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# Characteristics, management and outcome of Herpes Simplex and Varicella-Zoster virus encephalitis: a multicenter prospective cohort study

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1 **Original article**

2 **Characteristics, management and outcome of Herpes Simplex and Varicella-Zoster virus**  
3 **encephalitis: a multicenter prospective cohort study**

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Objective. To characterize differences between Herpes Simplex Virus and Varicella-Zoster Virus encephalitis (HSVE and VZVE) and other aetiologies of infectious encephalitis (IE), and to investigate the impact of time-to-aciclovir (ACV) start, ACV dose and duration on outcome.

Methods. We compared 132 HSVE, 65 VZVE, and 297 others IE enrolled in a prospective cohort (ENCEIF). We estimated associations between time-to-ACV start, dose or duration and outcome through adjusted odds-ratio (aOR) using logistic regression analysis.

Results. Prevalence of immunodepression differed among aetiologies: 15/65 (23%) for VZVE, 13/132 (10%) for HSVE and 30/297 (10%) for others IE ( $P<0.05$ ), as was presence of seizure at admission: 27/132 (20%) for HSVE, 4/65 (6%) for VZVE and 43/297 (14%) for others IE ( $P<0.05$ ). Poor outcome at hospital discharge (Glasgow outcome scale  $\leq 3$ ) differed among the three groups: 40/127 (31%) for HSVE, 12/65 (18%) for VZVE and 38/290 (13%) for other IE ( $P<0.05$ ). Time-to-ACV start was associated with outcome in HSVE (aOR 3.61 [1.25 – 10.40]), but not in VZVE (aOR 0.84 [0.18 – 3.85]). Increased ACV dose was not associated with outcome among HSVE (aOR 1.25 [0.44 – 3.64]) nor VZVE (aOR 1.16 [0.24 – 5.73]).

Conclusion. HSVE and VZVE are distinct in clinical presentation, outcome, and prognostic factors. The impact of early ACV initiation was more apparent for HSVE than for VZVE, however, this could be due to VZVE smaller sample size and lower outcome rate leading to low statistical power, or due to potential distinct IE pathophysiology.

## 47 **Introduction**

48 Herpes simplex virus (HSV) and varicella-zoster virus (VZV) are the most frequent identified  
49 pathogens responsible for infectious encephalitis (IE) outside of Asia, accounting for approximately 40% and  
50 20% of encephalitis cases with microbiological documentation [1–3]. They are associated with high  
51 morbidity and mortality rates, especially among immunodepression status[4]. The advent of aciclovir (ACV)  
52 during the mid-80's, was associated with a dramatic reduction of fatality rates, from 70% to <20% in HSV  
53 encephalitis (HSVE) [5]. However, the burden of long-term sequelae remains high, as less than 30% of  
54 patients with HSVE and 50% of patients with VZVE reach full recovery[6–10].

55 HSVE and VZV encephalitis (VZVE) can be challenging to differentiate from others IE at the initial  
56 phase, which underscores the importance of initiating intravenous ACV whenever acute IE is suspected [11].  
57 In addition, although HSVE and VZVE are often merged in the medical literature, certain distinctions have  
58 been identified, including predisposing factors, clinical presentation, imaging findings, and outcome, which  
59 suggest that their pathophysiology differ, which may have consequences on their optimal treatment [12].

60 In HSVE, time-to-ACV initiation is the main modifiable factor associated with outcome [7,13,14].  
61 However, few studies have investigated the impact of its dose and duration, while ACV is well known to  
62 induce acute renal failure and neurotoxicity, especially in case of overdosing [15,16]. Conversely, the role of  
63 time-to-ACV start, dose and duration remain poorly characterized for VZVE.

64 The 2017 French guidelines for IE advocate for early start of ACV as the empirical antiviral  
65 treatment of IE (target, within 6 hours after hospital admission), at 10 mg/kg every 8 h, to be increased at 15  
66 mg/kg every 8 h in cases at increased risk of VZVE (i.e., vesicular rash, immunodepression). French and  
67 British guidelines recommend a 14-day course of intravenous ACV for immunocompetent adults with HSVE  
68 and VZVE [17,18], while the 2008 guidelines elaborated by the Infectious Diseases Society of America  
69 (IDSA) recommended 14 to 21 days of ACV for HSVE [18,19]. For IE with no microbiological  
70 documentation, HSV may be ruled out with a negative PCR HSV with a high negative predictive value on  
71 cerebrospinal fluid (CSF) sample obtained at least 4 days after the onset of neurological symptoms, which  
72 allow discontinuation of ACV when pre-test probability of HSVE is low [20]. Indeed, recent studies have  
73 reported that some multiplex real-time PCRs had a low performance, particularly for HSV-1 [21].

74 In this ancillary study of the large prospective multicenter cohort ENCEIF, we aimed to characterize  
75 the differences between HSVE, VZVE and other etiologies of IE, and to investigate the impact of time-to-  
76 ACV start, duration and doses on outcome. Our secondary objective was to assess the practices regarding

77 ACV use in patients with IE, in a large network of French hospitals with investigators dedicated to the  
78 management of IE.

