Management and prognostic markers in patients with autoimmune encephalitis requiring ICU treatment

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Abstract

Objective
To assess intensive care unit (ICU) complications, their management, and prognostic factors associated with outcomes in a cohort of patients with autoimmune encephalitis (AE).

Methods
This study was an observational multicenter registry of consecutively included patients diagnosed with AE requiring Neuro-ICU treatment between 2004 and 2016 from 18 tertiary hospitals. Logistic regression models explored the influence of complications, their management, and diagnostic findings on the dichotomized (0–3 vs 4–6) modified Rankin Scale score at hospital discharge.

Results
Of 120 patients with AE (median age 43 years [interquartile range 24–62]; 70 females), 101 developed disorders of consciousness, 54 autonomic disturbances, 42 status epilepticus, and 39 severe sepsis. Sixty-eight patients were mechanically ventilated, 85 patients had detectable neuronal autoantibodies, and 35 patients were seronegative. Worse neurologic outcome at hospital discharge was associated with necessity of mechanical ventilation (sex- and age-adjusted OR 6.28; 95% CI, 2.71–15.61) tracheostomy (adjusted OR 6.26; 95% CI, 2.68–15.73), tumor (adjusted OR 3.73; 95% CI, 1.35–11.57), sepsis (adjusted OR 4.54; 95% CI, 1.99–10.43), or autonomic dysfunction (adjusted OR 2.91; 95% CI, 1.24–7.3). No significant association was observed with autoantibody type, inflammatory changes in CSF, or pathologic MRI.

Conclusion
In patients with AE, mechanical ventilation, sepsis, and autonomic dysregulation appear to indicate longer or incomplete convalescence. Classic ICU complications better serve as prognostic markers than the individual subtype of AE. Increased awareness and effective management of these AE-related complications are warranted, and further prospective studies are needed to confirm our findings and to develop specific strategies for outcome improvement.

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AE = autoimmune encephalitis; AED = antiepileptic drug; DWI = diffusion-weighted imaging; eCRF = electronic case report form; FDG-PET = fluorodeoxyglucose PET; FLAIR = fluid-attenuated inversion recovery; GENERATE = German Network for Research in Autoimmune Encephalitis; ICU = intensive care unit; IGNITE = Initiative of German Neurointensive Trial Engagement; IQR = interquartile range; mRS = modified Rankin Scale; RE = receptor encephalitis; SE = status epilepticus.

Autoimmune encephalitis (AE) is a potentially life-threatening inflammation of the CNS and constitutes 20%–30% of encephalitis cases in adults.4 AE often leads to subacute, severe, and debilitating encephalitis necessitating long-term management in a neurologic intensive care unit (ICU). Recent estimations on mortality due to AE range between 12% and 40%,2–4 although only limited data are available on in-hospital mortality and morbidity. Patients with AE-associated anti-NMDA receptor antibodies in particular,5 but also those with AE associated with antibodies against other neuronal surface or intracellular antigens, often require long-term ICU management.4 Moreover, more than 40% of patients with probable AE without antineuronal antibody detection and exclusion of other disorders require ICU treatment.5 In turn, long-term ICU treatment together with immunosuppression as mandatory therapy puts these patients at high risk of ICU treatment-related complications. Neurologic ICU complications due to AEc6 such as status epilepticus, severe hyperkinetic movement, and autonomic disorders, are usually dealt with on a case-by-case basis. In fact, there are limited data available on the frequency, management, and potential prognostic value of complications in the ICU for patients with AE.7

The ICU-CompoSE study (ICU–Complications of Severe Encephalitis) focuses on demographic and clinical characteristics in a large cohort of AE patients’ subtypes requiring neuro-ICU treatment. In the study, we aimed at identifying ICU-specific prognostic factors. In addition, we assessed potential factors for short-term outcome on discharge from hospital instead of long-term outcome, which reflects other factors of individual AE subtypes, e.g., relapse frequency and tumor association. Moreover, we also assessed potential prognostic factors for worse outcome at discharge from hospital.

We hypothesize that short-term outcome of patients with AE requiring ICU treatment is dependent on the occurrence of ICU complications rather than on diagnostic subtypes of AE.

Methods

Design and patients
We conducted a multicenter nationwide cohort study in 18 tertiary neurologic centers in Germany and consecutively included patients between January 1, 2004, and December 31, 2016. The cooperation of 2 German neurologic and neurointensive care networks (German Network for Research in Autoimmune Encephalitis [GENERATE], generate-net.de, and Initiative of German Neurointensive Trial Engagement [IGNITE], dgni.de/forschung/ignite-initiative-klinischer-multizenter-studien/ueber-ignite.html) facilitated compiling information in the GENERATE databank on patients with the clinical syndrome of AE requiring intensive care treatment.

