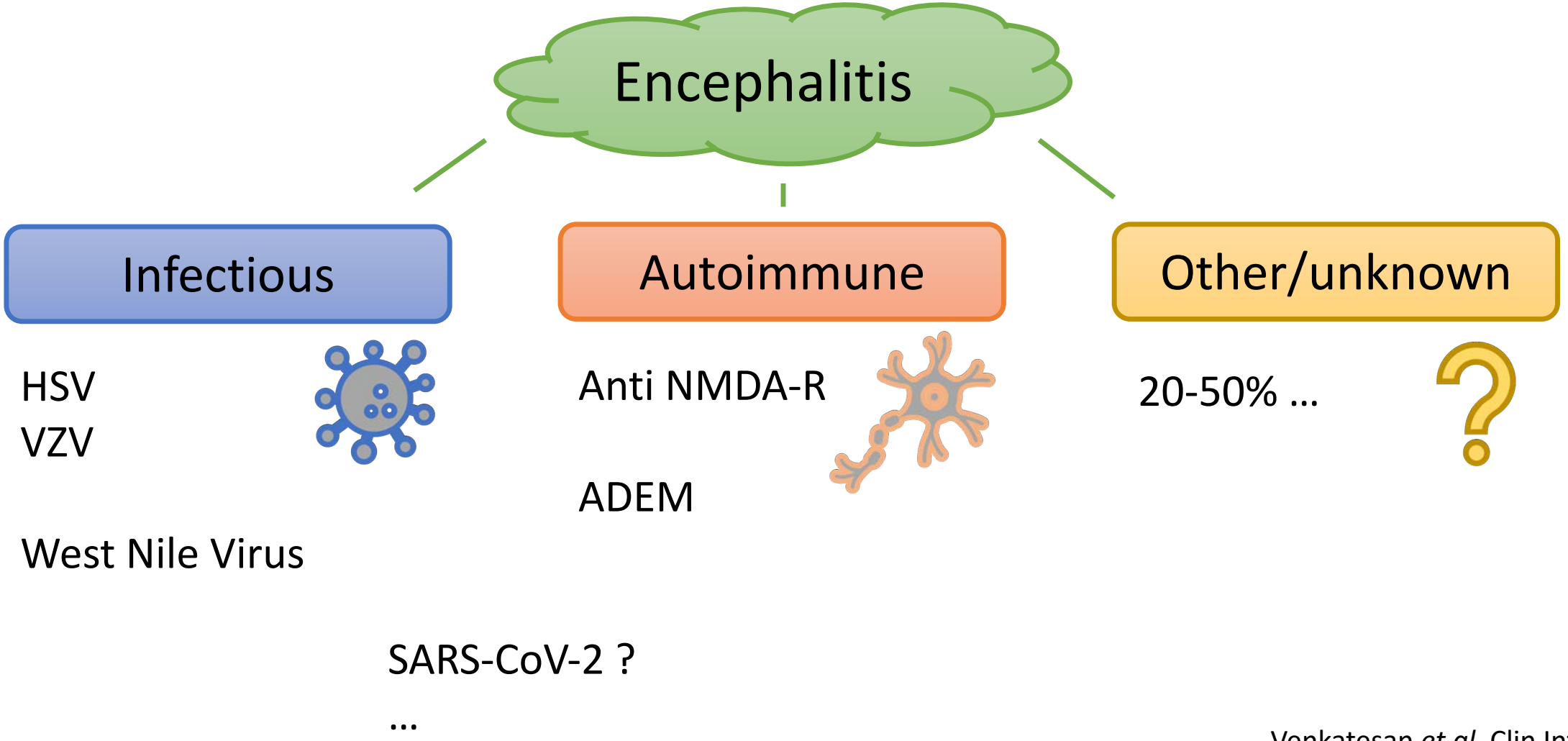
- **CSF pleocytosis** ≥ 5 cell/mm^3

- **Brain imaging** abnormalities (MRI)

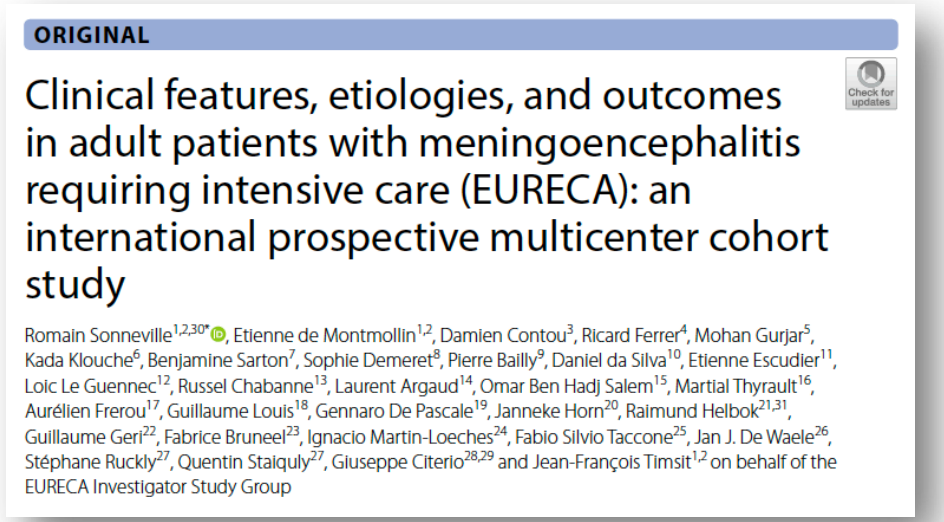
- **Abnormal EEG** consistent with acute neurologic dysfunction

Venkatesan *et al*. Clin Inf Dis 2013
Venkatesan *et al.*, Lancet 2019
Bloch et al., Clin Inf Dis 2023

Causes of encephalitis



Venkatesan *et al*. Clin Inf Dis 2013
Venkatesan *et al.*, Lancet 2019
Bloch et al., Clin Inf Dis 2023



ORIGINAL

Clinical features, etiologies, and outcomes in adult patients with meningoencephalitis requiring intensive care (EURECA): an international prospective multicenter cohort study

Romain Sonneville[1,2,30*], Etienne de Montmollin[1,2], Damien Contou[3], Ricard Ferrer[4], Mohan Gurjar[5], Kada Klouche[6], Benjamine Sarton[7], Sophie Demeret[8], Pierre Bailly[9], Daniel da Silva[10], Etienne Escudier[11], Loic Le Guennec[12], Russel Chabanne[13], Laurent Argaud[14], Omar Ben Hadj Salem[15], Martial Thyrault[16], Aurélien Frerou[17], Guillaume Louis[18], Gennaro De Pascale[19], Janneke Horn[20], Raimund Helbok[21,31], Guillaume Geri[22], Fabrice Bruneel[23], Ignacio Martin-Loeches[24], Fabio Silvio Taccone[25], Jan J. De Waele[26], Stéphane Ruckly[27], Quentin Staiquly[27], Giuseppe Citerio[28,29] and Jean-François Timsit[1,2] on behalf of the EURECA Investigator Study Group

Epidemiology and outcomes of **all-cause encephalitis** in the ICU

Prospective multicenter international cohort study

2017-2019

68 centres, **seven** countries

Inclusion ☑

Adults
ICU admission

+

Encephalopathy
(GCS ≤13)

+

CSF inflammation
(≥5cell /mm³)

+

2 criteria among:

Fever
Focal signs
Seizures
CT/MRI changes
EEG changes

May 2023

ORIGINAL

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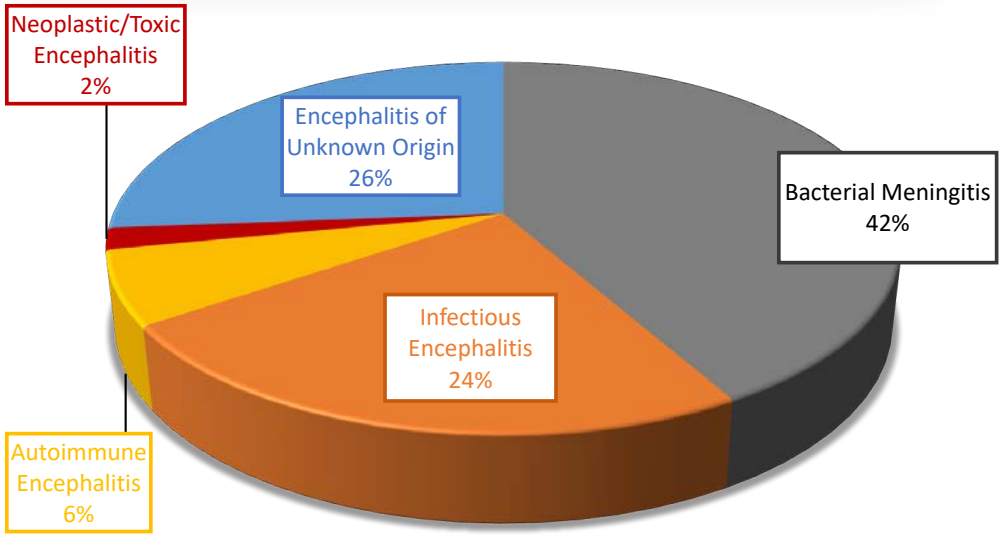

n=589

Categories	*n* (%)
Acute bacterial meningitis	**247 (41.8)**
Streptococcus pneumoniae	148 (25)
Neisseria meningitidis	17 (2.9)
Listeria monocytogenes	14 (2.4)
Other causes*	68 (11.5)
Infectious encephalitis	**140 (23.7)**
Viral causes	101 (17.1)
Herpes simplex virus 1/2	49 (8.3)
Varicella zoster virus	21 (3.6)
Enterovirus	3 (0.5)
Other causes**	28 (4.7)
Subacute bacterial causes	25 (4.2)
Mycobacterium tuberculosis	16 (2.7)
Other causes**	9 (1.5)
Fungal/parasitic causes	14 (2.4)
Toxoplasma gondii	7 (1.2)
Cryptococcus neoformans	3 (0.5)
Aspergillus spp.	2 (0.3)
Other causes**	2 (0.5)
Autoimmune	**38 (6.4)**
Anti-*N*-methyl-D-aspartate Receptor antibody	16 (2.7)
Acute disseminated encephalomyelitis	7 (1.2)
Other causes	15 (2.5)
Neoplastic/toxic	**11 (1.9)**
Unknown origin	**155 (26.2)**

May 2023

ORIGINAL

Clinical features, etiologies, and outcomes in adult patients with meningoencephalitis requiring intensive care (EURECA): an international prospective multicenter cohort study

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n=589

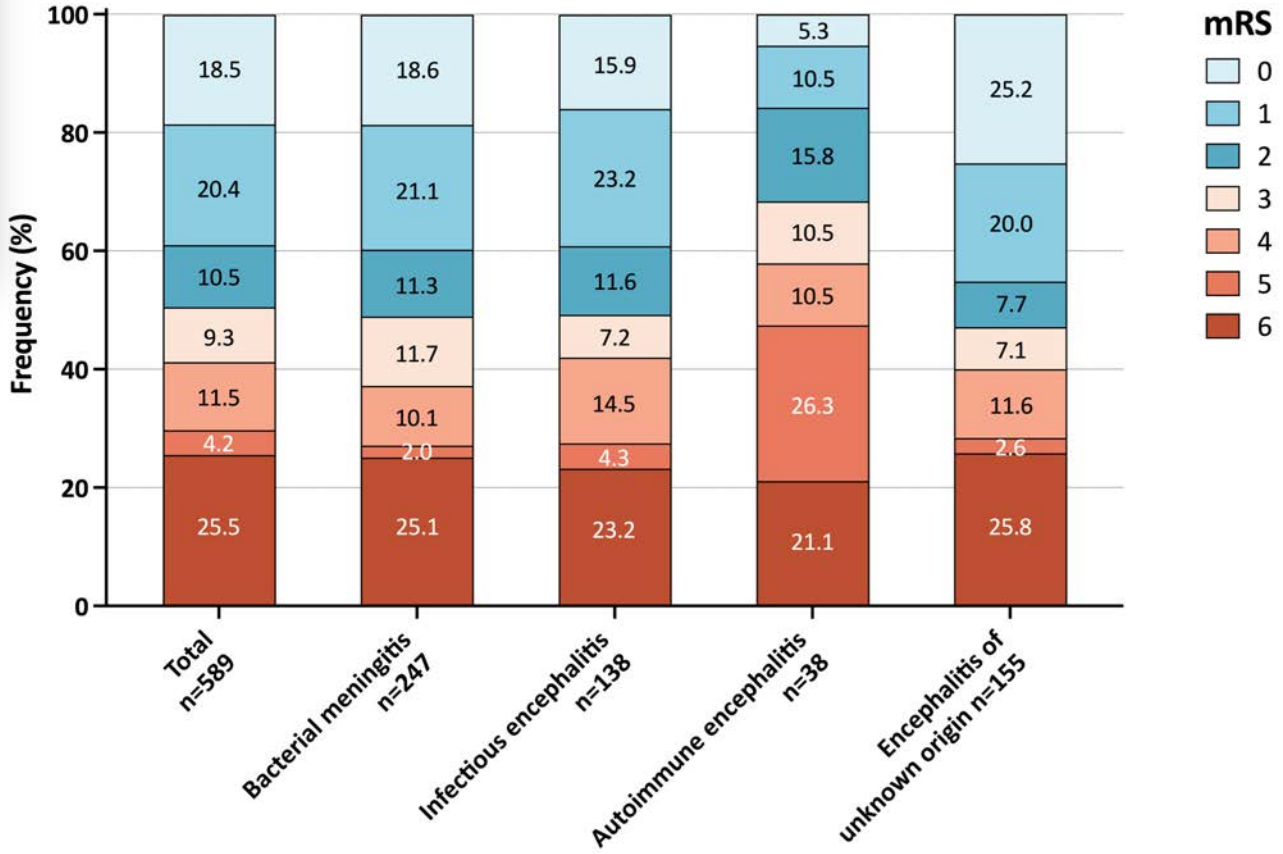
Prospective multicenter international

cohort study

2017-2019

68 centres, **seven** countries

Day-90 outcomes



May 2023

Encéphalites

- Epidémiologie
- Démarche diagnostique
- Corticostéroïdes ?
- Encéphalite auto-immune ?
- Pronostic

CURRENT OPINION

Critical care management of meningitis and encephalitis: an update

Michael Thy[a,b,c], Augustin Gaudemer[d], Geoffroy Vellieux[e,f] and Romain Sonneville[a,g]

Multimodal approach to diagnosis of encephalitis

Medical History

Recent illness ?

Immunosuppression

Seasonal/epidemic context ?

Recent travel ?

Contacts (animals/insects)

Vaccination(s)

Clinical Examination

Neurological examination

Optic nerve examination

Extra-neurological signs

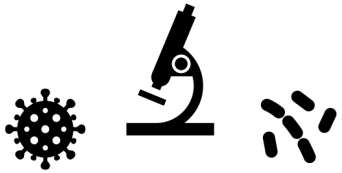
Brain Imaging

EEG

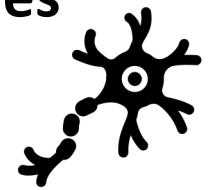
CSF

Serum

Biological Studies



Cultures, PCR, NGS



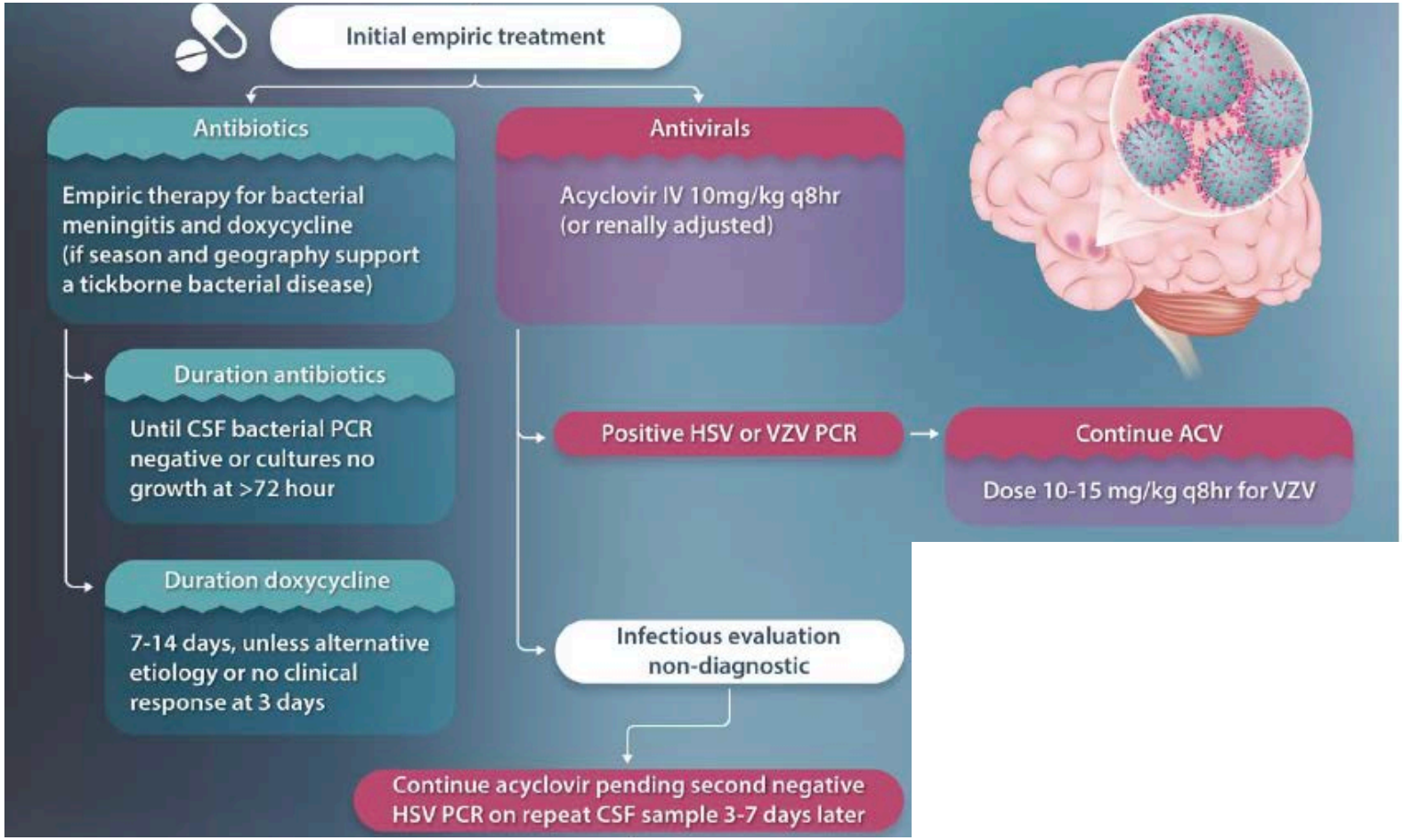
Immunology tests

State of the Art: Acute Encephalitis

Karen C. Bloch,[1] Carol Glaser,[2] David Gaston,[3,4] and Arun Venkatesan[4]

[1]Department of Medicine, Vanderbilt University Medical Center, Nashville, Tennessee, USA; [2]California Department of Public Health, Richmond, California, USA; [3]Department of Pathology, Microbiology, and Immunology, Vanderbilt University Medical Center, Nashville, Tennessee, USA; and [4]Department of Neurology, Johns Hopkins University, Baltimore, Maryland, USA

The diagnostic approach may require days to weeks …



Clin Inf Dis 2023

UNDERSTANDING THE DISEASE

Critical care management of infectious meningitis and encephalitis

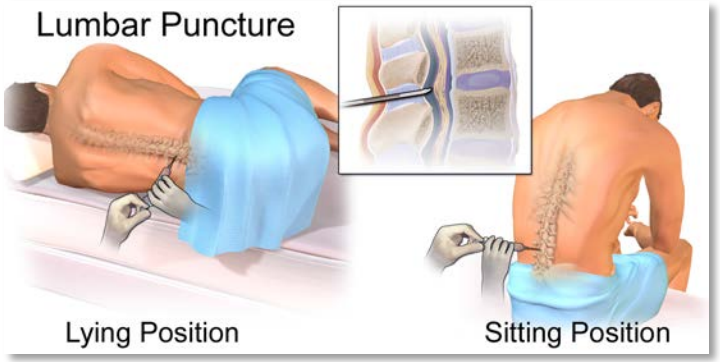
Geert Meyfroidt[1,2*], Pedro Kurtz[3] and Romain Sonneville[4,5]

First, rule out bacterial meningitis !