79

## 80 **Methods**

81 ENCEIF was a prospective cohort study with enrollment of successive adult patients diagnosed with  
82 IE, as defined by the International Encephalitis Consortium case definition [22] in 62 centers between January  
83 1, 2016 and December 31, 2019 [3]. All data were collected prospectively and recorded anonymously in a  
84 secured online database, using a standardized form. All research questions, data collections and general data  
85 analysis outlines were part of the study protocol before the enrollment of patients begun. No data were  
86 collected retrospectively.

87

88 We defined poor functional outcome by a Glasgow outcome scale (GOS) at discharge from 1 to 3 (i.e. death,  
89 persistent neurovegetative state or major sequelae) while good outcome was defined by GOS 4 (moderate  
90 sequelae) or 5 (minor or no sequelae). We defined immunodeficiency as having: i- an active cancer; ii-  
91 ongoing chemotherapy within the past year; iii- undergone a solid organ or haematopoietic stem cell  
92 transplantation; iv- a haematological malignancy; v- a myelodysplastic syndrome; or vi- undergoing  
93 immunosuppressive treatment. We compared patients with HSVE, VZVE and other causes of IE, using Chi<sup>2</sup>  
94 test or Fisher's test as appropriate, for categorical variables, which were described as numbers (%), and  
95 Kruskal-Wallis for continuous variables, which were described as medians [interquartile range].

96 In order to estimate associations between time-to-ACV start and ACV dose on outcome, we  
97 calculated adjusted odds-ratio (aOR) and its associated Wald confidence intervals (CIs) using logistic  
98 regression analysis. Background knowledge was used to guide adjustment variable selection. We limited  
99 number of independent variables included in the model in order to decrease the impact of the event-per-  
100 variable ratio for prevention of overfitting. Thus, among the HSVE patients, time-to-ACV start, and ACV  
101 dose were adjusted on age, immunodepression, and coma on admission. Among the VZVE patients, as the  
102 sample size was smaller, time-to-ACV start and ACV dose were only adjusted on age and immunodepression  
103 status. No imputation was used for those analysis. Log linearity of continuous variables were tested and, if  
104 necessary, variables were categorized according to median values. Statistical analyses were performed using  
105 R4.1.1.

106 To estimate the potential impact of 21 days of ACV treatment as compared to shorter treatment  
107 duration in HSVE, while reducing immortal time bias, we excluded patients who died within the first 21 days  
108 of admission, as those patients could not receive 21 days of ACV. Then we analyzed whether patients who  
109 received  $21 \pm 2$  days of ACV had better outcome, with logistic regression analysis, after adjusting for  
110 prespecified variables detailed above using patients who received  $14 \pm 2$  days of ACV as the reference.

111 In accordance with French regulation, we obtained informed non-opposition for the use of medical  
112 data from all patients or their close relatives. The study was approved by the French commission for data  
113 protection (Commission Nationale Informatique et Liberté, CNIL, authorization 915148).

114

## 115 **Results**

116 The ENCEIF cohort has enrolled 494 patients with IE, including 132 HSVE, 65 VZVE and 297  
117 others IE. Baseline characteristics are detailed in table 1. Prevalence of clinical symptoms on admission  
118 among the three groups were not statistically different except for fever, headache and seizures, less common  
119 among VZVE, and rash, present at admission in 29/65 (45%) VZVE. Prevalence of infratentorial signs differ  
120 in the three groups ( $P=0.003$ ), present in only 12/132 (9%) of HSVE patients. Abnormalities on EEG and  
121 imaging studies differ among the three groups ( $P<0.001$ ), present among HSVE in 98/107 (92%) and 115/130  
122 (88%) patients respectively for EEG and imaging abnormalities (table 2).

123 Treatment and outcomes are presented in table 3. Median time from symptoms onset to hospital  
124 admission was 2 days [0-4], similar in each group ( $P=0.60$ ). All VZVE and HSVE patients, and 234 patients  
125 with others IE (81% of 288 with available data on ACV administration) were treated with ACV. Of note,  
126 only 8/54 (15%) patients who did not receive ACV had an alternative diagnosis documented within the first  
127 day, mostly through CSF analysis (eg, PCR or microscopic findings). Time from symptoms onset, or hospital  
128 admission, to ACV start, was similar in the 3 groups. Patients with HSVE received ACV with a median delay  
129 of 0 [0-1] day after hospital admission, with 29 (22%), and 24 patients (18%) who received ACV with a delay  
130 of 1 day, and  $\geq 2$  days, respectively, after hospital admission. Patients with HSVE who received ACV  $\geq 1$   
131 day after admission had lower CSF white cells count, at 40 [10-142]/mm<sup>3</sup> vs 123 [35-332]/mm<sup>3</sup> in those who  
132 received ACV within 24 h after admission ( $P=0.005$ , data not shown). Time from admission to ACV start  
133 was longer in immunodeficient patients, with a median of 1 day [1-4], vs 0 [0-1] in immunocompetent  
134 patients ( $P<0.001$ , data not shown). ACV dose was 10 mg/kg t.i.d in 78% of HSVE patients and 40% of  
135 VZVE patients, 15 mg/kg t.i.d or more in the remaining. Median ACV duration was, respectively, 21 days

136 [14-21], 14 days [11-15], and 4 days [2-6], in patients with HSVE, VZVE, and others IE ( $P<0.001$ ), with no  
137 difference among immunocompetent and immunodeficient patients. Most patients with others IE (217/265,  
138 82%) had a negative PCR on a CSF sample obtained at least 4 days after symptoms onset before ACV  
139 discontinuation, as recommended in national guidelines.

140 Although case-fatality rates (CFR) were similar in the 3 groups, HSVE was associated with increased  
141 risk of ICU admission, and poor outcome, as compared to VZVE and others IE ( $P<0.001$ , figure 1). In HSVE,  
142 increased time between hospital admission and ACV start was associated with poor outcome after adjustment  
143 on age, immunodepression and coma (aOR 3.61 [1.25 – 10.4],  $P=0.017$  for 1 day and aOR 5.52 [1.80 –  
144 16.95],  $P=0.003$  for  $\geq 2$  days) (table 4). Increased ACV dose was not independently associated with outcome  
145 (aOR 1.25 [0.44 – 3.64],  $P=0.67$ ), nor was longer duration of ACV (i.e 21 days) which was prescribed in 68  
146 (65%) of patients, in the subgroup of patients still alive at 21 days (aOR 1.83 [0.64 – 5.59],  $P=0.260$ ). For  
147 patients with VZVE, immunodepression remained strongly associated with poor outcome while time-to-  
148 ACV and ACV dose were not associated with poor outcome (table 4).

149

## 150 **Discussion**

151 The main findings of this large multicentre prospective cohort focusing on HSVE, VZVE, and others  
152 IE, are the followings: i) patients with VZVE are older, with higher prevalence of diabetes, and  
153 immunosuppression, as compared to patients with HSVE, and others IE; ii) patients with HSVE are more  
154 likely to present with fever, headache, and seizures, with higher prevalence of EEG and brain imaging  
155 abnormalities, and higher risk of poor outcome; iii) time-to-ACV start is associated with poor outcome in  
156 patients with HSVE, but not in patients with VZVE; iv) we found no association between ACV dose and  
157 duration, and poor outcome in HSVE; v) immunodepression is strongly associated with poor outcome in  
158 patients with VZVE.

159 Previous studies have suggested that HSVE and VZVE are associated with worse prognosis as  
160 compared to others IE, including those of unknown origin. However, these studies merged HSVE and VZVE,  
161 on the ground that they are the 2 main causes of IE in contemporary studies, that HSV and VZV are both  
162 human herpes viruses, susceptible to ACV [6,11]. However, our cohort highlights important differences  
163 between HSVE and VZVE, as already described in a small cohort [12], and suggested in a large prospective  
164 cohort of all-causes encephalitis from England [1]. The striking differences in baseline characteristics (ie,  
165 VZVE affecting older patients with more comorbidities, notably immunodepression), clinical features on

166 admission (more headache, fever, seizure in HSVE), and higher prevalence of EEG abnormalities in patients  
167 with HSVE outline the distinct pathophysiology of HSVE and VZVE. Brain imaging findings also differ,  
168 HSVE being primarily associated with edema and necrosis leading to mass effect, predominantly in the  
169 temporal and frontal regions, and VZVE primarily associated with vascular lesions (i.e., contrast  
170 enhancement, hemorrhage, and vasculitis). Finally, time-to-ACV start, which has been independently  
171 associated with outcomes in several cohorts of HSVE [5,13], may not be so strongly associated with  
172 prognosis in patients with VZVE. Altogether, these findings suggest that HSV could be more aggressive to  
173 brain cells, with direct pathogenicity, and irreversible lesions, while VZV would primarily affect brain  
174 vascularization. These differences may explain the striking differences of clinical and imaging findings  
175 between HSVE and VZVE, as well as the major role of early ACV start in patients with HSVE, to interrupt  
176 direct pathogenicity of HSV on brain cells, while early start of ACV would be less important in VZVE.

177 Previous studies have reported prognostic factors in HSVE, including coma [5,13], supra-tentorial  
178 focal signs [14], restricted diffusion and extensive lesions on MRI (particularly with involvement of > 3  
179 lobes) [23–25]. Vasculitis has been associated with poor outcome in patients with VZVE [9]. This supports  
180 the pure encephalitic disease in HSV, with a functional prognosis proportional to the extent of lesions; versus  
181 a vascular disease in VZVE without anatomical predominance and with lower risk of long-term functional  
182 impairment. HSVE primarily affects cortical and sub-cortical regions, with a higher incidence of seizures  
183 and epileptiform activity on EEG, associated with poor outcome when bilateral [26].