1. • **Blood cultures**
   • **Lumbar puncture** (unless contraindicated)


2. • **Antimicrobial therapy**
   • +/- adjunctive **dexamethasone**

3. • Early **ICU admission ?**

UNDERSTANDING THE DISEASE

Critical care management of infectious meningitis and encephalitis

Geert Meyfroidt[1,2*], Pedro Kurtz[3] and Romain Sonneville[4,5]

Table 2 Interpretation of cerebrospinal fluid (CSF) findings

	Normal	Bacterial	Viral	Tuberculous	Fungal
Opening pressure	6–20 cmH_2O	20–50 cmH_2O	6–30 cmH_2O	20–40 cmH_2O	20–100 cmH_2O
Colour	Clear	Cloudy	"Gin" clear	Cloudy/yellow	Clear/cloudy
Cells	$<5/mm^3$	High-very high $>1000/mm^3$	Slightly increased $10–1000/mm^3$	Slightly increased $10–1000/mm^3$	Normal-high $0–1000/mm^3$
Differential	Lymphocytes	Neutrophils	Lymphocytes	Lymphocytes	Lymphocytes
CSF/blood glucose ratio	50–66%	Low < 40%	Normal	Low-very low < 30–40%	Normal-low
Protein level	< 0.45 g/l	> 1 g/l	0.5–1 g/l	1–5 g/l	0.5–5 g/l

Adapted from [37] and [57]

When performing a lumbar puncture for CSF sampling, the following should be observed:

The minimum amount of CSF sampled must be 120 drops (1 drop amounts to approximately 50 µL): 20 drops (1 mL) for biochemistry tests and 80–100 drops (4–5 mL) for microbiological and virological tests

Part of the CSF must be kept (at + 4 ℃ and then, if possible, at − 80 ℃) for additional biological tests (including tuberculosis diagnostic test)

CSF glucose level must imperatively be combined with a concomitant blood glucose level test

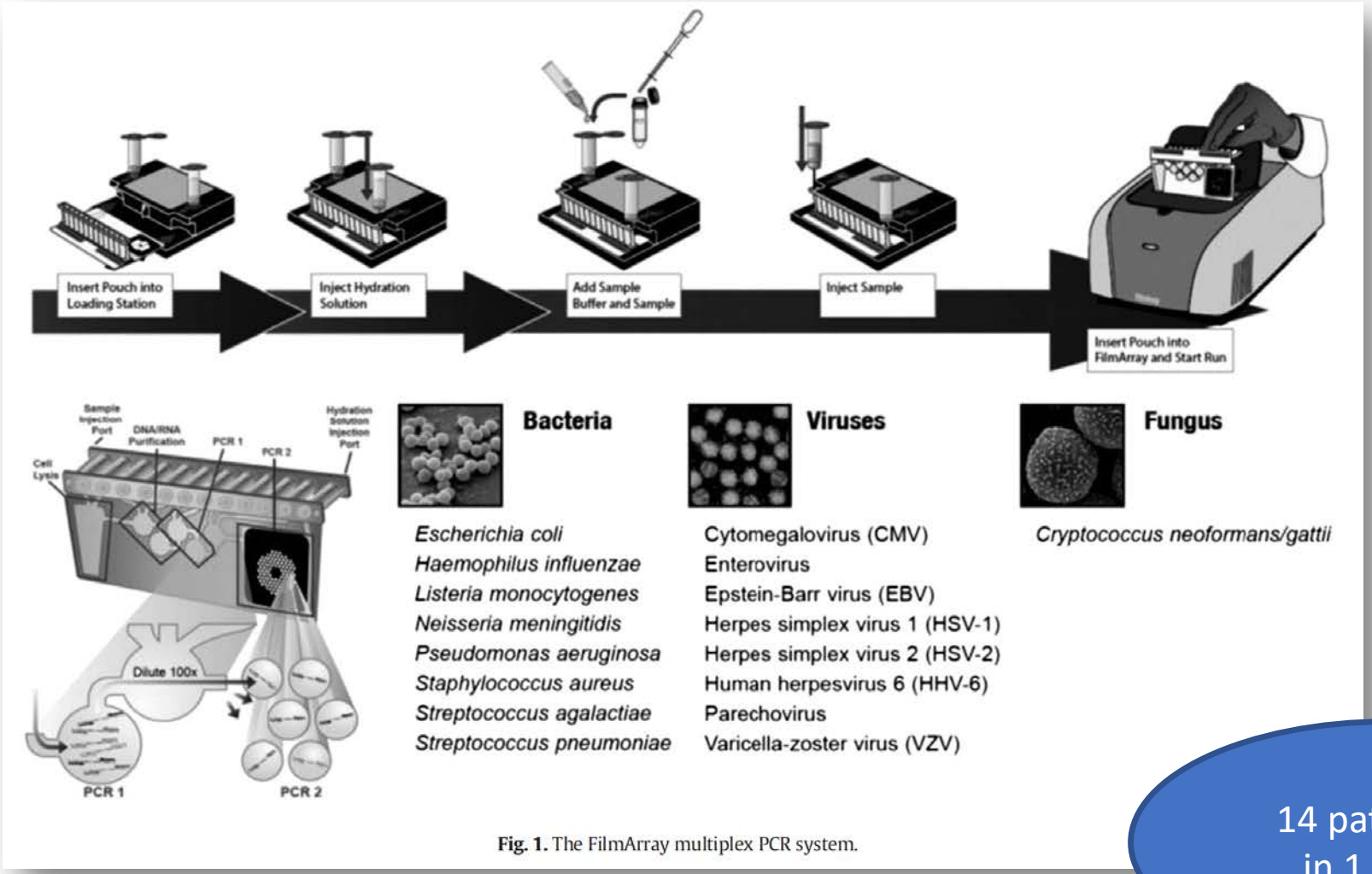


Fig. 1. The FilmArray multiplex PCR system.

14 pathogens
in 1 hour !

J. Rhein, Diagn Microbiol Infect Dis 2015

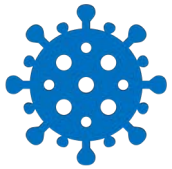
Biofire FilmArray Meningitis/Encephalitis panel for the aetiological diagnosis of central nervous system infections: A systematic review and diagnostic test accuracy meta-analysis

Juliana Trujillo-Gómez,[a,b,c] Sofia Tsokani,[d] Catalina Arango-Ferreira,[a,b] Santiago Atehortúa-Muñoz,[e,f] Maria José Jimenez-Villegas,[a,b] Carolina Serrano-Tabares,[a,e] Areti-Angeliki Veroniki,[g] and Ivan D. Florez[a,h,i,*]

Bacteria

mPCR ????
FilmArray
Meningitis/Encephalitis
"Rule in > rule out"!!

Virus



Reference CSF conventional tests / blood cultures

	No. Studies / No. Patients (Ref. studies)	Sensitivity (95%CI) X^2; p value§	Specificity (95%CI). X^2; p value§
All bacteria	16/6183[10,17,22,24–27,29–33]	89.5 (81.1–94.4) 6.00; 0.98	97.4 (94–98.9) 251.9; <0.0001
S. pneumoniae	16/7090[10,17–22,24–26,30,34]	87.5 (77–94) 3.71; 0.999	98.5 (97–99.3) 144.7; <0.0001
H. influenzae	10/4959[10,17,18,20–22,24,25,30,32]	64.9 (39.5–84) 4.91; 0.842	99.4 (98.9–99.6) 22.4; 0.07
S. agalactiae	10/5266[10,17,18,20,22,25–27,31,33]	71.5 (49.6–86.5) 7.67; 0.56	99.5 (98.5–99.9) 7.67; 0.56
E. coli	11/4743[10,17–21,25,27,30,32,33]	70.9 (50.2–85.5) 4.93; 0.896	99.6 (99.1–99.8) 25.5; 0.0043
N. meningitidis	10/3501[17,18,20–22,24,25,29–31]	74.5 (52.9–88.4) 2.26; 0.986	99.1 (98.6–99.5) 20.9; 0.013
L. *monocytogenes*	7/1332[18,21,24,25,29,31,32]	70.4 (40–89.5) 0.504; 0.008	98.9 (96.9–99.6) 5.62; 0.22
Enterovirus	3/6883[10,22,23]	93.8 (87–97.2) 2.91; 0.23	99.3 (98.7–99.7) 28.53; <0.001
HSV-1	3/6883[10,22,23]	75.5 (51.2–90.1) 1.18;0.554	99.9 (94.7–100) 2.55;0.28
HSV-2	3/6883[10,22,23]	94.4 (83.9–98.2) 0.435;0.804	99.9 (99.7–100) 1.36;0.507
VZV	4/6897[10,21,23,29]	91.4 (78.9–96.9) 0.82;0.84	99.8 (98.7–100) 23.55;<0.001

ONLINE BRIEF REPORT

Herpes Simplex Virus Encephalitis With Initial Negative Polymerase Chain Reaction in the Cerebrospinal Fluid: Prevalence, Associated Factors, and Clinical Impact

Etienne de Montmollin, MD, PhD[1,2]
Claire Dupuis, MD, PhD[3]
Pierre Jaquet, MD[2]
Benjamine Sarton, MD[4,5]
Charline Sazio, MD[6]
Vincent Susset, MD[7]
Marie Conrad, MD[8]
Laurent Argaud, MD, PhD[9]
Sophie Demeret, MD[10]
Jean Marc Tadié, MD, PhD[11]
François Barbier, MD, PhD[12]
Michel Wolff, MD, PhD[13]
Jean-François Timsit, MD, PhD[1,2]
Benoit Visseaux, MD, PhD[1,14]
Romain Sonneville, MD, PhD[2,15]
the ENCEPHALITICA Study Group

273 patients with severe HSE. Initial CSF HSV PCR was negative in 11 (4%) cases

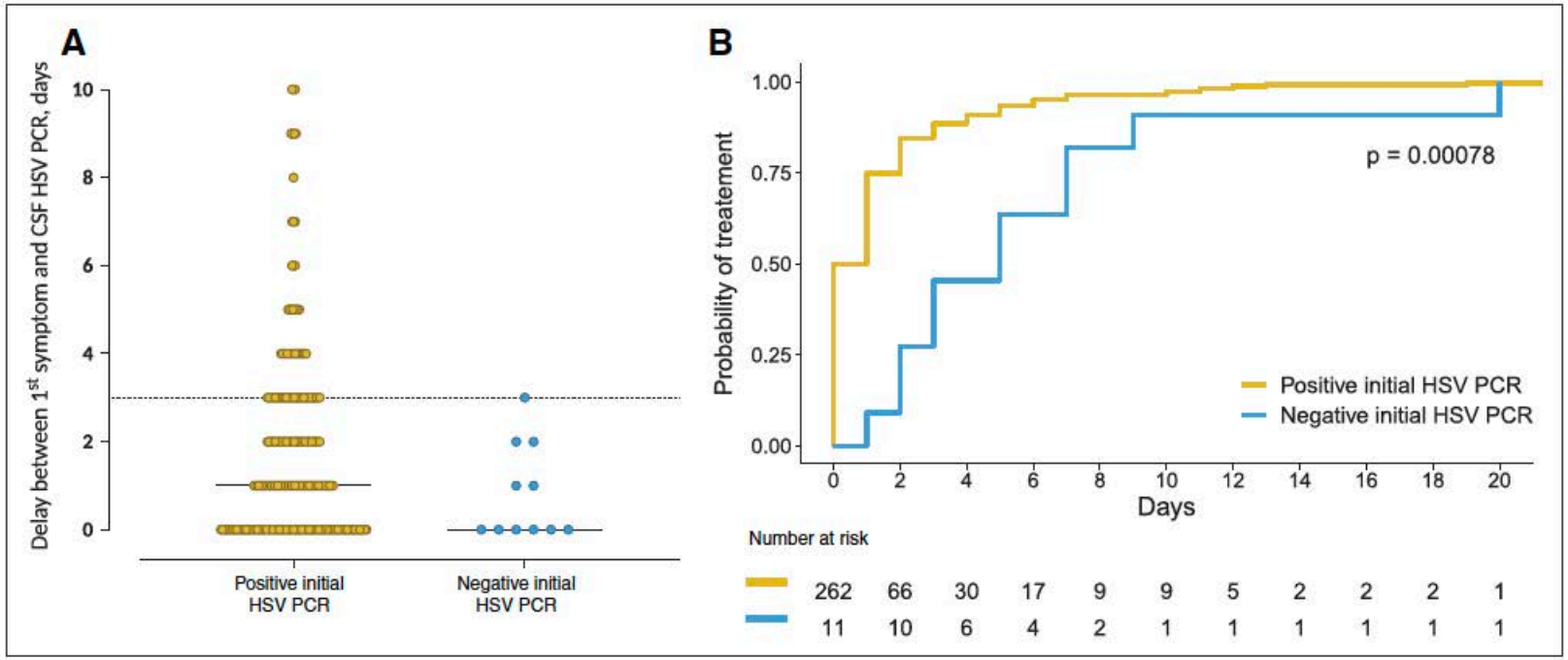


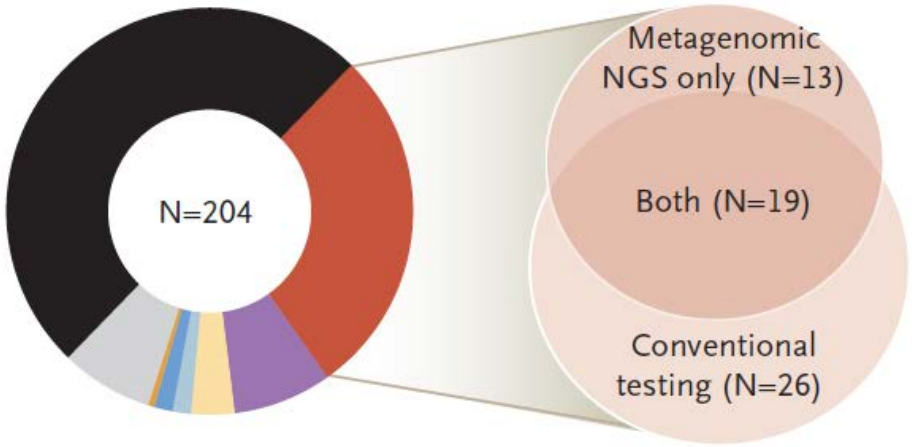
Figure 1. A, Delay from first symptom onset to lumbar puncture according to herpes simplex virus (HSV) polymerase chain reaction (PCR) positivity in initial cerebrospinal fluid (CSF) testing. **B**, Probability of acyclovir treatment from hospital admission, according to initial HSV PCR results. *p* value is based on log-rank test.

Crit Care Med 2022

ORIGINAL ARTICLE

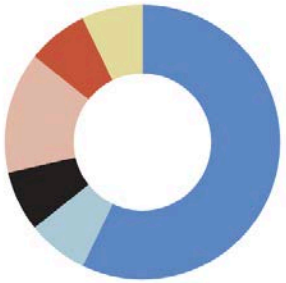
Clinical Metagenomic Sequencing for Diagnosis of Meningitis and Encephalitis

A Established Diagnoses in the Study Patients



- 57 (27.9%) Infectious
- 17 (8.3%) Autoimmune
- 7 (3.4%) Neoplastic
- 3 (1.5%) Postinfectious
- 3 (1.5%) Toxic metabolic
- 1 (0.5%) Vascular
- 15 (7.4%) Other
- 101 (49.5%) Unknown

Metagenomic NGS identified 13/58 (22%) infections that were not diagnosed by conventional testing ….