184 Retrospective studies found that time from hospital admission to ACV start  $\geq 2$  days was associated  
185 with poor functional outcome [7,13]. Our study confirms the crucial importance of prompt administration of  
186 ACV in HSVE, with an odd-ratio of poor outcome at 3.61 [1.25-10.40] when ACV is started after the first  
187 day of admission. Of note, approximately half of HSVE patients were admitted to the hospital within two  
188 days of symptom onset in our cohort. Patients with early admission may have normal CSF on the first lumbar  
189 puncture, and should not be denied early start of ACV when clinical features, EEG, and/or brain imaging are  
190 suggestive of IE.

191 The absence of association between time-to-ACV start and outcome in VZVE in our present study  
192 and in previous cohorts raised questions [9,10]. However, as VZV replicates in endothelial cells of large- and  
193 small-vessels, leading to infarctions [27], the impact of early antiviral treatment may be limited. The higher  
194 ACV dose recommended for VZVE (i.e., 15 mg/kg t.i.d.), is supported by *in vitro* data showing higher ACV  
195 inhibitory concentration (IC<sub>50</sub>) for VZV than HSV [28], but to our knowledge, no clinical study found an

196 association with increased ACV dose, and outcome, in patients with VZE. In addition, Herlin and al. found  
197 a similar case-fatality rate (9%) as in our study, although all patients have been treated with 10 mg/kg t.i.d  
198 [9]. Of note, high-doses ACV are associated with increased risk of neurological and renal toxicity, although  
199 these toxicities may be reduced by careful adjustment of ACV dose to previous renal function, attention to  
200 co-medications, correct hydration and urine output, and prolonged infusion [15,29,16,30].

201 A second objective of our prospective nationwide study was to explore the compliance with national  
202 guidelines, published in 2017, but communicated in national conferences in 2015, before the study started.  
203 We found that 20% of patients with IE not caused by HSV or VZV did not receive ACV at all. Out of the  
204 132 patients with HSVE, 53 (40%) received ACV with a delay of 1 day or more after hospital admission.  
205 This is in line with another recent study in the Greater Houston area, which found that compliance with  
206 international guidelines regarding empiric ACV was sub-optimal, as only 64% of patients with IE patients  
207 received ACV, with a time-to-ACV start at 12 h [0-264][31].

208 Our study has limitations. Firstly, due to the multicenter observational design, over a long period of  
209 time (4 years), IE management was not fully standardized, and the study may suffer from heterogeneity.  
210 However, participating sites were all voluntary, and national guidelines were regularly communicated to all  
211 investigators through the study period. Secondly, although this is one of the largest prospective studies on IE  
212 to date, our findings may not apply to other countries, with different epidemiology, and practices for the  
213 management of IE. Besides, the ENCEIF cohort was not primarily designed to analyze ACV use, so that we  
214 did not collect standardized data on ACV administration, and adverse events. In addition, time-to-ACV start  
215 was only collected as days, which jeopardizes precise identification of thresholds that may have an impact  
216 on outcome (e.g., we were unable to differentiate patients who started ACV within 6 h, or between 6 and 24  
217 h after admission). Finally, small sample size in subgroups, particularly in VZVE, may expose to lack of  
218 power in our analysis. We also had no specific information about vasculitis and its management, although  
219 we collected data on vascular abnormalities. However, our study also has strengths, including prospective  
220 collection of standardized data by committed investigators from large clinical sites, which supports a good  
221 external validity.

222 In conclusion, HSVE and VZVE are IE with distinct pathophysiology, clinical presentation,  
223 prognostic factors, and outcome. Early start of ACV is a major independent prognostic factor for HSVE,  
224 along with age and coma on admission, while immunodepression was the only independent prognostic factor  
225 for VZVE.

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228 LP: Formal analysis, Roles/Writing – original draft,  
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279

- 281 [1] Granerod J, Ambrose HE, Davies NW, Clewley JP, Walsh AL, Morgan D, et al. Causes of  
282 encephalitis and differences in their clinical presentations in England: a multicentre, population-based  
283 prospective study. *Lancet Infect Dis* 2010;10:835–44. [https://doi.org/10.1016/S1473-3099\(10\)70222-](https://doi.org/10.1016/S1473-3099(10)70222-)  
284 X.
- 285 [2] Mailles A, Stahl J. Infectious Encephalitis in France in 2007: A National Prospective Study. *Clin*  
286 *Infect Dis* 2009;49:1838–47. <https://doi.org/10.1086/648419>.
- 287 [3] Mailles A, Argemi X, Biron C, Fillatre P, De Broucker T, Buzel  R, et al. Changing profile of  
288 encephalitis: Results of a 4-year study in France. *Infect Dis Now* 2022;52:1–6.  
289 <https://doi.org/10.1016/j.idnow.2021.11.007>.
- 290 [4] Tan IL, McArthur JC, Venkatesan A, Nath A. Atypical manifestations and poor outcome of herpes  
291 simplex encephalitis in the immunocompromised. *Neurology* 2012;79:2125–32.  
292 <https://doi.org/10.1212/WNL.0b013e3182752ceb>.
- 293 [5] Whitley RJ. Vidarabine versus acyclovir therapy in herpes simplex encephalitis. *N Engl J Med*  
294 1986;314:144–9. <https://doi.org/10.1056/NEJM198601163140303>.
- 295 [6] Mailles A, De Broucker T, Costanzo P, Martinez-Almoyna L, Vaillant V, Stahl J-P, et al. Long-term  
296 Outcome of Patients Presenting With Acute Infectious Encephalitis of Various Causes in France. *Clin*  
297 *Infect Dis* 2012;54:1455–64. <https://doi.org/10.1093/cid/cis226>.
- 298 [7] Raschilas F, Wolff M, Delatour F, Chaffaut C, De Broucker T, Chevret S, et al. Outcome of and  
299 Prognostic Factors for Herpes Simplex Encephalitis in Adult Patients: Results of a Multicenter Study.  
300 *Clin Infect Dis* 2002;35:254–60. <https://doi.org/10.1086/341405>.
- 301 [8] Hansen A-BE, Vestergaard HT, Dessau RB, Bodilsen J, Andersen NS, Omland LH, et al. Long-Term  
302 Survival, Morbidity, Social Functioning and Risk of Disability in Patients with a Herpes Simplex  
303 Virus Type 1 or Type 2 Central Nervous System Infection, Denmark, 2000–2016. *Clin Epidemiol*  
304 2020;12:745–55. <https://doi.org/10.2147/CLEP.S256838>.
- 305 [9] Herlin LK, Hansen KS, Bodilsen J, Larsen L, Brandt C, Andersen C , et al. Varicella Zoster Virus  
306 Encephalitis in Denmark From 2015 to 2019—A Nationwide Prospective Cohort Study. *Clin Infect*  
307 *Dis* 2021;72:1192–9. <https://doi.org/10.1093/cid/ciaa185>.
- 308 [10] Le Bot A, Ballerie A, Pronier C, B n zit F, Reizine F, Tas M, et al. Characteristics and outcome of  
309 varicella-zoster virus central nervous system infections in adults. *Eur J Clin Microbiol Infect Dis*  
310 2021;40:2437–42. <https://doi.org/10.1007/s10096-021-04245-y>.
- 311 [11] Le Mar chal M, Mailles A, Seigneurin A, Tattevin P, Stahl J-P,  paulard O, et al. A Prospective  
312 Cohort Study to Identify Clinical, Biological, and Imaging Features That Predict the Etiology of  
313 Acute Encephalitis. *Clin Infect Dis* 2021;73:264–70. <https://doi.org/10.1093/cid/ciaa598>.
- 314 [12] Pollak L, Dovrat S, Book M, Mendelson E, Weinberger M. Varicella zoster vs. herpes simplex  
315 meningoencephalitis in the PCR era. A single center study. *J Neurol Sci* 2012;314:29–36.  
316 <https://doi.org/10.1016/j.jns.2011.11.004>.
- 317 [13] Singh TD, Fugate JE, Hocker S, Wijidicks EFM, Aksamit AJ, Rabinstein AA. Predictors of outcome  
318 in HSV encephalitis. *J Neurol* 2016;263:277–89. <https://doi.org/10.1007/s00415-015-7960-8>.
- 319 [14] Sonnevile R, de Montmollin E, Contou D, Ferrer R, Gurjar M, Klouche K, et al. Clinical features,  
320 etiologies, and outcomes in adult patients with meningoencephalitis requiring intensive care  
321 (EURECA): an international prospective multicenter cohort study. *Intensive Care Med* 2023;49:517–  
322 29. <https://doi.org/10.1007/s00134-023-07032-9>.
- 323 [15] Lee EJ, Jang HN, Cho HS, Bae E, Lee TW, Chang S-H, et al. The incidence, risk factors, and clinical  
324 outcomes of acute kidney injury (staged using the RIFLE classification) associated with intravenous  
325 acyclovir administration. *Ren Fail* 2018;40:688–93.  
326 <https://doi.org/10.1080/0886022X.2018.1487866>.
- 327 [16] Brandariz-Nu ez D, Correas-Sanahuja M, Maya-Gallego S, Mart n Herranz I. Neurotoxicity  
328 associated with acyclovir and valacyclovir: A systematic review of cases. *J Clin Pharm Ther*  
329 2021;46:918–26. <https://doi.org/10.1111/jcpt.13464>.
- 330 [17] Stahl JP, Azouvi P, Bruneel F, De Broucker T, Duval X, Fantin B, et al. Guidelines on the  
331 management of infectious encephalitis in adults. *M decine Mal Infect* 2017;47:179–94.  
332 <https://doi.org/10.1016/j.medmal.2017.01.005>.
- 333 [18] Solomon T, Michael BD, Smith PE, Sanderson F, Davies NWS, Hart IJ, et al. Management of  
334 suspected viral encephalitis in adults – Association of British Neurologists and British Infection  
335 Association National Guidelines. *J Infect* 2012;64:347–73. <https://doi.org/10.1016/j.jinf.2011.11.014>.
- 336 [19] Tunkel AR, Glaser CA, Bloch KC, Sejvar JJ, Marra CM, Roos KL, et al. The Management of  
337 Encephalitis: Clinical Practice Guidelines by the Infectious Diseases Society of America. *Clin Infect*  
338 *Dis* 2008;47:303–27. <https://doi.org/10.1086/589747>.