- 7 (54%) Will affect management and treatment
- 1 (8%) Provided reassurance that coinfection is not present (EBV-associated lymphoma)
- 1 (8%) Increased confidence in clinical decisions (neisseria)
- 2 (15%) Viral genotyping useful for epidemiologic purposes (enterovirus)
- 1 (8%) Unclear clinical significance (MW polyomavirus)
- 1 (8%) Provided reassurance to patient or surrogate (SLEV)

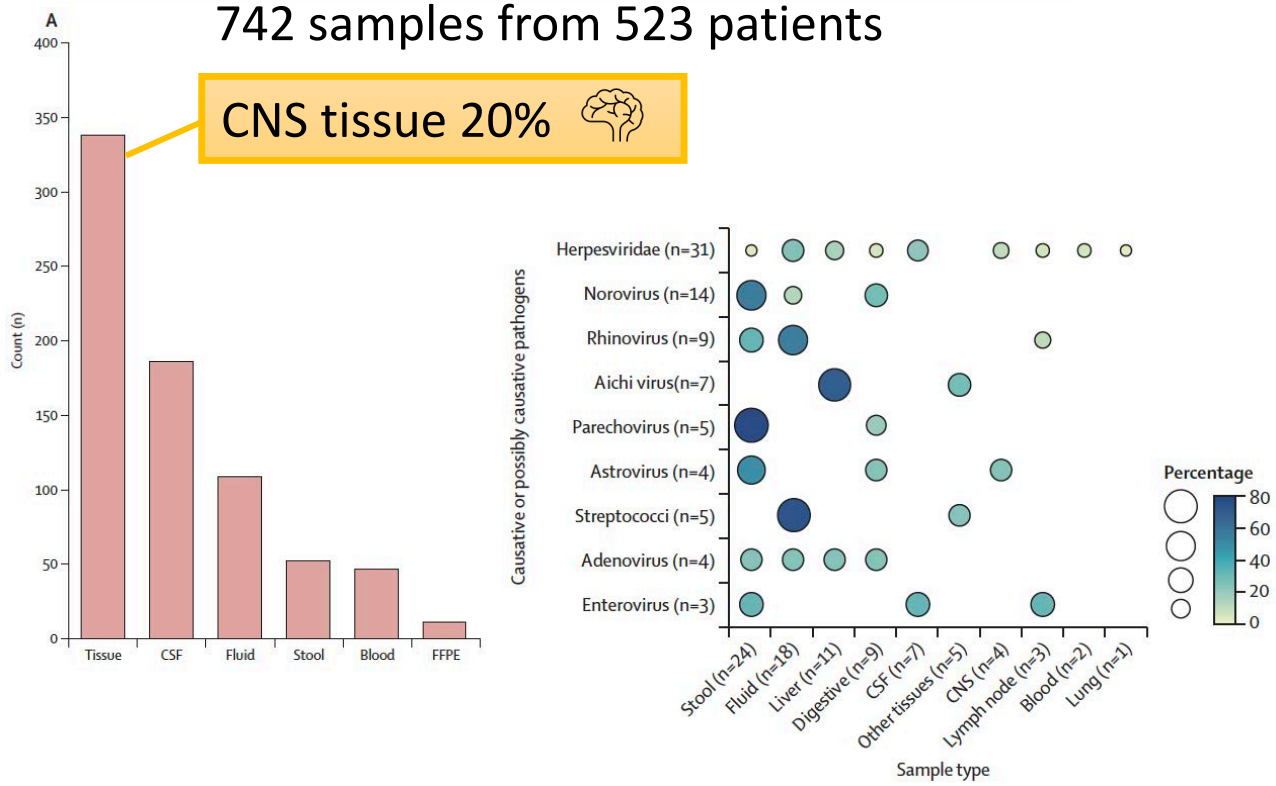
Wilson *et al.*, New Eng J Med 2018

Performance of clinical metagenomics in France: a prospective observational study

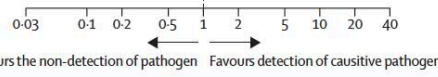
Jacques Fourgeaud, Béatrice Regnault*, Vichita Ok, Nicolas Da Rocha, Émilie Sitterlé, Meryem Mekouar, Hélène Faury, Catherine Milliancourt-Seels, Florence Jagorel, Delphine Chrétien, Thomas Bigot, Éric Troadec, Isabelle Marques, Alexandra Serris, Danielle Seilhean, Bénédicte Neven, Pierre Frange, Agnès Ferroni, Marc Lecuit, Xavier Nassif, Olivier Lortholary†, Marianne Leruez-Ville†, Philippe Pérot†, Marc Eloit‡, Anne Jamet‡*

742 samples from 523 patients

CNS tissue 20%



	Samples, n (%)	Pathogen detection, n (%)	OR (95% CI)	p value
Total	742 (100%)	126 (17%)		
Gender	742 (100%)			
Female	313 (42%)	44 (14%)	Ref	
Male	429 (58%)	82 (19%)	1·1 (0·71–1·8)	0·6329
Age (years)	742 (100%)			
>18	333 (45%)	48 (14%)	Ref	
0–12	268 (36%)	55 (21%)	1·2 (0·69–2·2)	0·4950
[illegible]	141 (19%)	23 (16%)	0·73 (0·35–1·5)	0·3916
Immune status	742 (100%)			
Immunocompetent	356 (48%)	31 (9%)	Ref	
PID	224 (30%)	60 (27%)	2·0 (1·1–3·8)	0·0292
SID	135 (18%)	29 (21%)	2·9 (1·5–5·5)	0·0012
HIV	27 (4%)	6 (22%)	2·5 (0·79–7·1)	0·0988
Initial suspicion of infection	742 (100%)			
Low	272 (37%)	9 (3%)	Ref	
High	470 (63%)	117 (25%)	9·1 (4·6–20·4)	<0·0001
Indication	742 (100%)			
Other indications*	157 (21%)	12 (8%)	Ref	
Neurological	274 (37%)	36 (13%)	1·5 (0·53–4·0)	0·4616
Respiratory	50 (7%)	13 (26%)	1·2 (0·44–3·4)	0·6839
Digestive	61 (8%)	19 (31%)	0·69 (0·23–2·1)	0·5032
Inflammatory	47 (6%)	6 (13%)	0·56 (0·12–2·4)	0·4490
Haematological	25 (3%)	9 (36%)	3·4 (0·94–12·1)	0·0606
Liver	128 (17%)	31 (24%)	1·1 (0·38–3·0)	0·9220
Tissue	338 (46%)			
Other tissues†	152 (45%)	11 (7%)	Ref	
CNS	63 (19%)	14 (22%)	3·9 (0·77–26·1)	0·1246
Lymph node	33 (10%)	6 (18%)	2·2 (0·34–15·9)	0·4093
Liver	72 (21%)	16 (22%)	0·19 (0·03–1·1)	0·0686
Digestive tissue	18 (5%)	8 (44%)	4·5 (0·72–40·6)	0·1281
Other samples	393 (53%)			
Sterile fluid	101 (26%)	17 (17%)	Ref	
CSF	185 (47%)	13 (7%)	0·21 (0·066–0·67)	0·0082
Non-sterile fluid	55 (14%)	15 (27%)	2 (0·75–5·1)	0·1694
Stool	52 (13%)	24 (46%)	5·7 (2·0–17·0)	0·0013
Neurological	248 (33%)			
CSF	185 (75%)	13 (7%)	Ref	
CNS	63 (25%)	14 (22%)	4·1 (1·7–10·7)	0·0025
Digestive	70 (9%)			
Stool	52 (74%)	24 (46%)	Ref	
Digestive tissue	18 (26%)	8 (44%)	0·57 (0·16–2·0)	0·3749



Lancet Microbe 2023

Original article

Changing profile of encephalitis: Results of a 4-year study in France

A. Mailles[a,b,*], X. Argemi[c], C. Biron[d], P. Fillatre[b,e], T. De Broucker[f], R. Buzelé[g], A. Gagneux-Brunon[h], I. Gueit[i], C. Henry[f], S. Patrat-Delon[j], A. Makinson[k], E. Piet[l], H. Wille[m], M.O. Vareil[m], O. Epaulard[b,n], M. Martinot[o], P. Tattevin[b,j], J.P. Stahl[b,n], the scientific committee[1] the investigators[2],

494 patients
2016-2019
France

Age: 65 (IQR, 47-75) years
Comorbidities: 112 (23%)
Immunocompromised: 59 (12%)

Causes of encephalitis	*n*	% of cases with an identified cause	Total %
Herpes simplex virus	132	40.7	26.7
Varicella-zoster virus	65	20.1	13.2
Tick-borne encephalitis virus (TBEV)	26	8.0	5.3
Listeria monocytogenes	23	7.1	4.7
Mycobacterium tuberculosis	11	3.4	2.2
Influenza virus	11	3.1	2.0
Epstein–Barr virus (EBV)	6	1.9	1.2
Enterovirus	6	1.9	1.2
Mycoplasma pneumoniae	4	1.2	0.8
West Nile Virus	4	1.2	0.8
Cryptococcus neoformans	4	1.2	0.8
JC virus	3	0.9	0.6
Borrelia burgdorferi	3	0.9	0.6
Measles virus	3	0.9	0.6
Human Herpes Virus 6 (HHV-6)	2	0.6	0.4
Japanese Encephalitis Virus (JEV)	2	0.6	0.4

Unknown cause
n=170/494 (34%) patients ….

Inf Dis Now, 2022

Encéphalites

- Epidémiologie
- Démarche diagnostique
- Corticostéroïdes ?
- Encéphalite auto-immune ?
- Pronostic

Early Adjunctive Steroids ?

Yes

Acute Bacterial Meningitis

De Gans, New Eng J Med 2002

(Reduced mortality and disability)

Tuberculous Meningitis

Thwaites, New Eng J Med 2004

(Reduced mortality)

Donovan, New Eng J Med 2023

(HIV+ patients ?)

Maybe ?

Viral (HSV) Encephalitis

T Solomon, DEXENCEPH trial…

(Improved cognitive function ?)

Listeria monocytogenes meningitis

Brouwer, eClinical Med 2023

(Reduced mortality and disability)

No

Cryptococcal Meningitis

Beardsley, New Eng J Med 2016

(More disability, more adverse events)

RCT
DXM 10mg x 4 / j pdt 4 jours
vs.
placebo

?

Herpes simplex **positive** in cerebrospinal fluid (CSF)
(meets inclusion and exclusion criteria)

Enroll to DexEnceph Randomised controlled trial
Target 90 participants

Intervention arm
45 patients
Dexamethasone 10mg four times daily for 4 days
Plus Standard care

Non-intervention arm
45 patients
Standard care only

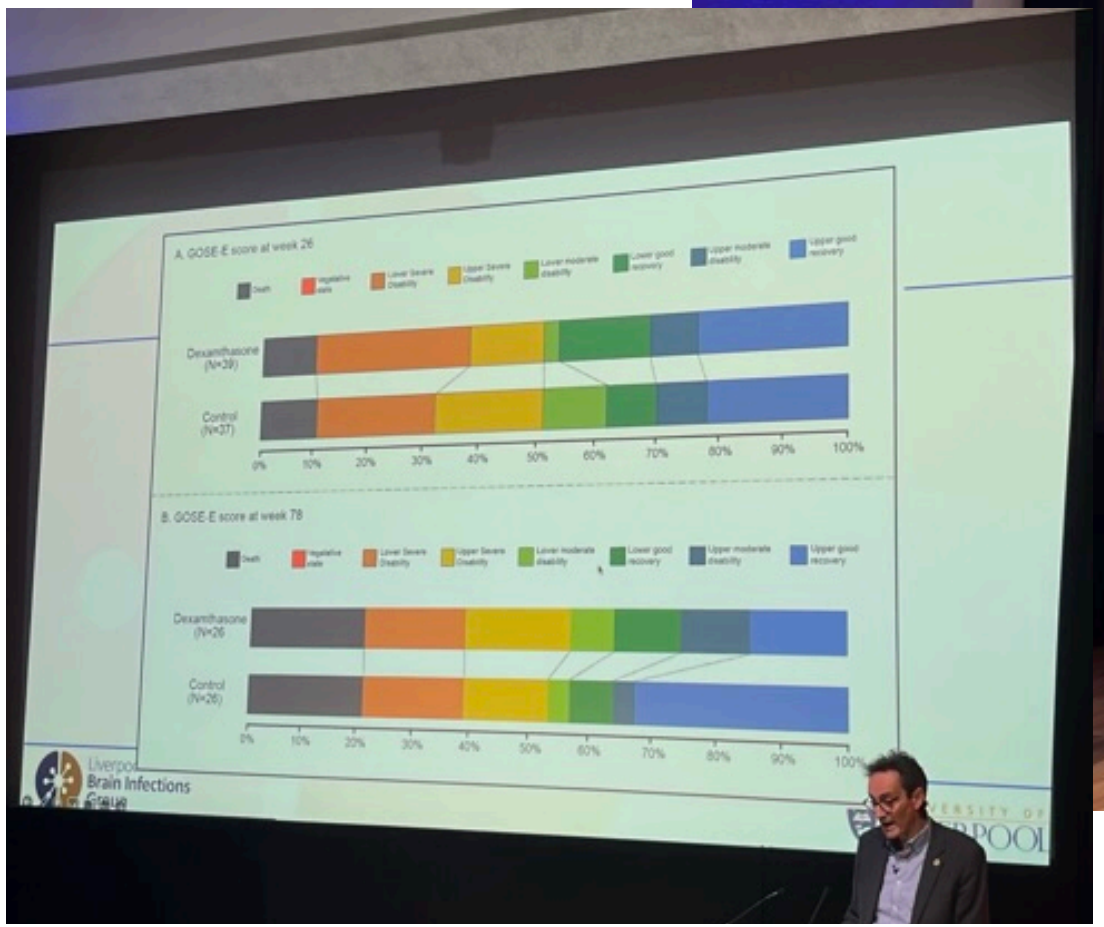
During admission

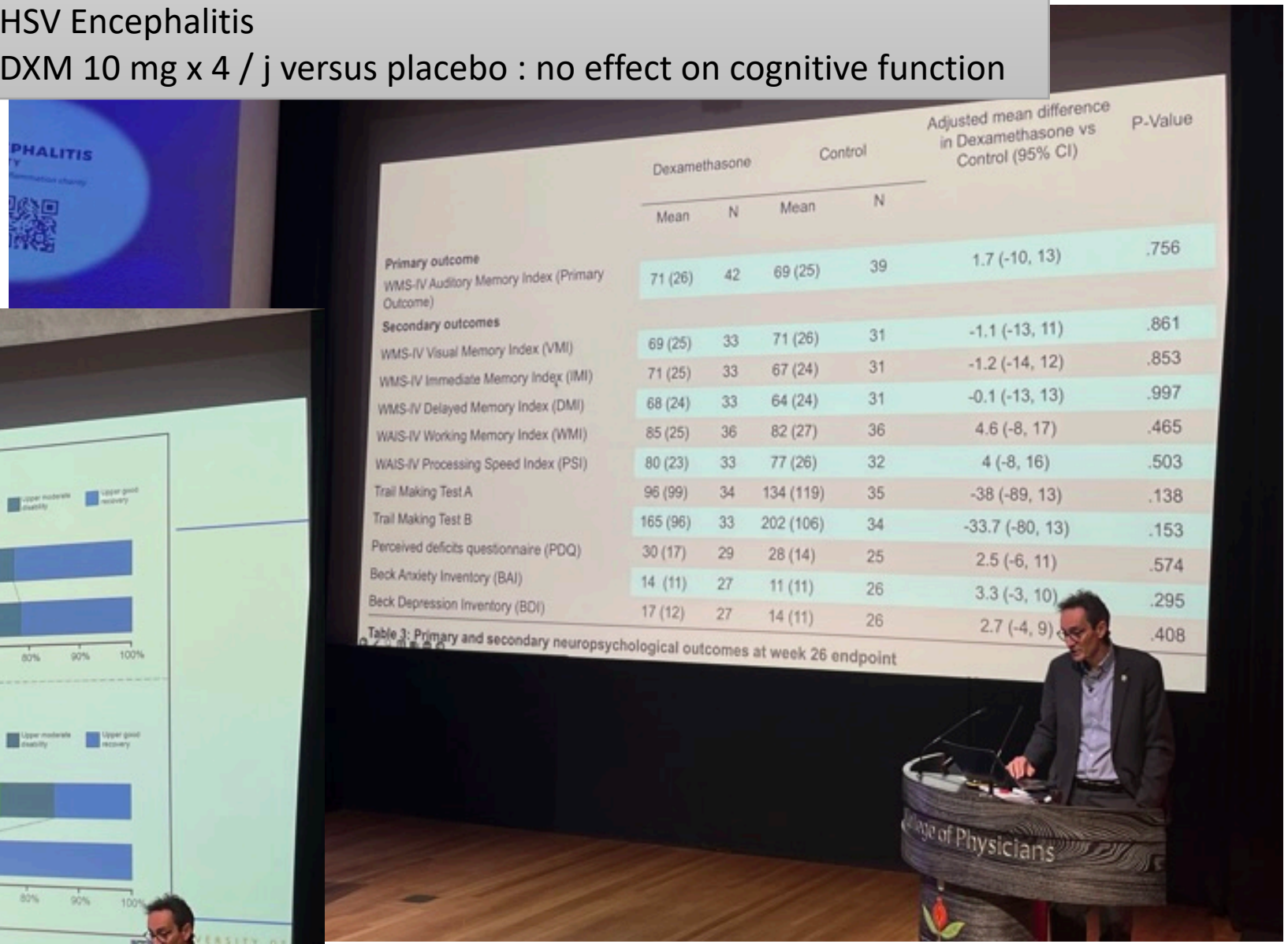
Baseline:	Magnetic Resonance imaging of the brain (MRI), Blood and CSF sampling, data collection
Day 14:	MRI, Blood and CSF sampling,
Day 30/ Discharge:	Disability and functional outcome scores, Addenbrookes cognitive examination III (ACE III), data collection

Follow up 26 weeks
Neuropsychological assessment (including Verbal Memory Score - Primary Outcome)
Disability and functional outcome scores
MRI scan
Blood sampling
Quality of life and health status questionnaires
Data collection

Follow up 78 weeks
Neuropsychological assessment
Disability and functional outcome scores
MRI scan
Quality of life and health status questionnaires
Data collection

DEXENCEPH
HSV Encephalitis
DXM 10 mg x 4 / j versus placebo : no effect on cognitive function





	Dexamethasone		Control		Adjusted mean difference in Dexamethasone vs Control (95% CI)	P-Value
	Mean	N	Mean	N		
Primary outcome						
WMS-IV Auditory Memory Index (Primary Outcome)	71 (26)	42	69 (25)	39	1.7 (-10, 13)	.756
Secondary outcomes						
WMS-IV Visual Memory Index (VMI)	69 (25)	33	71 (26)	31	-1.1 (-13, 11)	.861
WMS-IV Immediate Memory Index (IMI)	71 (25)	33	67 (24)	31	-1.2 (-14, 12)	.853
WMS-IV Delayed Memory Index (DMI)	68 (24)	33	64 (24)	31	-0.1 (-13, 13)	.997
WAIS-IV Working Memory Index (WMI)	85 (25)	36	82 (27)	36	4.6 (-8, 17)	.465
WAIS-IV Processing Speed Index (PSI)	80 (23)	33	77 (26)	32	4 (-8, 16)	.503
Trail Making Test A	96 (99)	34	134 (119)	35	-38 (-89, 13)	.138
Trail Making Test B	165 (96)	33	202 (106)	34	-33.7 (-80, 13)	.153
Perceived deficits questionnaire (PDQ)	30 (17)	29	28 (14)	25	2.5 (-6, 11)	.574
Beck Anxiety Inventory (BAI)	14 (11)	27	11 (11)	26	3.3 (-3, 10)	.295
Beck Depression Inventory (BDI)	17 (12)	27	14 (11)	26	2.7 (-4, 9)	.408