- 339 [20] Stahl JP, Mailles A, De BROUCKER T, the Steering Committee and Investigators Group. Herpes  
340 simplex encephalitis and management of acyclovir in encephalitis patients in France. *Epidemiol*  
341 *Infect* 2012;140:372–81. <https://doi.org/10.1017/S0950268811000483>.
- 342 [21] López N, Cuesta G, Rodríguez-Vega S, Rosas E, Chumbita M, Casals-Pascual C, et al. Multiplex  
343 real-time PCR FilmArray performance in the diagnosis of meningoencephalitis: lights and shadows.  
344 *Infection* 2023. <https://doi.org/10.1007/s15010-023-02076-x>.
- 345 [22] Venkatesan A, Tunkel AR, Bloch KC, Luring AS, Sejvar J, Bitnun A, et al. Case Definitions,  
346 Diagnostic Algorithms, and Priorities in Encephalitis: Consensus Statement of the International  
347 Encephalitis Consortium. *Clin Infect Dis* 2013;57:1114–28. <https://doi.org/10.1093/cid/cit458>.
- 348 [23] Sarton B, Jaquet P, Belkacemi D, de Montmollin E, Bonneville F, Sazio C, et al. Assessment of  
349 Magnetic Resonance Imaging Changes and Functional Outcomes Among Adults With Severe Herpes  
350 Simplex Encephalitis. *JAMA Netw Open* 2021;4:e2114328.  
351 <https://doi.org/10.1001/jamanetworkopen.2021.14328>.
- 352 [24] Sili U, Kaya A, Mert A. Herpes simplex virus encephalitis: Clinical manifestations, diagnosis and  
353 outcome in 106 adult patients. *J Clin Virol* 2014;60:112–8. <https://doi.org/10.1016/j.jcv.2014.03.010>.
- 354 [25] ENCEPHALITICA study group, Jaquet P, de Montmollin E, Dupuis C, Sazio C, Conrad M, et al.  
355 Functional outcomes in adult patients with herpes simplex encephalitis admitted to the ICU: a  
356 multicenter cohort study. *Intensive Care Med* 2019;45:1103–11. <https://doi.org/10.1007/s00134-019-05684-0>.
- 357 [26] Jeantin L, Dupuis C, Vellieux G, Jaquet P, de Montmollin E, Timsit J-F, et al.  
358 Electroencephalography for prognostication of outcome in adults with severe herpes simplex  
359 encephalitis. *Ann Intensive Care* 2023;13:10. <https://doi.org/10.1186/s13613-023-01110-3>.
- 360 [27] Gildeen D, Cohrs RJ, Mahalingam R, Nagel MA. Varicella zoster virus vasculopathies: diverse  
361 clinical manifestations, laboratory features, pathogenesis, and treatment. *Lancet Neurol* 2009;8:731.  
362 [https://doi.org/10.1016/S1474-4422\(09\)70134-6](https://doi.org/10.1016/S1474-4422(09)70134-6).
- 363 [28] Chemaly RF, Hill JA, Voigt S, Peggs KS. In vitro comparison of currently available and  
364 investigational antiviral agents against pathogenic human double-stranded DNA viruses: A  
365 systematic literature review. *Antiviral Res* 2019;163:50–8.  
366 <https://doi.org/10.1016/j.antiviral.2019.01.008>.
- 367 [29] Ryan L, Heed A, Foster J, Valappil M, Schmid ML, Duncan CJA. Acute kidney injury (AKI)  
368 associated with intravenous aciclovir in adults: Incidence and risk factors in clinical practice. *Int J*  
369 *Infect Dis* 2018;74:97–9. <https://doi.org/10.1016/j.ijid.2018.07.002>.
- 370 [30] Hellden A, Odar-Cederlof I, Diener P, Barkholt L, Medin C, Svensson J-O, et al. High serum  
371 concentrations of the acyclovir main metabolite 9-carboxymethoxymethylguanine in renal failure  
372 patients with acyclovir-related neuropsychiatric side effects: an observational study. *Nephrol Dial*  
373 *Transplant* 2003;18:1135–41. <https://doi.org/10.1093/ndt/gfg119>.
- 374 [31] Samannodi M, Hansen M, Allana A, Hasbun R. Compliance with international guidelines in adults  
375 with encephalitis. *J Clin Virol* 2020;127:104369. <https://doi.org/10.1016/j.jcv.2020.104369>.
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379 **Table 1.** Baseline characteristics of patients with infectious encephalitis, ENCEIF cohort, France 2016-19