Table 3: Primary and secondary neuropsychological outcomes at week 26 endpoint

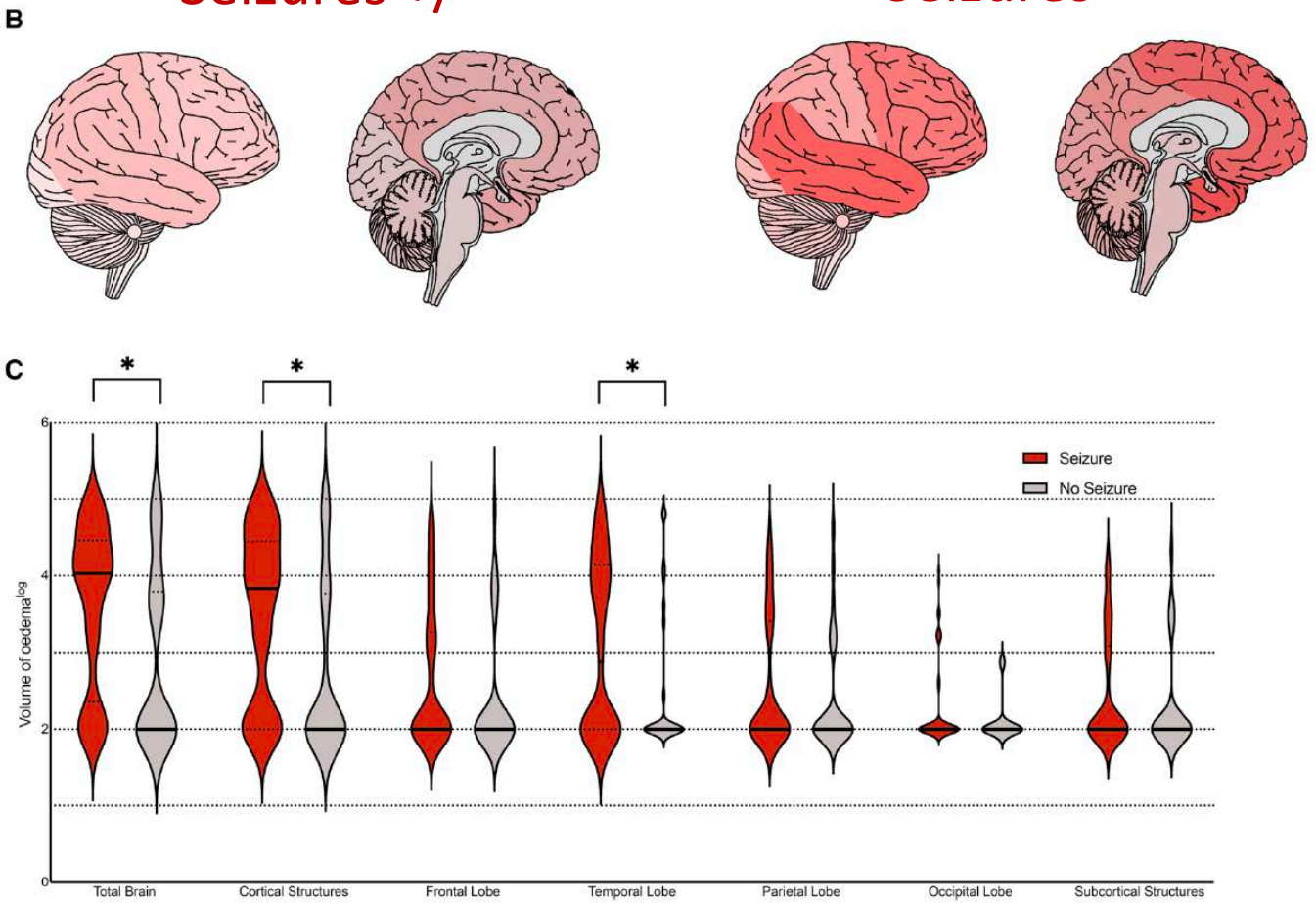
Increased volume of cerebral oedema is associated with risk of acute seizure activity and adverse neurological outcomes in encephalitis – regional and volumetric analysis in a multi-centre cohort

Ali M. Alam[1,2], Jian P. K. Chen[3], Greta K. Wood[1,2], Bethany Facer[4], Maneesh Bhojak[5], Kumar Das[5], Sylviane Defres[1,2,6], Anthony Marson[4,7], Julia Granerod[8], David Brown[9], Rhys H. Thomas[10], Simon S. Keller[4], Tom Solomon[1,2,7] and Benedict D. Michael[1,2,7*]

Cerebral oedema ?

\- +

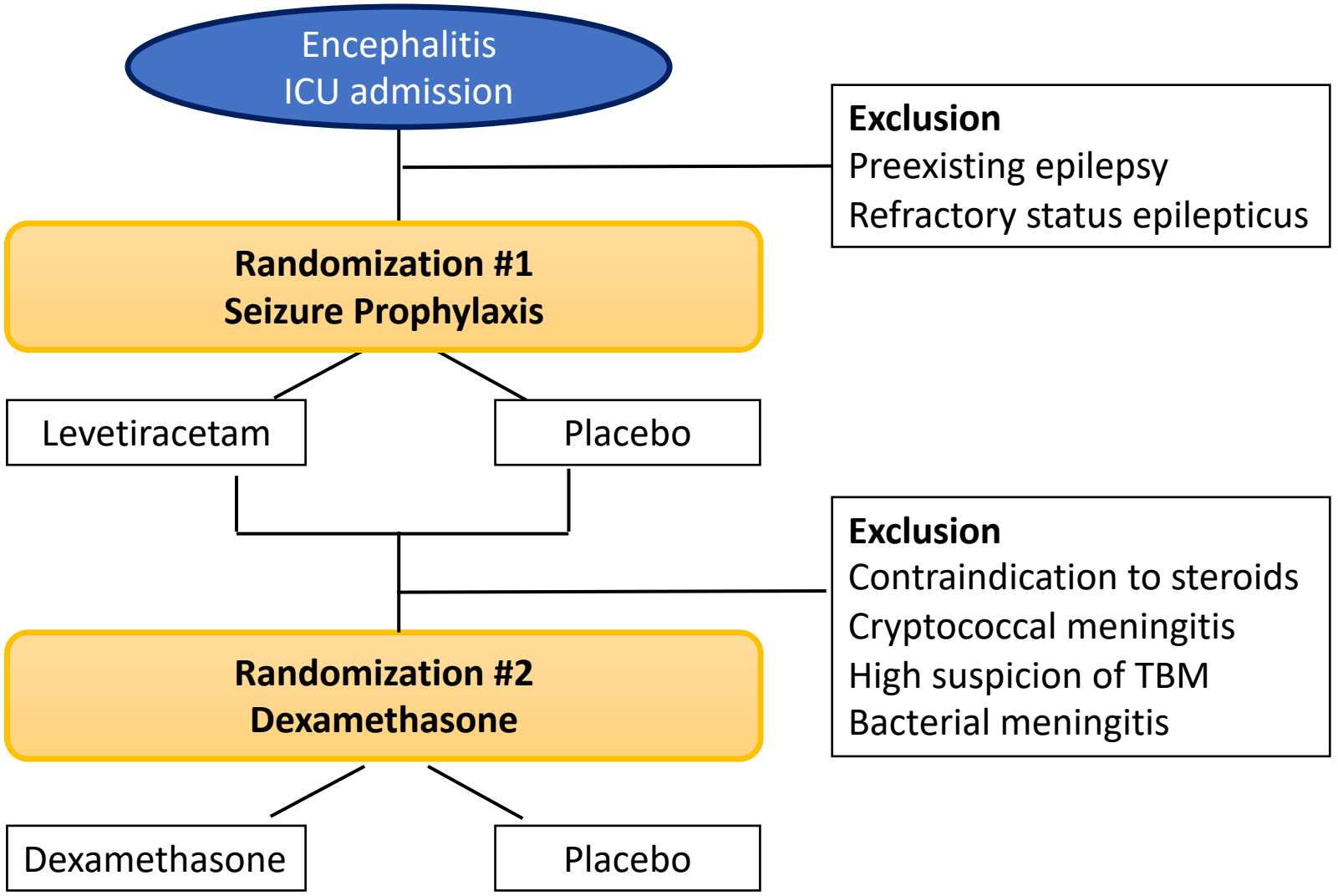
Seizures +/- Seizures ++



BMC Neurol 2022

SeizURe PRophylaxIs and adjunctive Steroids in meningoEncephalitis "SURPRISE"

LI PHRC-N 2023

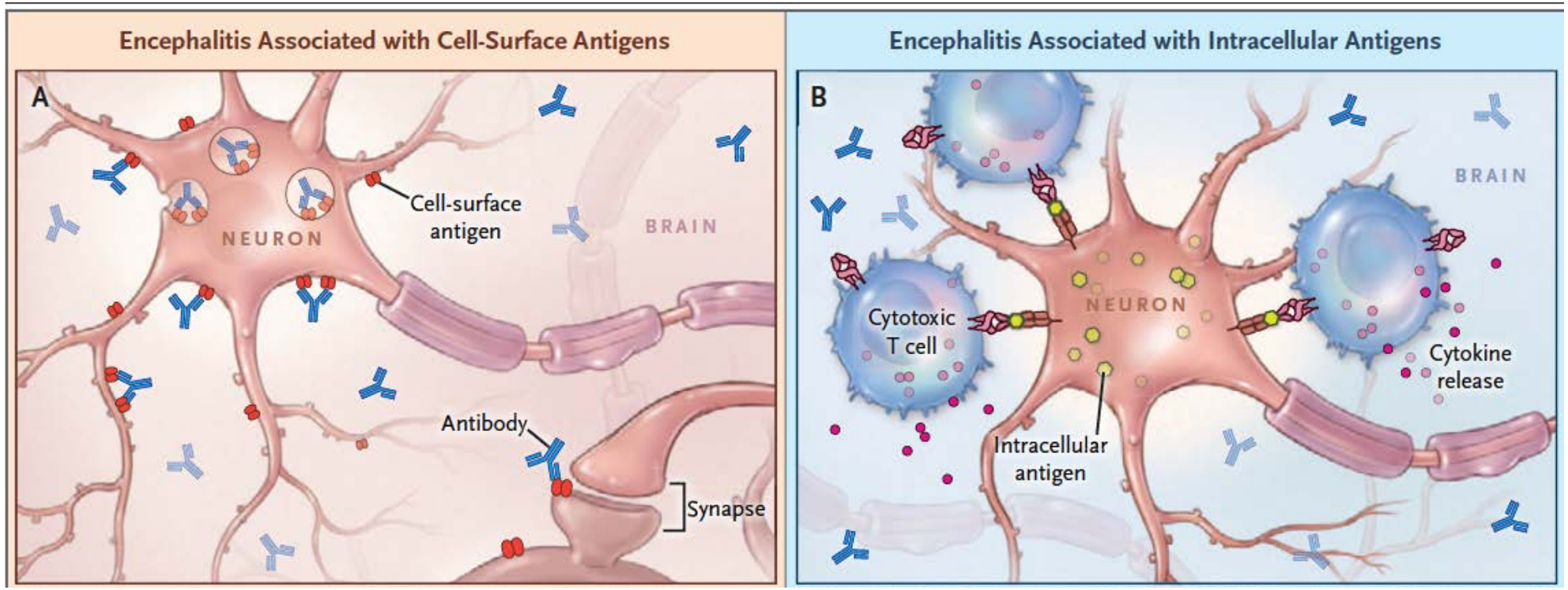


Encéphalites

- Epidémiologie
- Démarche diagnostique
- Corticostéroïdes ?
- Encéphalite auto-immune ?
- Pronostic

Antibody-Mediated Encephalitis

Josep Dalmau, M.D., Ph.D., and Francesc Graus, M.D., Ph.D.

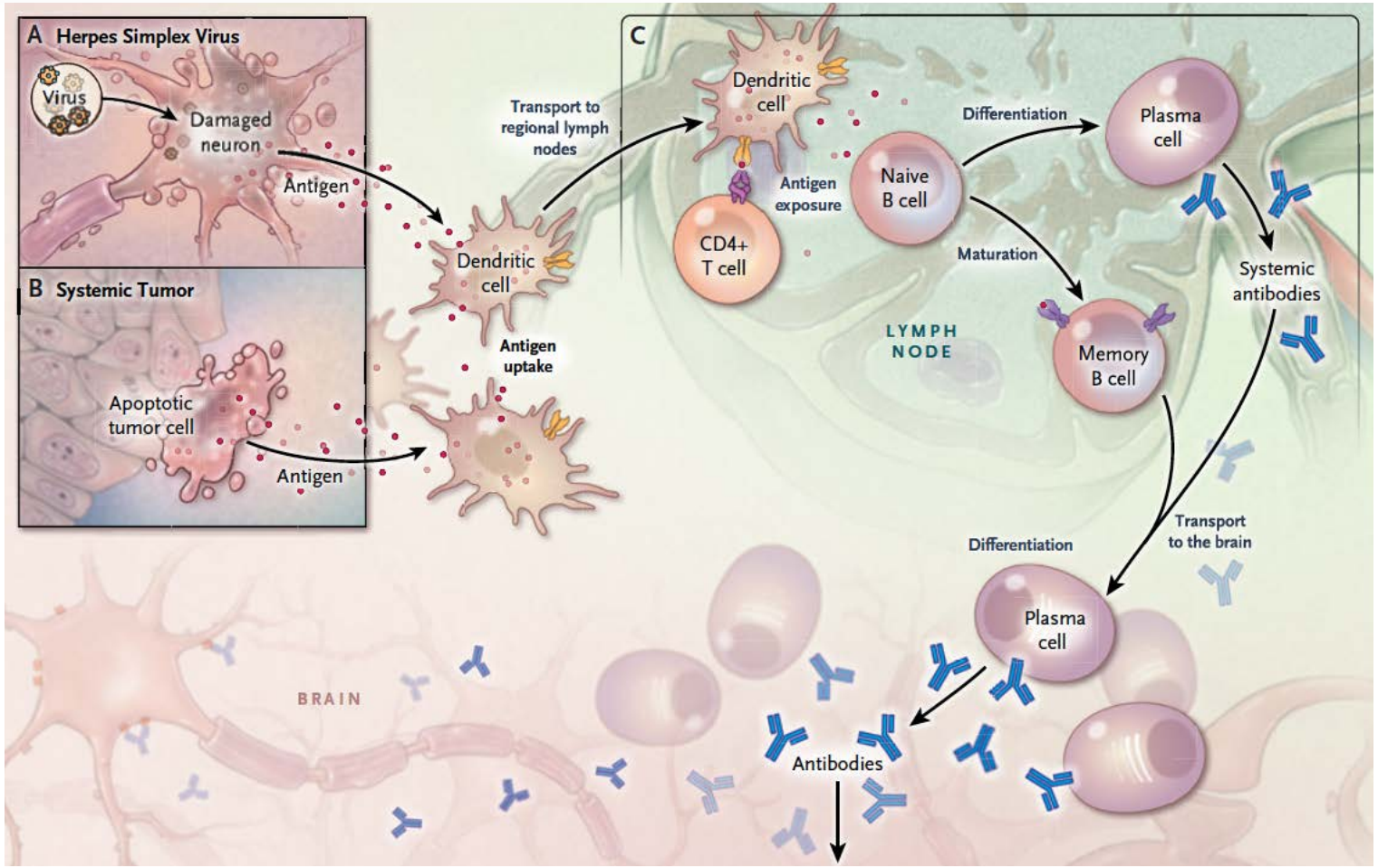


New Eng J Med 2018

Antibody-Mediated Encephalitis

Josep Dalmau, M.D., Ph.D., and Francesc Graus, M.D., Ph.D.

NMDAR- Encephalitis



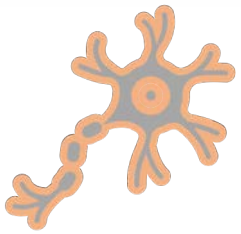
New Eng J Med 2018

Development and Validation of a Risk Score to Differentiate Viral and Autoimmune Encephalitis in Adults

Alejandro Granillo,[1,a,*] Marion Le Maréchal,[2,a] Luisa Diaz-Arias,[2] John Probasco,[2] Arun Venkatesan,[2,a] and Rodrigo Hasbun[1,3,a]

[1]Department of Infectious Diseases, UT Health McGovern Medical School, Houston, Texas, USA; [2]Johns Hopkins Encephalitis Center, Johns Hopkins University, Baltimore, Maryland, USA; and [3]Department of Internal Medicine, UT Health McGovern Medical School, Houston, Texas, USA

Autoimmune cause ?



Subacute/ chronic presentation (>6 days)

No comorbidities (Charlson comorbidity index <2)

Psychiatric / memory complaint

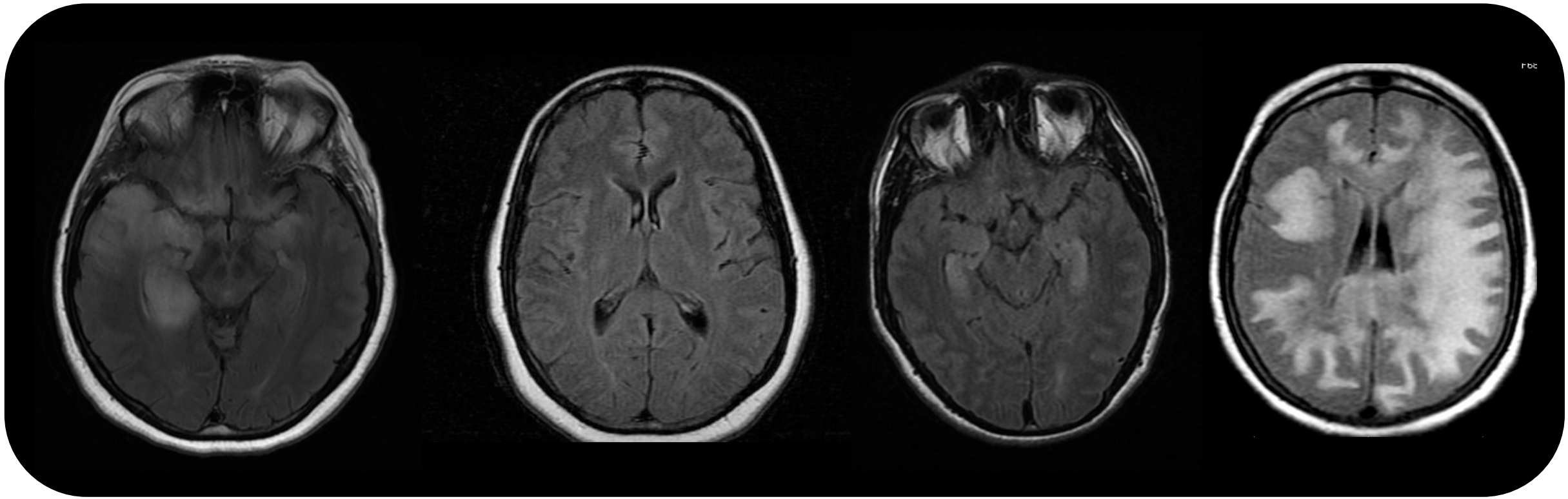
Absence of robust CSF inflammation (Prot <0.5 g/L, cell <50/mm³)

	Sensitivity	Specificity	PPV	NPV
Development cohort				
0	100%	0%	29%	…
1	100%	20%	34%	100%
2	100%	58%	49%	100%
3	75%	84%	66%	89%
4	3%	100%	100%	89%
Validation cohort				
0	100%	0%	44%	…
1	100%	27%	52%	100%
2	98%	75%	76%	98%
3	67%	92%	87%	78%
4	27%	98%	93%	63%

Abbreviations: NPV, negative predictive value; PPV, positive predictive value.

Clin Inf Dis 2023

Brain MRI Patterns



« HSV »

Normal

« Limbic »

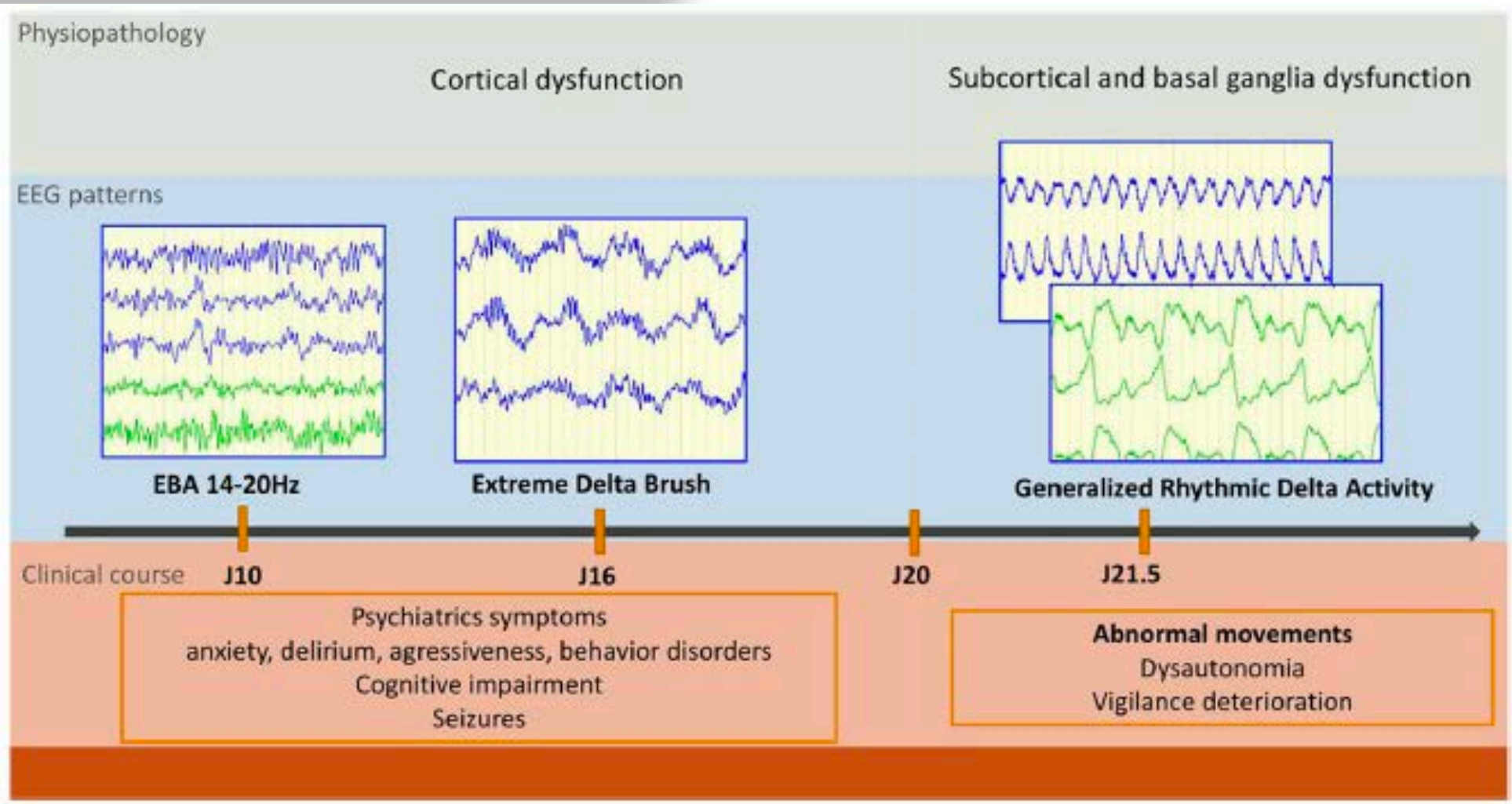
« Demyelination »

Autoimmune encephalitis ?

R Sonneville, Rev Neurol 2023

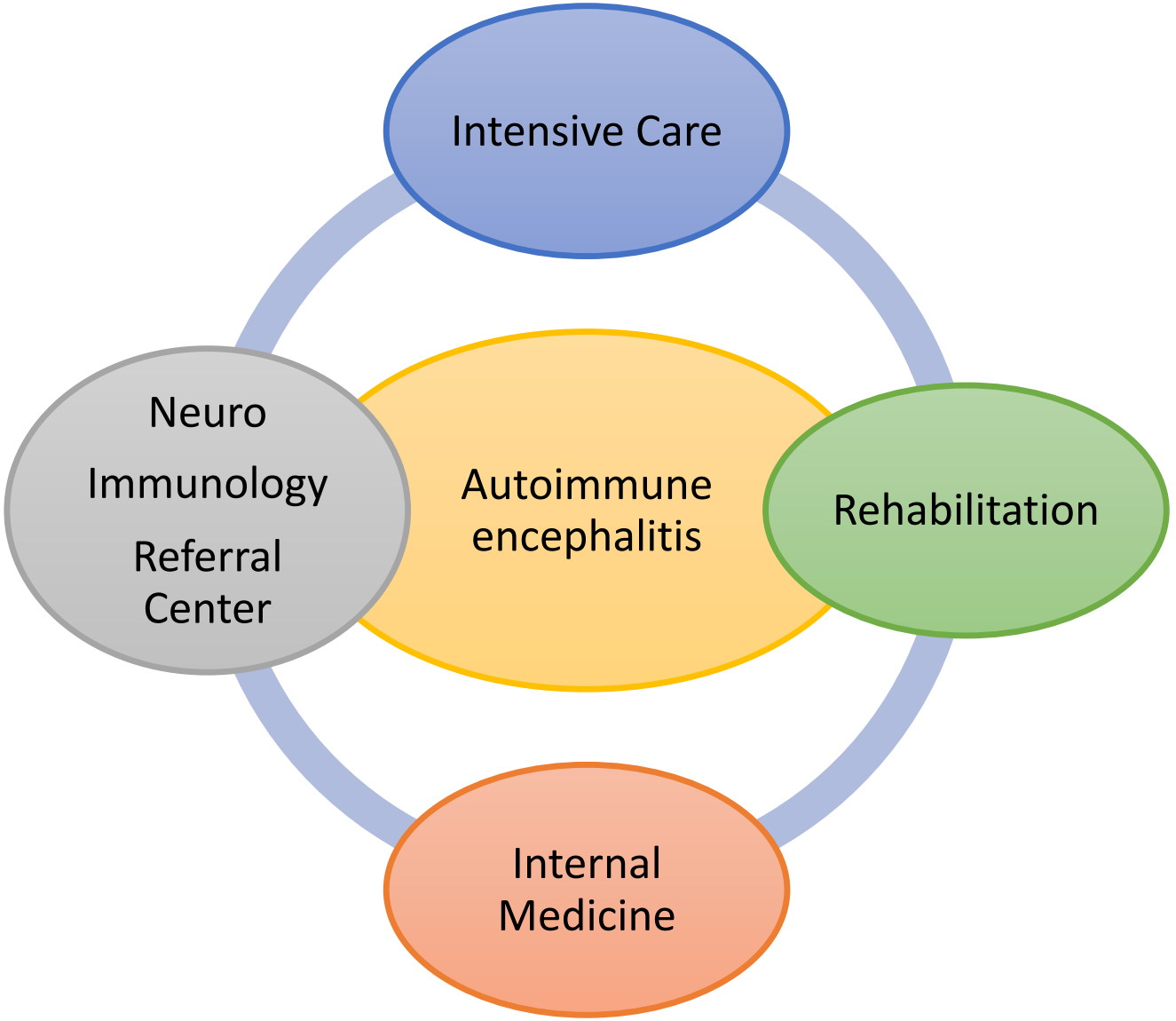
EEG analysis in anti-NMDA receptor encephalitis: Description of typical patterns

S. Jeannin-Mayer [a,*], N. André-Obadia [b,g], S. Rosenberg [c], C. Boutet [d], J. Honnorat [e,f], J.C. Antoine [a], L. Mazzola [a,g]



Clin Neurophysiology 2019

Centre de référence des syndromes neurologiques paranéoplasiques et encéphalites auto-immunes



Autoanticorps LCS et sérum

Review

Autoimmune encephalitis: proposed best practice recommendations for diagnosis and acute management

Hesham Abboud [1,2] John C Probasco,[3] Sarosh Irani [4] Beau Ances,[5] David R Benavides,[6] Michael Bradshaw,[7,8] Paulo Pereira Christo,[9] Russell C Dale,[10] Mireya Fernandez-Fournier,[11] Eoin P Flanagan [12] Avi Gadoth,[13] Pravin George,[14] Elena Grebenciucova,[15] Adham Jammoul,[14] Soon-Tae Lee,[16] Yuebing Li,[14] Marcelo Matiello,[17,18] Anne Marie Morse,[19] Alexander Rae-Grant,[14] Galeno Rojas,[20,21] Ian Rossman,[22] Sarah Schmitt,[23] Arun Venkatesan,[3] Steven Vernino,[24] Sean J Pittock [12] Maarten J Titulaer [25] Autoimmune Encephalitis Alliance Clinicians Network

Severe presentation* = combination therapy

*severe NMDARE, refractory status epilepticus, severe dysautonomia …

FIRST LINE
High dose corticosteroids
+
IgIV or PLEX

No improvement ?

SECOND LINE
Rituximab
OR
Cyclophosphamide

IVIg first if agitation or bleeding disorders
PLEX first if hyponatremia, high risk of thrombosis, or brain/spinal demyelination

Rituximab in known or highly suspected antibody-mediated immunity (e.g. NMDARE)
Cyclophosphamide in case of cell-mediated immunity (classical paraneoplastic syndromes)

J Neurol Neurosurg Psychiatry 2021

Anti–*N*-Methyl-D-Aspartate Receptor Encephalitis in Adult Patients Requiring Intensive Care

Etienne de Montmollin[1], Sophie Demeret[2], Noëlle Brulé[3], Marie Conrad[4], Frédéric Dailler[5], Nicolas Lerolle[6], Jean-Christophe Navellou[7], Carole Schwebel[8], Mikaël Alves[9], Martin Cour[10], Nicolas Engrand[11], Jean-Marie Tonnelier[12], Eric Maury[13], Stéphane Ruckly[14], Géraldine Picard[15], Véronique Rogemond[15], Éric Magalhaes[16], Tarek Sharshar[17], Jean-François Timsit[14,16], Jérôme Honnorat[15,18*], and Romain Sonneville[16,19*]; on behalf of the ENCEPHALITICA Study Group[‡]

Multivariate analysis of factors of good neurological outcome at 6 months (mRS < 2)

Variable	Odds Ratio (95% CI)	*P* Value
First-line immunotherapy		0.008
Late immunotherapy	Reference	
Early* intravenous immunoglobulin administration only	3.33 (0.66–16.79)	0.14†
Early* steroid administration only	4.96 (0.76–32.23)	0.09†
Early* combined immunotherapy‡ administration	16.16 (3.32–78.64)	<0.001†
Second-line immunotherapy	0.19 (0.05–0.69)	0.01
White blood cells in first CSF		0.04
>50 cells/mm^3	Reference	
5–50 cells/mm^3	3.97 (1.16–13.65)	0.03†
<5 cells/mm^3	9.83 (1.07–90.65)	0.04†

*before ICU admission or following 8 days of ICU admission

Am j Resp Crit Care Med 2017

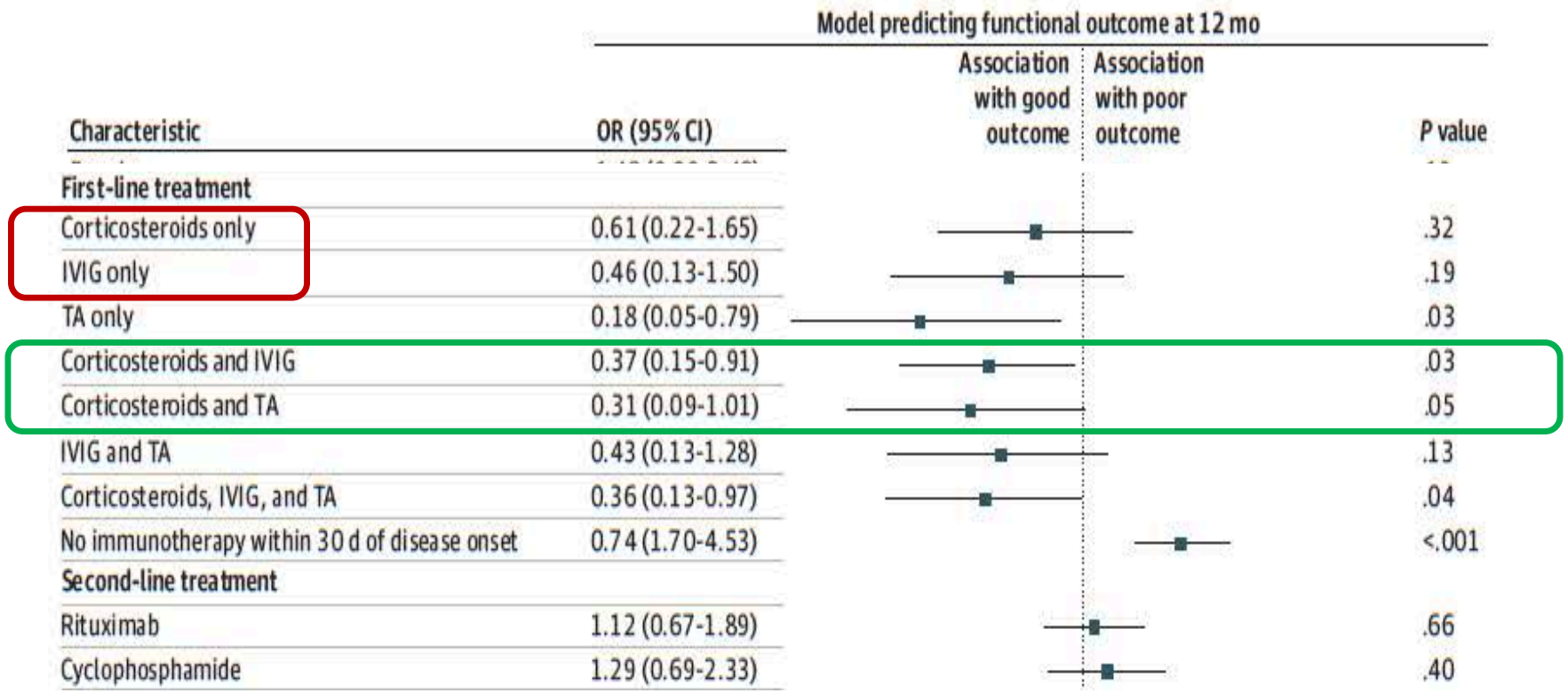
JAMA Neurology | Original Investigation

Use and Safety of Immunotherapeutic Management of *N*-Methyl-D-Aspartate Receptor Antibody Encephalitis
A Meta-analysis

Margherita Nosadini, MD, PhD; Michael Eyre, MD; Erika Molteni, PhD; Terrence Thomas, MD; Sarosh R. Irani, MD, PhD; Josep Dalmau, MD, PhD; Russell C. Dale, MD, PhD; Ming Lim, MD, PhD; and the International NMDAR Antibody Encephalitis Consensus Group

N=1552 patients with NMDAR Encephalitis

ICU admission 51%



Characteristic	OR (95% CI)	Model predicting functional outcome at 12 mo: Association with good outcome / Association with poor outcome	*P* value
First-line treatment			
Corticosteroids only	0.61 (0.22-1.65)		.32
IVIG only	0.46 (0.13-1.50)		.19
TA only	0.18 (0.05-0.79)		.03
Corticosteroids and IVIG	0.37 (0.15-0.91)		.03
Corticosteroids and TA	0.31 (0.09-1.01)		.05
IVIG and TA	0.43 (0.13-1.28)		.13
Corticosteroids, IVIG, and TA	0.36 (0.13-0.97)		.04
No immunotherapy within 30 d of disease onset	0.74 (1.70-4.53)		<.001
Second-line treatment			
Rituximab	1.12 (0.67-1.89)		.66
Cyclophosphamide	1.29 (0.69-2.33)		.40