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Variables	Available observations	HSV encephalitis, n=132	VZV encephalitis, n=65	Others, n=297	P-value
Age, years	494	65 [52-73]	74 [65-82]	63 [41-72]	<0.001
Male gender	493	83/131 (63)	44/65 (68)	176/297 (59)	0.4
Diabetes mellitus	491	15/131 (11)	18/65 (28)	34/295 (12)	0.002
Cancer	491	14/132 (11)	6/65 (9)	19/294 (7)	0.3
Hematologic malignancy	489	4/131 (3)	5/65 (8)	18/293 (6)	0.3
Solid organ transplant	490	2/132 (2)	3/ 65 (5)	11/293 (4)	0.4
Immunodeficiency	494	13 (10)	15 (23)	30 (10)	0.010
Independence for daily activities	488	125/130 (96)	57/64 (89)	284/294 (97)	0.044

381 Categorical variables are reported as numbers (%), continuous variables, as medians [interquartile range]

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Variables	Available data	HSV encephalitis, n=132	VZV encephalitis, n=65	Others, n=297	P-value
Confusion	494	96 (73)	43 (66)	167 (56)	0.004
Altered mental status	494	44 (33)	24 (37)	129 (43)	0.12
Coma	494	8 (6)	2 (3)	28 (9)	0.2
Supra-tentorial focal signs	494	61 (46)	26 (40)	119 (40)	0.5
- Sensitive or motor deficit	494	22 (17)	7 (11)	30 (10)	0.15
- Speech disorders	494	47 (36)	21 (32)	102 (34)	0.9
Infra-tentorial signs	494	12 (9)	12 (18)	68 (23)	0.003
- Cranial nerve palsy	494	9 (7)	9 (14)	37 (12)	0.2
- Cerebellar syndrome	494	4 (3)	5 (8)	35 (12)	0.012
Seizures	494	27 (20)	4 (6)	43 (14)	0.028
Headache	494	58 (44)	17 (26)	158 (53)	<0.001
Fever	494	111 (84)	41 (63)	231 (78)	0.004
Rash	494	3 (2)	29 (45)	19 (6)	<0.001
Respiratory signs	494	11 (8)	2 (3)	42 (14)	0.018
Digestive symptoms	494	31 (23)	6 (9)	57 (19)	0.056
Arthralgia	494	2 (2)	0 (0)	16 (5)	0.038
Cerebrospinal fluid (CSF)					
- Erythrocytes count, /mm <sup>3</sup>	415	14 [2-60]	19 [1-92]	10 [2-78]	0.9
- Leucocytes count, /mm <sup>3</sup>	478	91 [20-243]	120 [55-310]	68 [19-226]	0.059
- Lymphocytes (%)	406	88 [70-96]	90 [69-95]	80 [38-95]	0.015
- Neutrophils (%)	388	4 [1-12]	5 [1-18]	10 [1-50]	0.004
- Protein, g/L	483	0.75 [0.55-1.19]	1.21 [0.70-2.80]	0.90 [0.60-1.42]	<0.001
- Glucose CSF/plasma ratio	405	0.58 [0.48-0.68]	0.47 [0.41-0.59]	0.55 [0.45-0.67]	0.018
Abnormal EEG	366	98/107 (92)	27/45 (42)	150 (51)	<0.001
- Slow frequency rhythms		71/88 (81)	22/24 (92)	107/143 (75)	0.15
- Epileptiform activity		37/94 (39)	3/26 (12)	22/142 (15)	<0.001
- Periodic patterns		31/75(41)	2/23 (9)	15/126 (12)	<0.001
Abnormal imaging	483	115/130 (88)	32/63 (51)	135/290 (47)	<0.001
- Contrast enhancement		33/89 (37)	10/16 (62)	26/80 (32)	0.077
- Hemorrhage		20/110 (18)	8/30 (27)	9/124 (7)	0.004
- Mass effect		27/103 (26)	1/20 (5)	6/87 (7)	<0.001
- Vascular abnormalities		7/108 (6)	9/31 (29)	25/128 (20)	0.002

Categorical variables are reported as numbers (%), continuous variables, as medians [interquartile range].

389 **Table 3.** Treatment and outcome of patients with infectious encephalitis, ENCEIF cohort, France 2016-19

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Variables	Available data	HSV encephalitis, n=132	VZV encephalitis, n=65	Others, n=297	P-value
Aciclovir administration	481	129/129 (100)	64/64 (100)	234/288 (81)	<0.001
Time from symptoms onset to aciclovir start, days	421	3 [1-6]	3 [2-5]	2 [1-5]	0.14
Time from symptoms onset to hospital admission, days	494	2 [1-4]	1 [0-3]	2 [0-5]	0.6
Time from hospital admission to aciclovir start	421	0 [0-1]	1 [0-1]	0 [0-1]	0.5
Aciclovir dose	407				<0.001
- 10 mg/kg t.i.d		98/126 (78)	24/60 (40)	177/221 (80)	
- $\geq$ 15 mg/kg t.i.d		28/126 (22)	36/60 (60)	44/221 (20)	
Aciclovir duration	394*	21 [14-21]	14 [11-15]	4 [2-6]	<0.001
- immunocompetent patients		21 [14-21]	14 [10-14]	4 [3-6]	
- immunocompromised patients		21 [16-21]	14 [10-14]	4 [2-5]	
Corticosteroids administration	464	16/124 (13)	8/62 (13)	69/278 (25)	0.007
Admission in intensive care unit	494	75 (57)	20 (31)	111 (37)	<0.001
In hospital death	490	12/131 (9)	8/65 (12)	17/294 (6)	0.13
Poor outcome **	482	40/127 (31)	12/65 (18)	38/290 (13)	<0.001

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392 Categorical variables are reported as numbers (%), continuous variables, as medians [interquartile range].