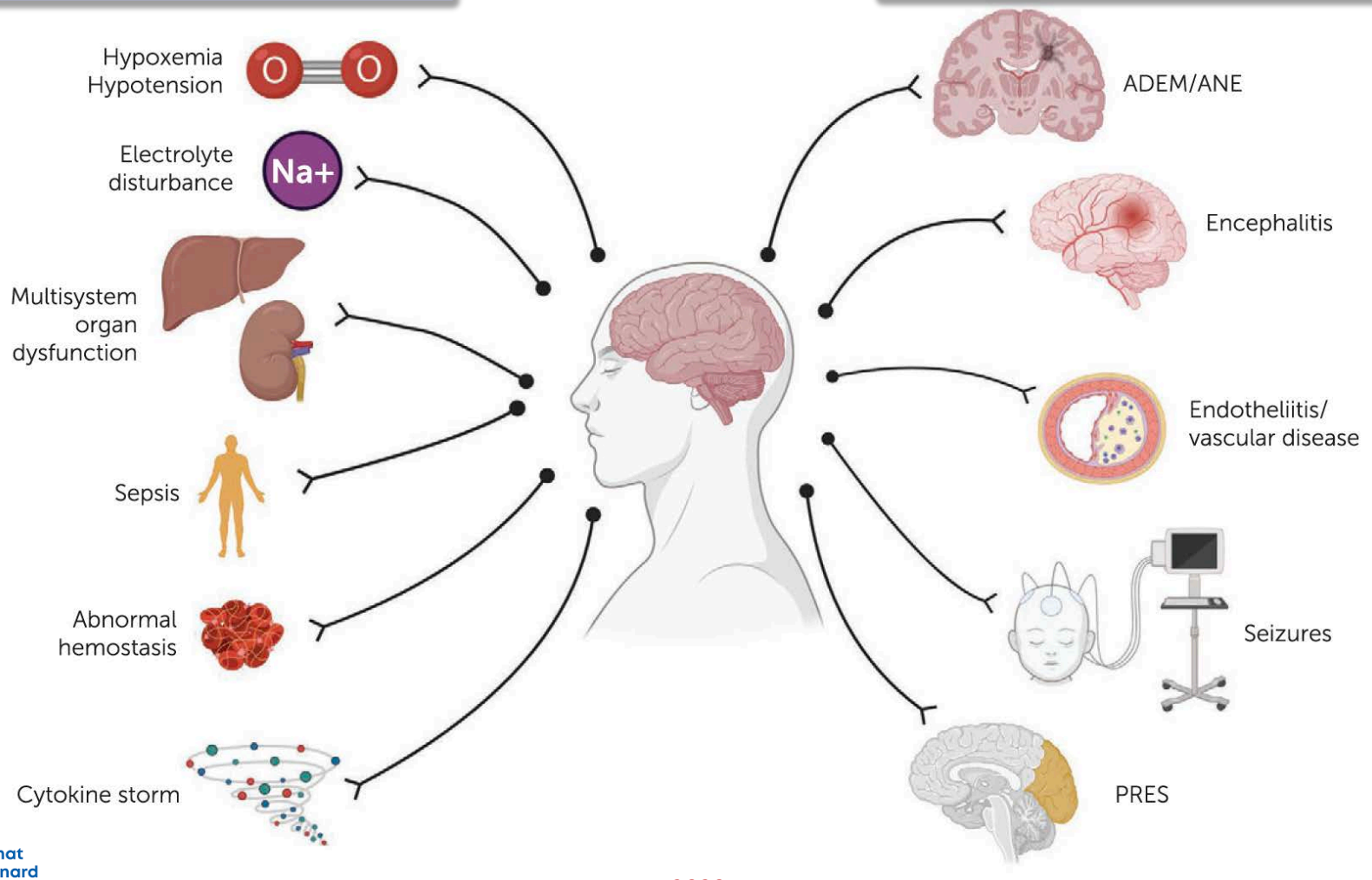
JAMA Neurol 2021

Consensus Clinical Guidance for Diagnosis and Management of Adult COVID-19 Encephalopathy Patients

Benedict D. Michael, Ph.D., M.R.C.P., Dean Walton, M.B.B.Ch., B.Sc., Erica Westenberg, M.Sc., David García-Azorín, M.D., Ph.D., Bhagteshwar Singh, M.R.C.P., Arina A. Tamborska, M.R.C.P., M. Netravathi, D.M., Mashina Chomba, M.B.Ch.B., M.Med., Greta K. Wood, M.Res., Ava Easton, Ph.D., Omar K. Siddiqi, M.D., Thomas A. Jackson, Ph.D., M.R.C.P., Thomas A. Pollak, Ph.D., M.R.C.Psych., Timothy R. Nicholson, Ph.D., M.R.C.P., Shalini Nair, M.D., D.N.B., Gerome Breen, Ph.D., Kameshwar Prasad, D.M., Kiran T. Thakur, M.D., Sherry H.-Y. Chou, M.D., Erich Schmutzhard, M.D., Jennifer A. Frontera, M.D., Raimund Helbok, M.D., Ph.D., Alessandro Padovani, M.D., Ph.D., David K. Menon, M.D., Ph.D., Tom Solomon, Ph.D., F.R.C.P., Andrea S. Winkler, M.D., Ph.D., On behalf of the Global COVID-19 Neuro Research Coalition

Systemic Pathophysiology +++

Acute CNS disease (less frequent)



AER
ACTUALITÉS EN RÉANIMATION

CURRENT OPINION

Neurological complications of critically ill COVID-19 patients

Romain Sonneville[a,b], Neha S. Dangayach[c] and Virginia Newcombe[d]

Multimodal Approach

	Encephalopathy	Stroke	Encephalitis	Guillain-Barré syndrome
Context	Acute COVID-19 illness	Acute COVID-19 illness	Days to weeks post-COVID-19 infection	Days to weeks post-COVID-19 infection
Risk factors	Age Preexisting neurological disorder	Age Hypertension	Recent COVID-19 infection or vaccination	Recent COVID-19 infection or vaccination
Pathophysiology	Hypoxemia Systemic inflammation Toxic/metabolic causes	Thrombosis Systemic inflammation	Immune-mediated Brain inflammation	Immune-mediated Peripheral nervous system inflammation
Clinical findings	Acute onset Delirium or coma	Acute onset Focal signs	(Sub)acute onset Delirium or coma +/– seizures +/– focal signs	Acute neuromuscular weakness Areflexia +/– respiratory failure +/– dysautonomia
Neuroimaging findings	Normal PRES	Ischaemic stroke +/– large vessel occlusion Cerebral Haemorrhage Microhaemorrhages	Normal ADEM Limbic encephalitis	Normal
CSF	Normal	Normal	Pleocytosis Negative PCR and cultures +/– intrathecal synthesis	Normal cell count +/– elevated protein level
EEG	Diffuse slowing +/– triphasic waves +/– seizures	Focal slowing +/– periodic discharges +/– seizures	Diffuse or focal slowing +/– periodic discharges +/– seizures	Normal
Specific therapy	None	Thrombolysis and/or thrombectomy, if indicated	Steroids Intravenous immunoglobulins or plasma exchange	Intravenous immunoglobulins or plasma exchange

Université Paris Cité

Hôpital Bichat Claude-Bernard AP-HP

Current Opinion in Critical Care 2022

Encéphalites

- Epidémiologie
- Démarche diagnostique
- Corticostéroïdes ?
- Encéphalite auto-immune ?
- Pronostic

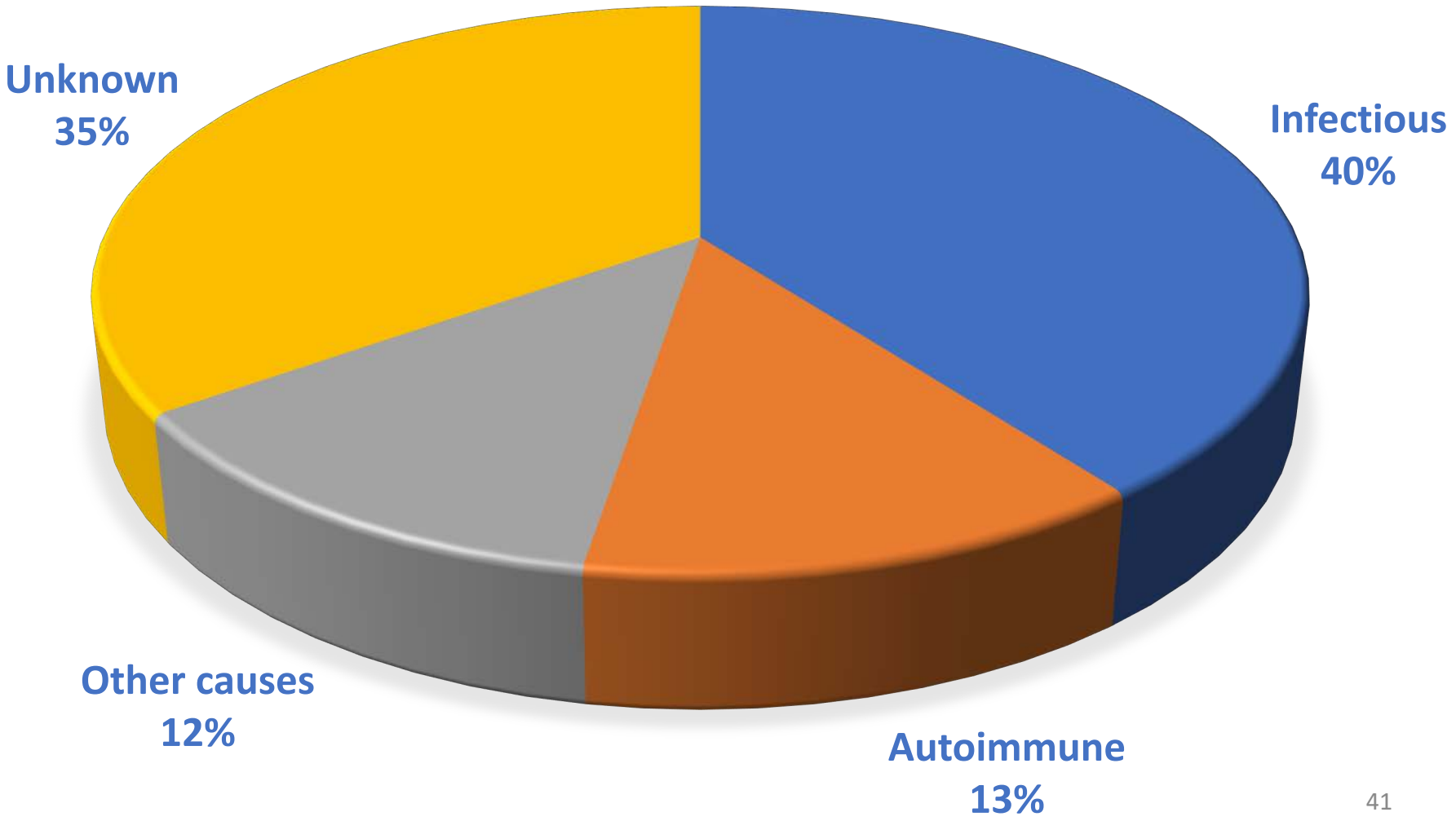
n=310 patients

EncephalitICa : Encephalitis in Intensive Care
PHRC-IR 2015

Encephalitica

Results

Aetiological groups



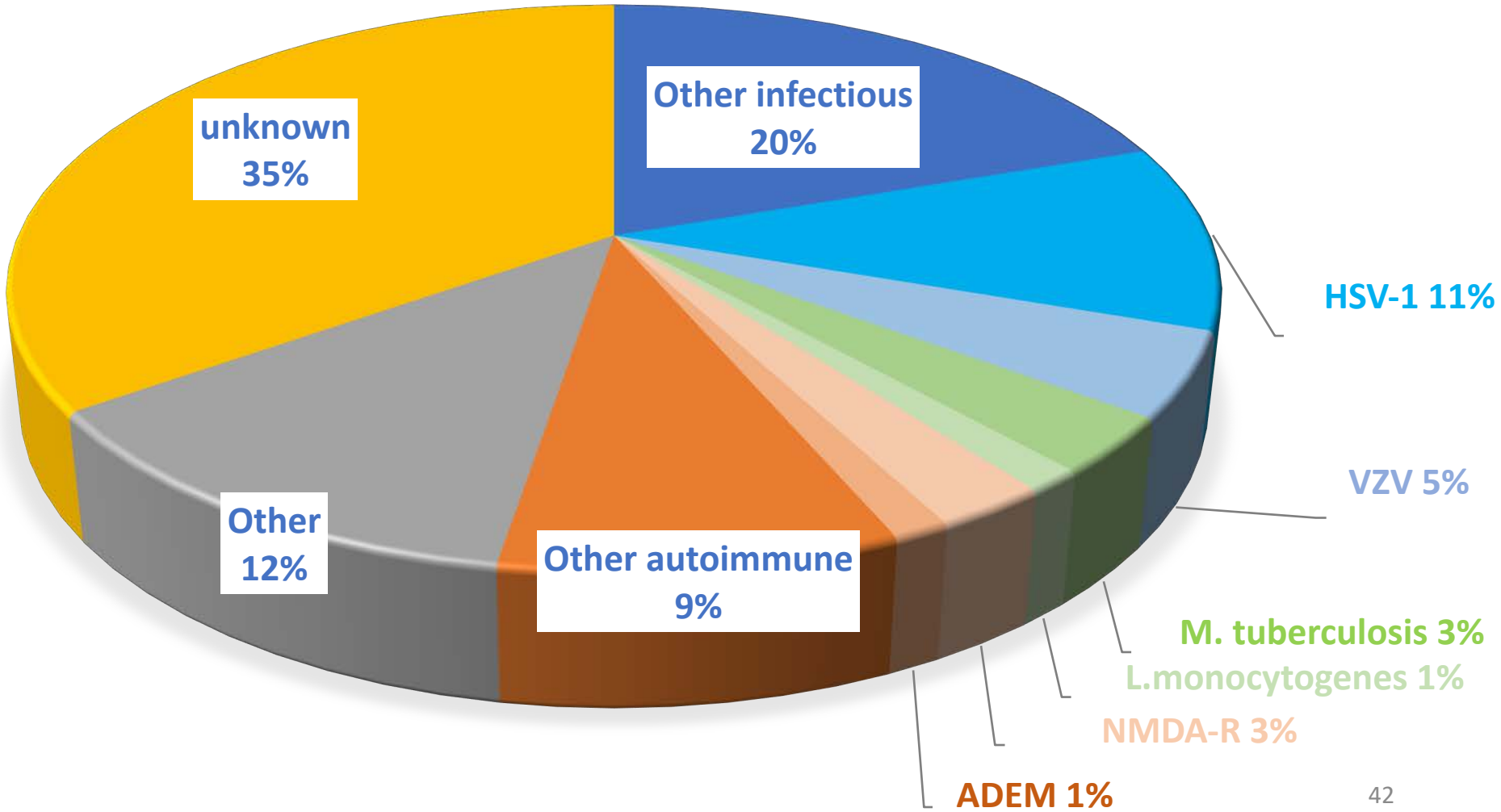
n=310 patients

EncephalitICa : Encephalitis in Intensive Care
PHRC-IR 2015

Encephalitica

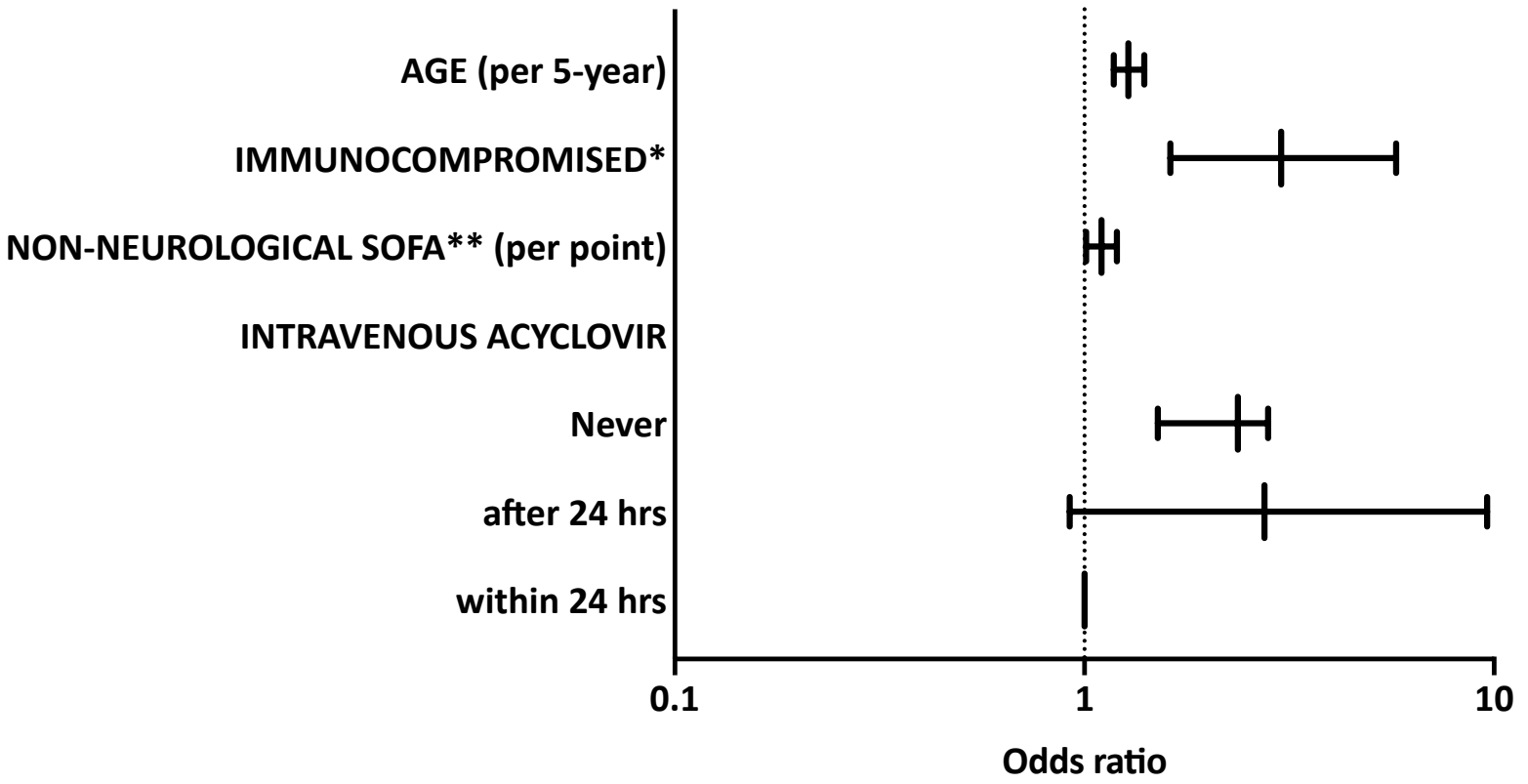
Results

Aetiological groups



n=310 patients

Poor outcome predictors (3-month mRS score 3-6)



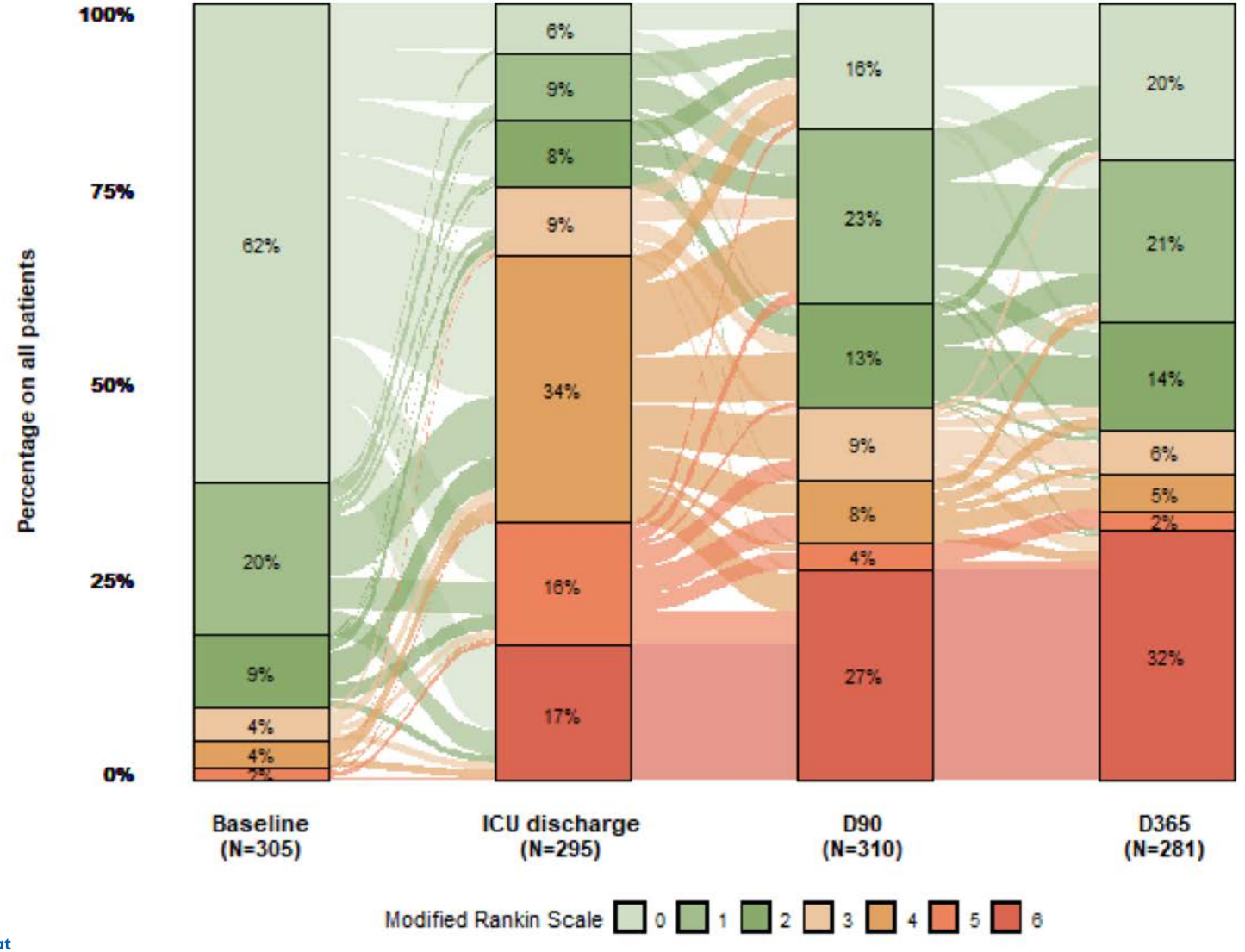
	Odds Ratio	95%CI
AGE (per 5-year)	1.28	1.18 - 1.40
IMMUNOCOMPROMISED*	3.02	1.62 - 5.77
NON-NEUROLOGICAL SOFA** (per point)	1.10	1.01 - 1.20
INTRAVENOUS ACYCLOVIR		
Never	2.81	1.51 - 5.37
after 24 hrs	2.75	0.92 - 9.62
within 24 hrs	Ref	-

**HIV infection, SOT, onco-hematology and/or long term steroids or immunosuppressive drugs*

***SOFA Sequential Organ Faillure Assessment. A score of 2 or more indicates organ failure(s)*

Results 1-year trajectories

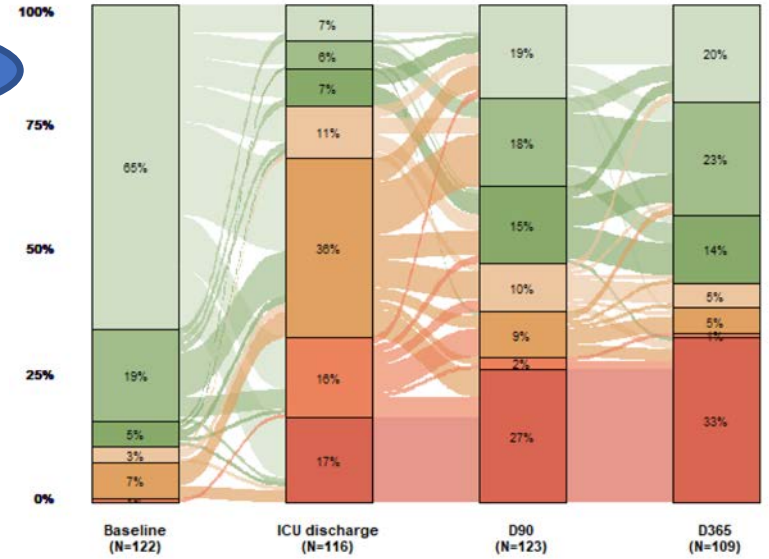
All patients



55% mRS 0-2 @ 1yr

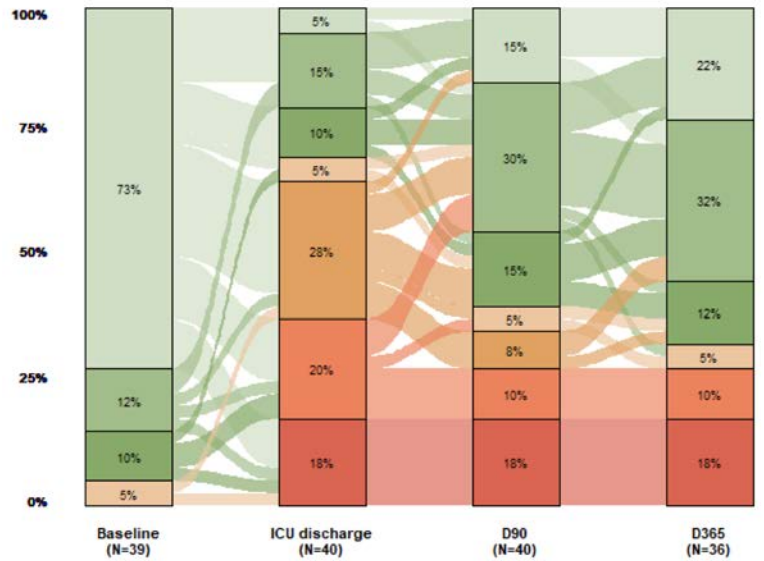
Infectious

57%
mRS 0-2
@ 1yr



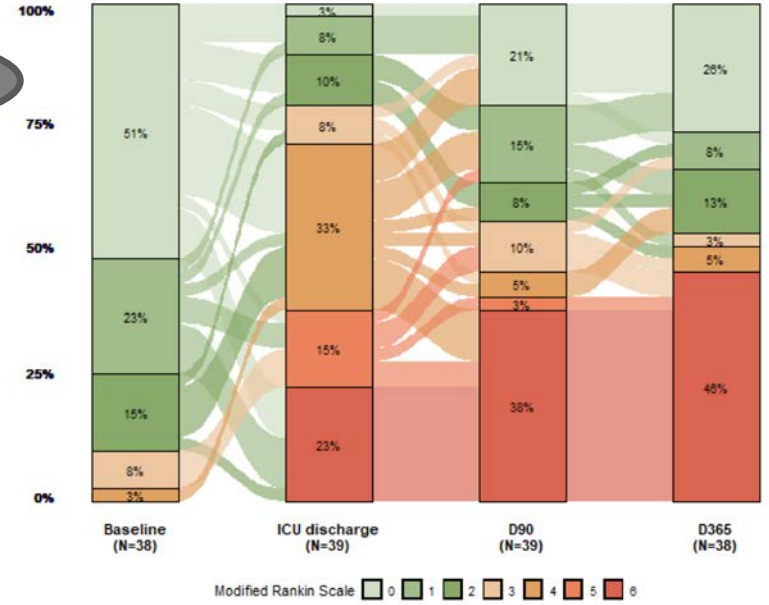
Autoimmune

66%
mRS 0-2
@ 1yr



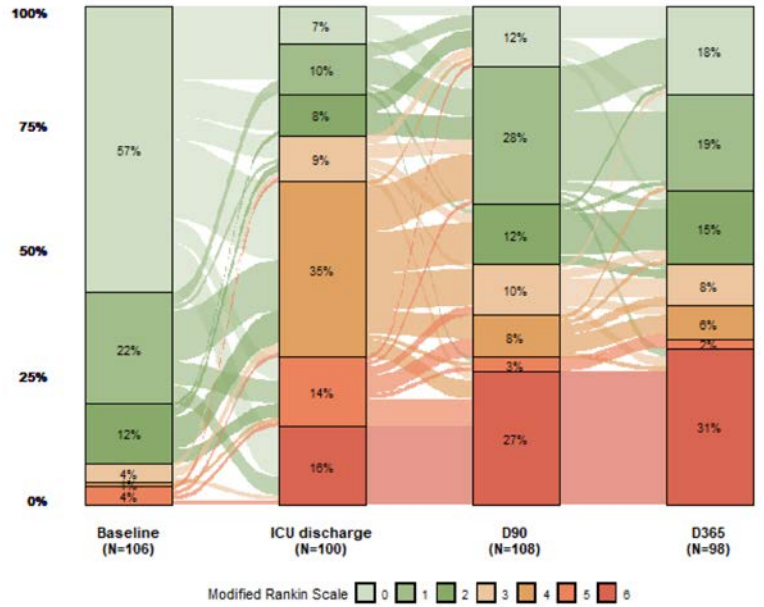
Other

47%
mRS 0-2
@ 1yr



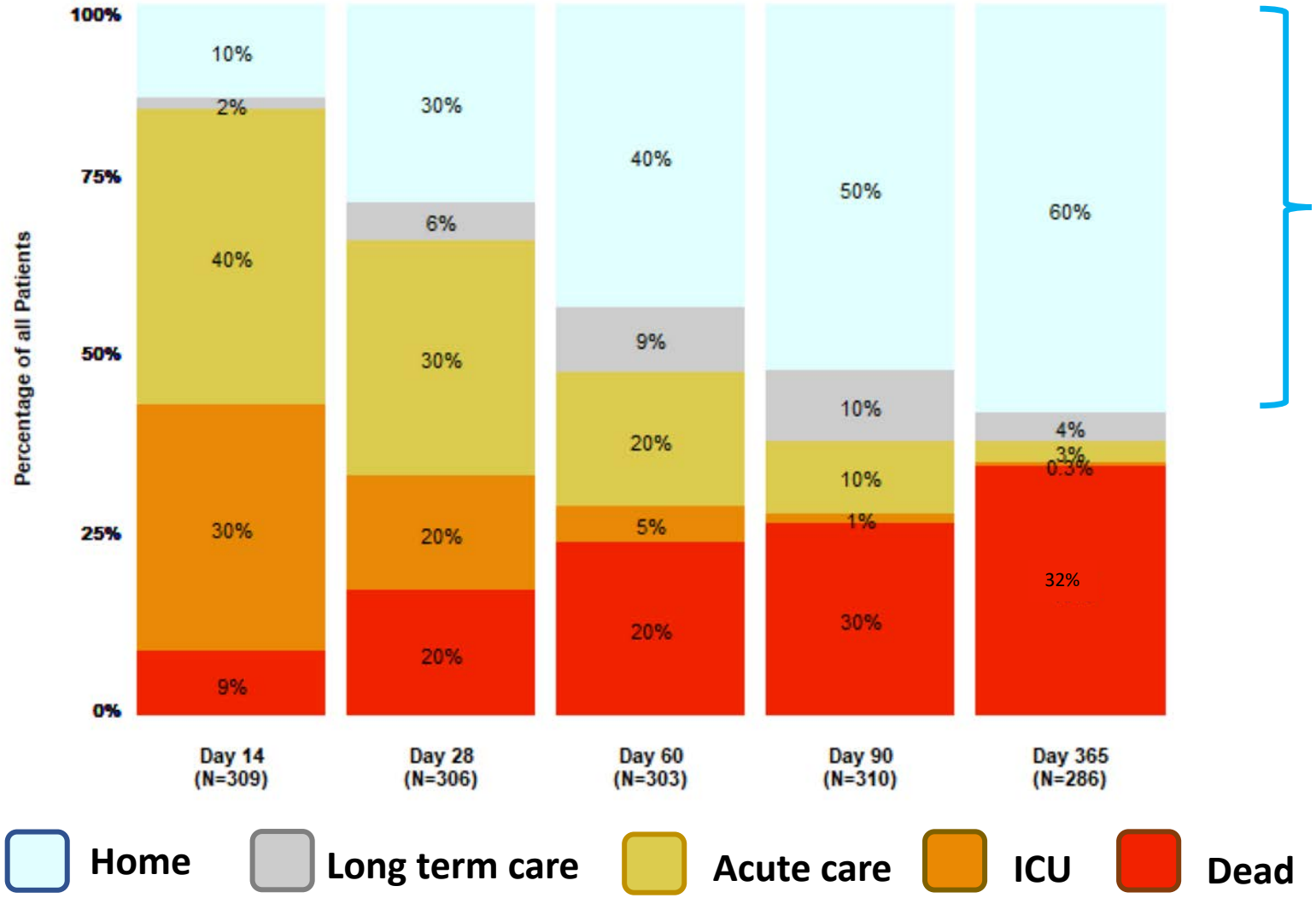
Unknown

52%
mRS 0-2
@ 1yr



Results 1-year trajectories

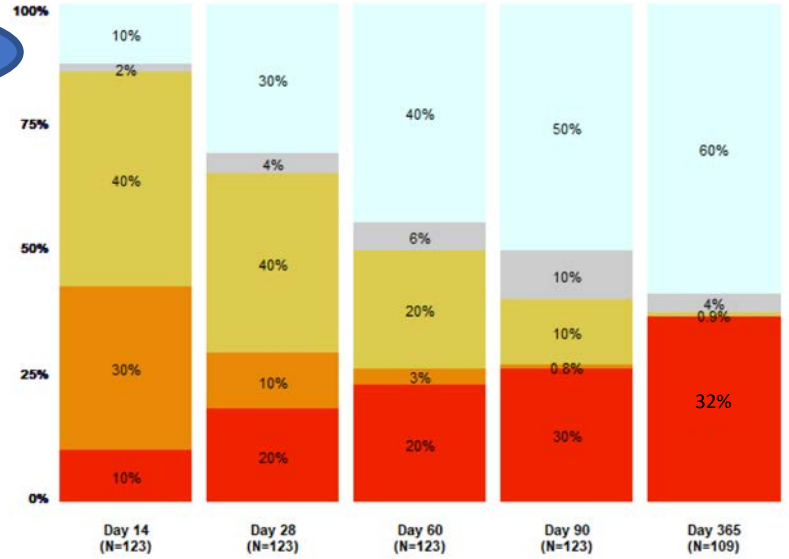
All patients



@ 1yr : 60%

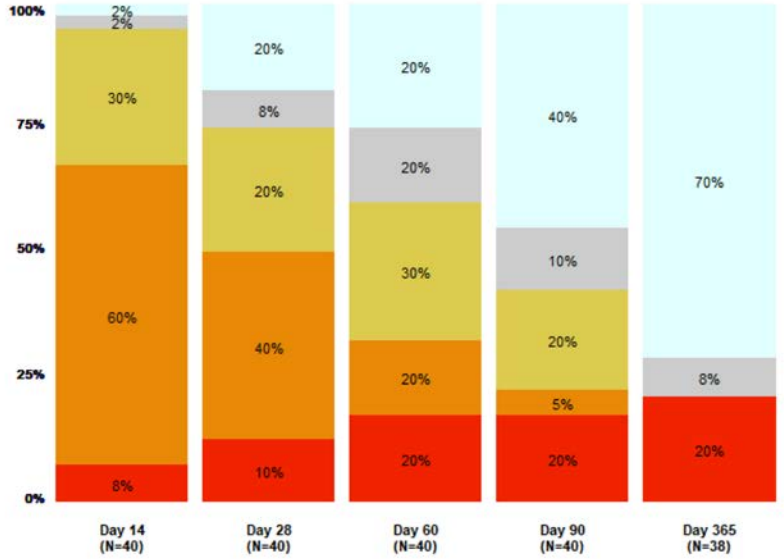
Infectious

60%
@ 1yr



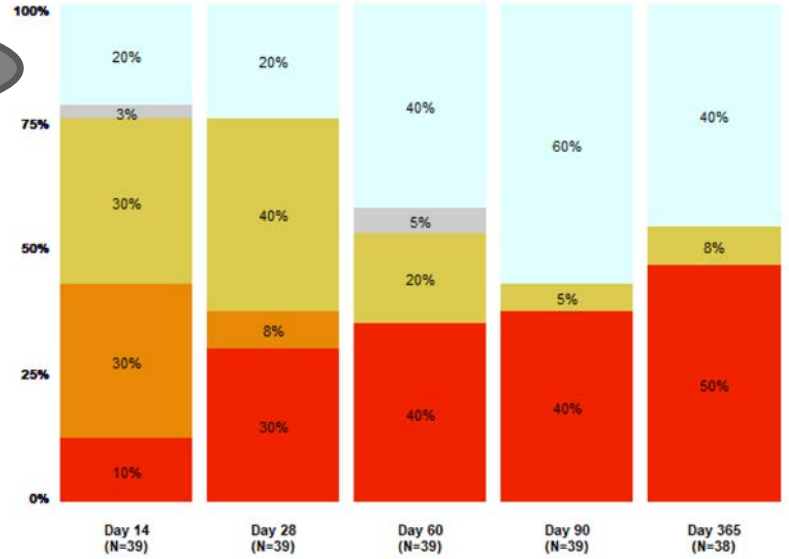
Autoimmune

70%
@ 1yr



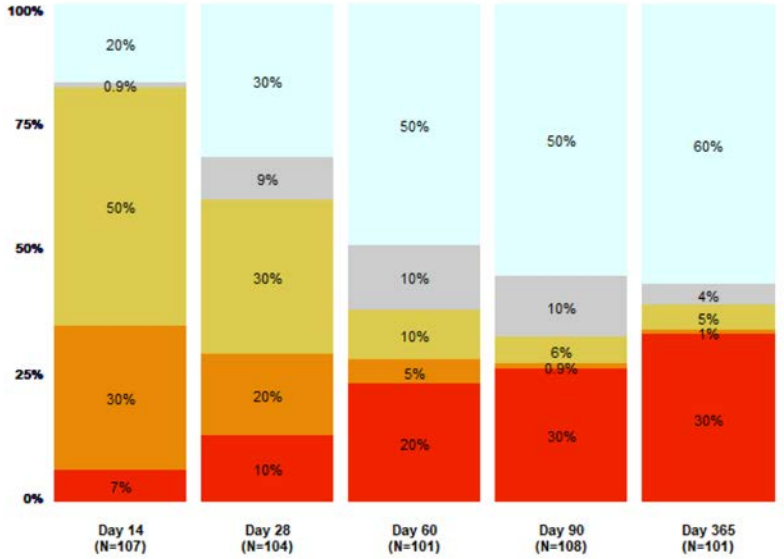
Other

40%
@ 1yr



Unknown

60%
@ 1yr



Home | Long term care | Acute care | ICU | Dead

ORIGINAL

Functional outcomes in adult patients with herpes simplex encephalitis admitted to the ICU: a multicenter cohort study