393 \* missing data for aciclovir duration (n=100) : HSV encephalitis (n=19), VZV encephalitis (n=5), Others (n=76)

394 \*\* Poor outcome was defined by a Glasgow outcome scale (GOS) at discharge from 1 to 3 (death, persistent  
395 neurovegetative state or major sequelae).

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398 **Table 4.** Adjusted odds-ratio of poor outcome\* at discharge in patients with HSVE (n=119) and VZVE  
399 (n=59).

	HSV encephalitis			VZV encephalitis		
	aOR	CI 95%	P-value	aOR	CI 95%	P-value
Age > median <sup>§</sup>	2.77	1.10 - 6.94	0.030	2.55	0.53 - 12.31	0.243
Immunodeficiency	0.92	0.21 - 4.01	0.913	9.68	2.08 - 45.1	0.004
Coma on admission	5.57	1.02-30.28	0.047			
Time from admission to acyclovir start (reference, 0)						
- 1 day	3.61	1.25 - 10.40	0.017	0.84	0.18 - 3.85	0.818
- 2 days	5.52	1.80 - 16.95	0.003			
Aciclovir dose 15 mg/kg t.i.d (reference, 10 mg/kg t.i.d)	1.25	0.44 - 3.64	0.670	1.16	0.24 - 5.73	0.850

400 \* Poor outcome was defined by a Glasgow outcome scale (GOS) at discharge from 1 to 3 (death, persistent  
401 neurovegetative state or major sequelae).

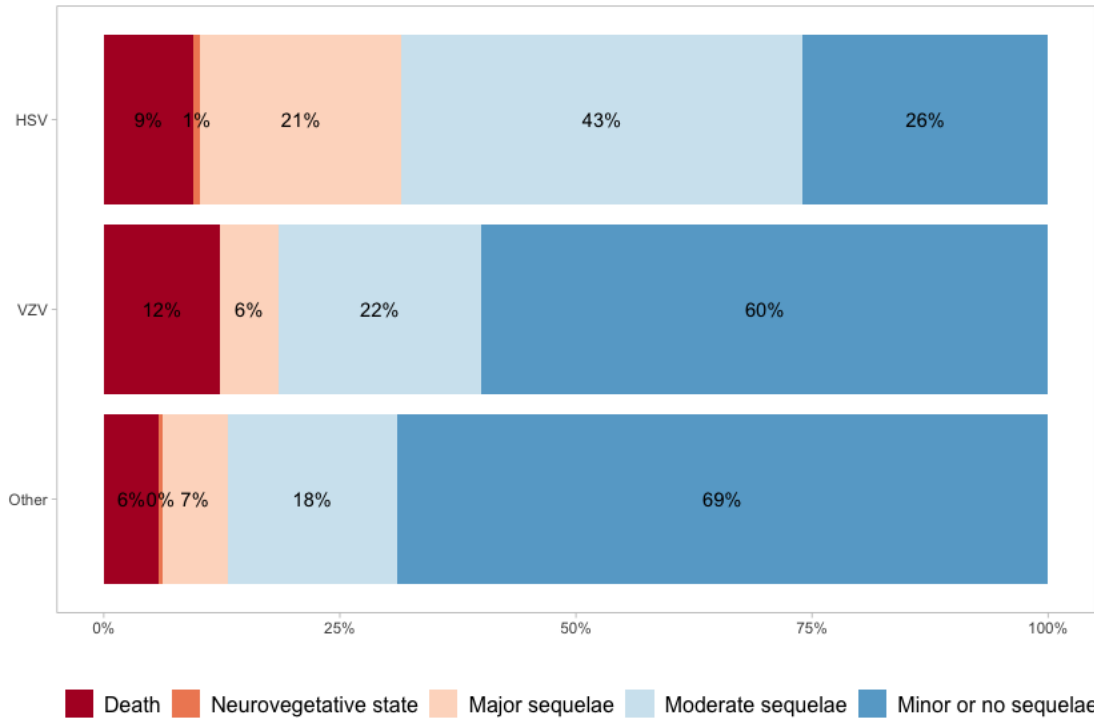
402 <sup>§</sup>Median values: 65 years for HSV encephalitis, 74 years for VZV encephalitis

403 aOR, adjusted odds ratio; CI95%, confidence interval 95%

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**Figure 1.** Distribution of Glasgow Outcome Scale at discharge according to infectious encephalitis etiology, ENCEIF cohort, France 2016-19



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