P. Jaquet[1], E. de Montmollin[1,2], C. Dupuis[1,2], C. Sazio[3], M. Conrad[4], V. Susset[5], S. Demeret[6], J. M. Tadie[7], L. Argaud[8], F. Barbier[9], B. Sarton[10], R. Chabane[11], D. Daubin[12], N. Brulé[13], N. Lerolle[14], M. Alves[15], D. Da Silva[16], A. El Kalioubi[17], S. Silva[10], P. Bailly[18], M. Wolff[1], L. Bouadma[1,2], J. F. Timsit[1,2], R. Sonneville[1,19*] and ENCEPHALITICA study group

N= 259 patients with HSV encephalitis

Multicenter study, 46 ICUs

France, 2006-2016

At 90 days:

Mortality : 19%

Functional independence : 29%

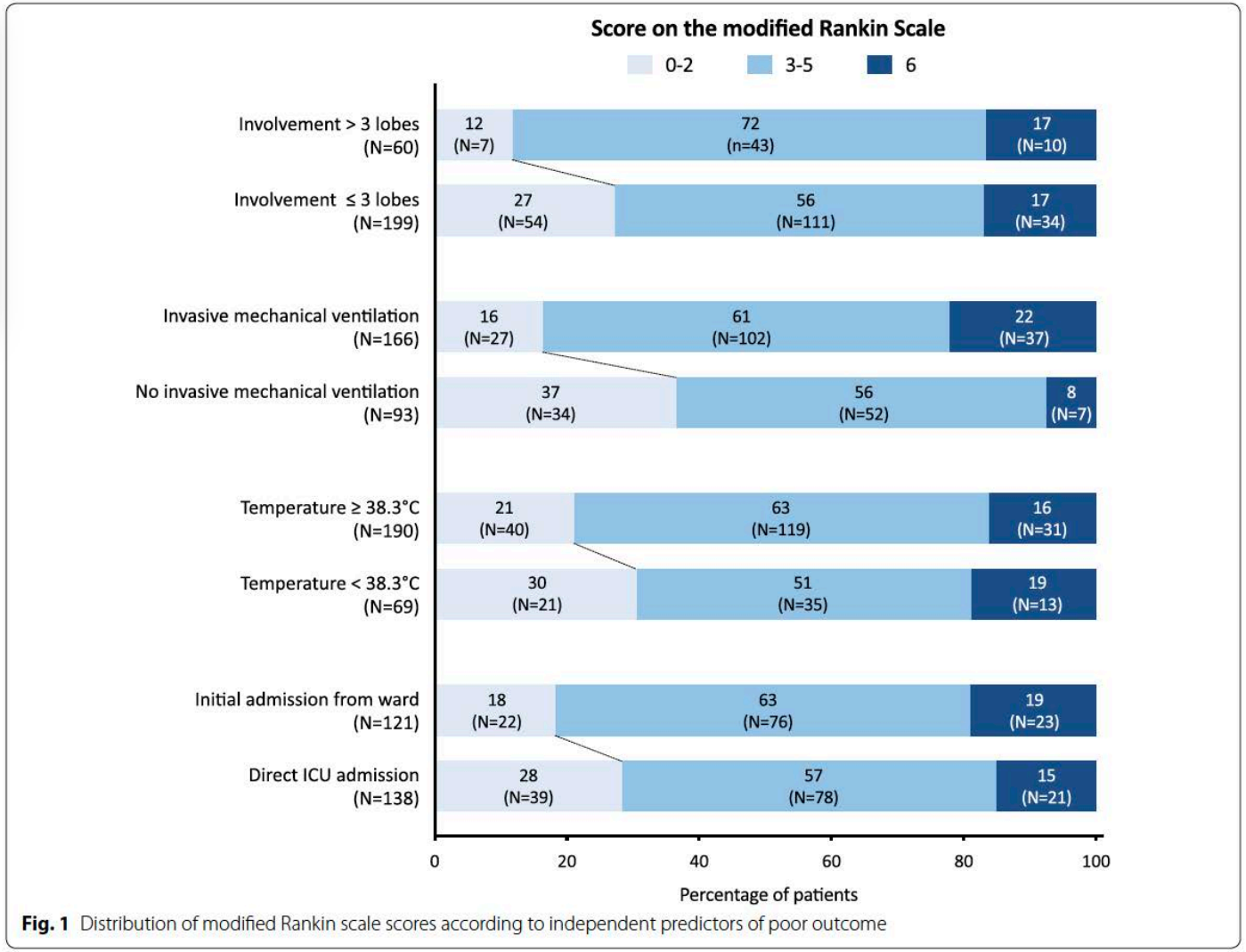


Fig. 1 Distribution of modified Rankin scale scores according to independent predictors of poor outcome

Original Investigation | Critical Care Medicine

Assessment of Magnetic Resonance Imaging Changes and Functional Outcomes Among Adults With Severe Herpes Simplex Encephalitis

Benjamine Sarton, MD; Pierre Jaquet, MD; Djida Belkacemi, MD; Etienne de Montmollin, MD, PhD; Fabrice Bonneville, MD, PhD; Charline Sazio, MD; Aurelien Frérou, MD; Marie Conrad, MD; Delphine Daubin, MD; Russell Chabanne, MD; Laurent Argaud, MD, PhD; Frédéric Dailler, MD; Noëlle Brulé, MD; Nicolas Lerolle, MD; Quentin Maestraggi, MD; Julien Marechal, MD; Pierre Bailly, MD; Keyvan Razazi, MD; Francois Mateos, MD; Bertrand Guidet, MD, PhD; Albrice Levrat, MD; Vincent Susset, MD; Alexandre Lautrette, MD, PhD; Jean-Paul Mira, MD, PhD; Ahmed El Kalioubie, MD; Alexandre Robert, MD, PhD; Alexandre Massri, MD; Jean François Albucher, MD; Jean Marc Olivot, MD, PhD; Jean Marie Conil, MD, PhD; Lila Boudma, MD, PhD; Jean-François Timsit, MD, PhD; Romain Sonneville, MD, PhD; Stein Silva, MD, PhD; for the ENCEPHALITICA Consortium

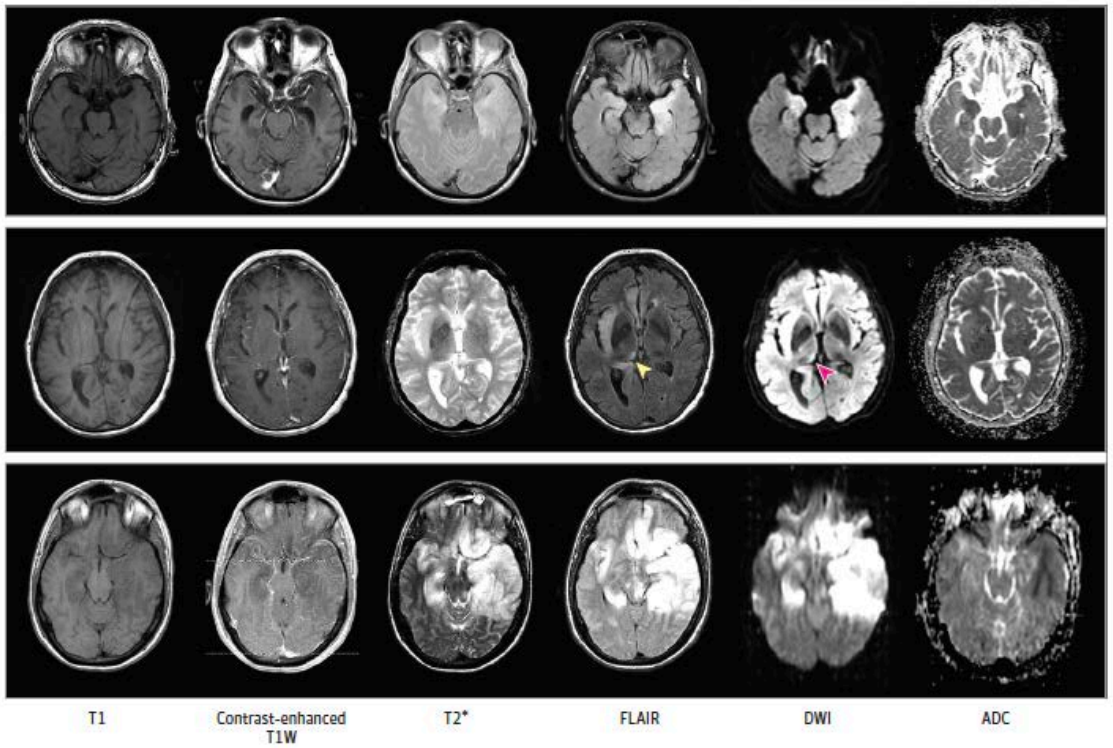
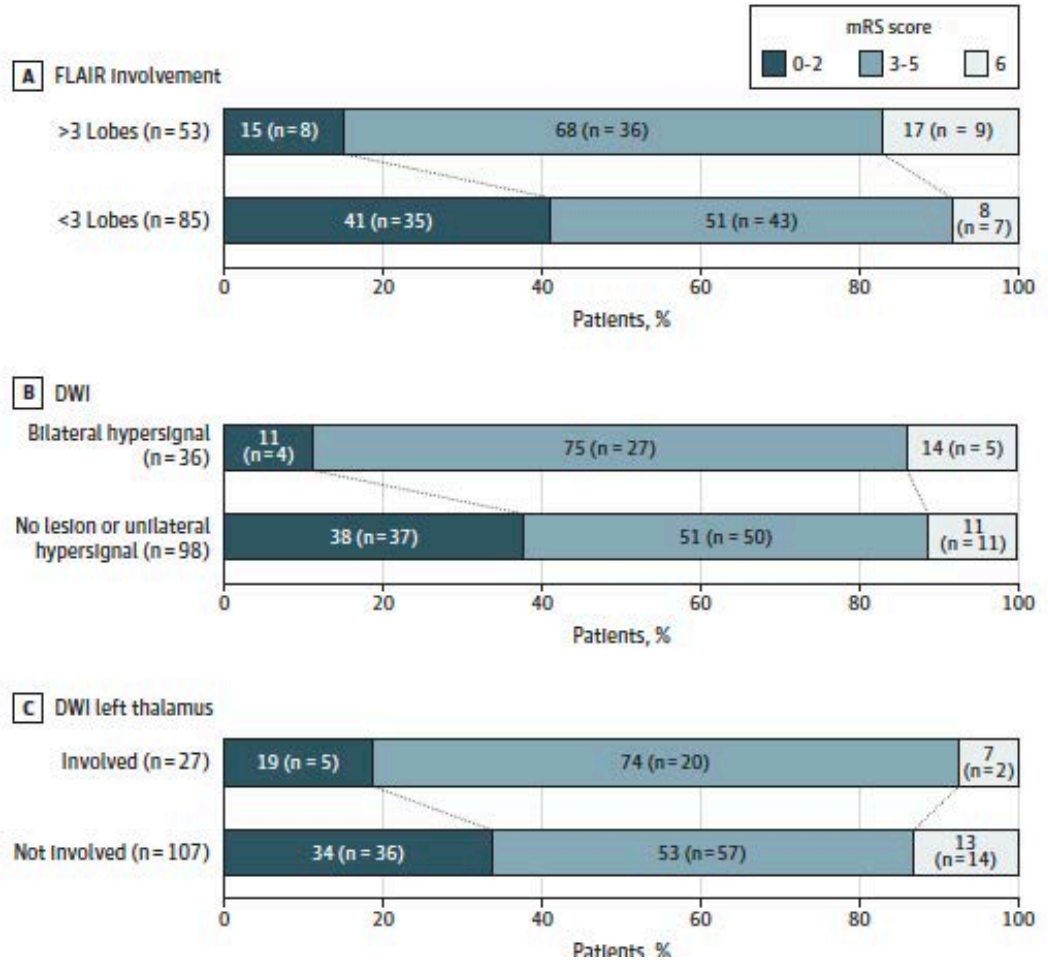


Figure 2. Distribution of Modified Rankin Scale (mRS) at Day 90 According to Magnetic Resonance Imaging Data



JAMA Network Open 2021

RESEARCH Open Access

Electroencephalography for prognostication of outcome in adults with severe herpes simplex encephalitis

Lina Jeantin[1], Claire Dupuis[2], Geoffroy Vellieux[3,4], Pierre Jaquet[5], Etienne de Montmollin[6,7], Jean-François Timsit[6,7], Romain Sonneville[6,7*] and the ENCEPHALITICA Study Group

214 ICU patients with *Herpes simplex* encephalitis

	Model including EEG variables		Model including clinical and EEG variables	
	Adjusted odds ratio*	95% CI	Adjusted odds ratio**	95% CI
Whole cohort (n = 214)				
Present reactivity	1	–	1	–
Reactivity not tested	1.11	0.53–2.30	0.73	0.45–1.20
Absent reactivity	2.80	1.19–6.58	2.03	1.18–3.49
Patients under mechanical ventilation (n = 138)				
Present reactivity	1	–	1	–
Reactivity not tested	1.92	0.73–5.07	1.12	0.57–2.20
Absent reactivity	4.99	1.60–15.59	2.62	1.25–5.50

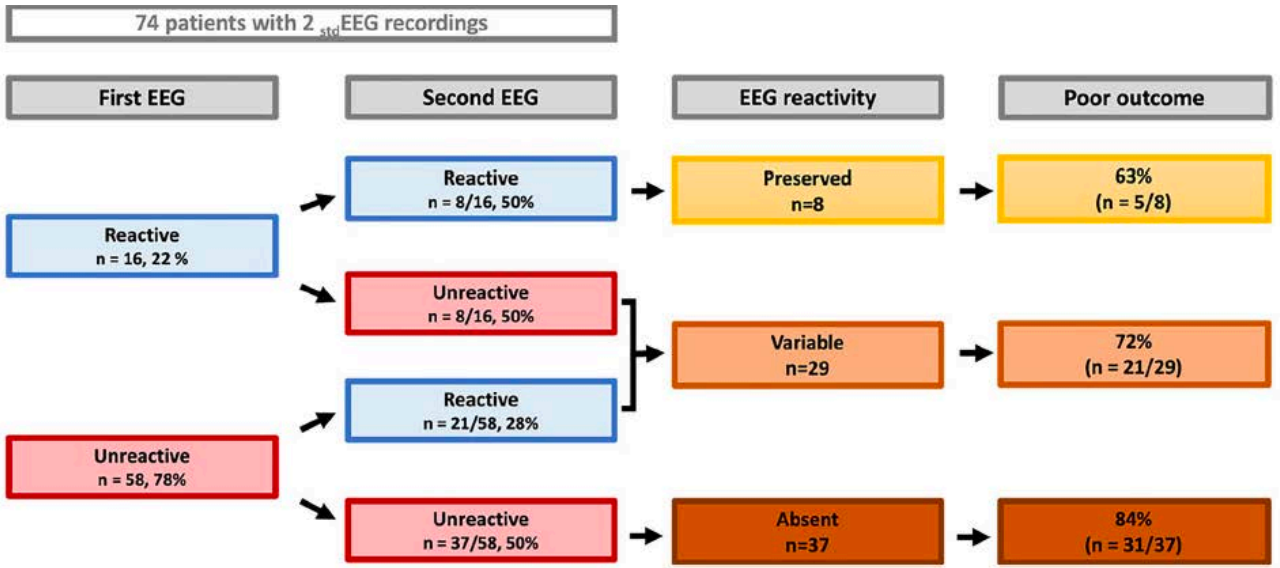


Fig. 2 Association of EEG reactivity on the first and second stdEEGs with outcome. If more than one stdEEG study was available, we collected data from the first and second studies. We classified patients as "preserved reactivity" when both stdEEG were reactive to external stimuli, "absent reactivity" when none of the two stdEEG was reactive, and "variable reactivity" in patients with discordant reactivity between stdEEG studies (presence of reactivity followed by absence of reactivity, or vice versa). A poor outcome was defined by a score of 3–6 on the modified Rankin scale

Conclusions Absence of EEG reactivity to auditory/noxious stimuli is an independent marker of poor functional outcome in severe herpes simplex encephalitis.

Annals of Intensive Care 2023

En conclusion, les encéphalites en réanimation …

- Un **syndrome neurologique aigu sévère**
- Une **évaluation multimodale** précoce (IRM, EEG, LCS / sérum)
- **Virus neurotropes (HSV, VZV) & autres étiologies infectieuses** selon **contexte …**
- **Causes auto-immunes 10-20%**
- **Place des traitements adjuvants (DXM, antiépileptiques..) ?**
- **Bonne récupération fonctionnelle >50% des cas**
- **Suivi à long terme nécessaire**

Merci ☺ !

APHP, Hôpital Bichat Claude Bernard, Paris
Médecine Intensive Réanimation

romain.sonneville@aphp.fr @romsonnevil

Université Paris Cité

Hôpital Bichat Claude-Bernard AP-HP

iame UMR 1137 Infection • Antimicrobials • Modelling • Evolution