The inclusion criteria for patients were as follows: patients of any age with the clinical syndrome of encephalopathy including disturbance of consciousness for more than 24 hours with accompanying lethargy, irritability, and any change in personality or behavior1 were included in this study if at least 2 of the following criteria were met: (1) fever or history of fever, (2) epileptic seizures and/or new neurologic deficits, (3) CSF pleocytosis (>4 cells/μl), (4) EEG abnormalities, and (5) pathologic neuroimaging findings (MRI/CT). Furthermore, infectious or other alternative causes of encephalopathic syndrome had to be excluded. In addition, only patients admitted to an ICU during the course of the disease were included. ICU admission was necessary if the patient had one or more of the following symptoms: decreased level of consciousness, severe dyskinesia, autonomic dysfunction, epileptic seizure(s)/status epilepticus, and need for mechanical ventilation or other complications, such as severe sepsis, thrombosis, embolic events, other relevant organ failure, cardiac arrhythmia, resuscitation, and increased intracranial pressure.

Standard protocol approvals, registration, and patient consents
The study protocol was approved by the local research ethics committee at each center. Written informed consent was obtained from every patient or their representative.

Data collection
Data were collected at the participating GENERATE and IGNITE centers on the basis of cooperation within the network. At each collaborating center, a local investigator retrospectively gathered demographic information (sex, age, ethnic background, and patient’s medical history) and all clinical AE features (prodromi, symptoms at presentation, and onset and duration dates). In addition, ICU charts were used to retrieve patient data on the management of ICU complications. Major complications and their therapeutic management during the patient’s stay in the ICU and patient’s clinical outcome were documented using an electronic case report form (ICU-CompoSE-eCRF) extending the existing GENERATE-eCRF.

The major clinical ICU problems consisted of the following:

1. Disturbance of consciousness: coma duration and onset in course of the disease, somnolence, sopor, mutism, and delirium;
2. Autonomic dysfunction: hyperthermia, hypoventilation/hyperventilation, tachycardia/bradycardia, cardiac arrhythmia, cardiac arrest, hypotensive/hypertensive arterial blood pressure, diarrhea, hyperhidrosis, and sialorrhea;
3. Status epilepticus (SE)/seizures: semiology (if available), duration and frequency of seizures/status, refractory status, detection of SE, use of EEG monitoring, and antiepileptic drugs (AEDs) used;
4. Movement disorder and hyperkinetic status: clinical manifestation, management, and drugs used;
5. Other complications: severe sepsis/septic shock, other relevant organ failure, increase in intracranial pressure, resuscitation, surgical complications, and psychiatric complications (e.g., suicide attempt);
6. Ethical conflicts: ovariectomy (prophylactic or diagnostic), change in therapeutic goal, therapy limitation or disruption, and interdisciplinary ethical consultation.

Additional systematically assessed data included the following:

1. Mechanical ventilation: reason for intubation, time of intubation during the course of the disease, duration of ventilation, ventilation mode, time and reason for tracheostomy, reintubation, and other ventilatory problems;
2. Algesia and sedation: duration, drugs used, and use of inhalative sedation (isoflurane and sevoflurane).

Diagnostic workup data included laboratory testing for autoantibodies from CSF and serum, neurophysiologic data (i.e., EEG results), and brain imaging results (pathologic MRI suggestive for AE was defined as a hyperintense signal on T2-weighted fluid-attenuated inversion recovery (FLAIR) sequences highly restricted to one or both medial temporal lobes or in multifocal areas involving gray matter, white matter, or both compatible with demyelination or inflammation). If available, cerebral fluorodeoxyglucose PET (FDG-PET) results were also retrieved. Furthermore, in case a tumor had been detected, the entity of the tumor and antitumor therapy were retrieved.

For outcome analysis, values of the modified Rankin Scale (mRS) were retrieved by the treating physician from clinical charts during the ICU stay, revealing both the poorest value (maximum mRS—obtained at the poorest neurologic/functional status of the patient) and the mRS at the end of the hospital stay. Good neurologic outcome was defined as a dichotomized (mRS) score of 0–3 for no disability to moderate disability at hospital discharge, whereas mRS scores of 4–6 were defined as poor outcome.

Statistical analyses

Descriptive statistics summarize the patient’s characteristics (continuous variables: quartiles/count data: absolute and relative frequencies). Because we had to work with the given sample of this rare disease, we performed no formal sample size calculations. Consequently, we limited the modeling, avoided data imputations, did not examine subgroups or interactions, and did not strictly control the type I error rate; results are explorative. We performed crude and adjusted logistic regressions (adjusted for age [linear and per year] and sex) to derive factors associated with good to moderate (mRS scores 0–3) or poor (mRS scores 4–6) neurologic outcome at hospital discharge. Because linear regression models with untransformed mRS scores lead to the same conclusions, we decided to focus on the logistic regression results. In total, we explored 19 potential prognostic factors. In light of only 7 observed in-hospital deaths, we decided not to run additional regression models for hospital mortality. We report crude and adjusted ORs with 2-sided 95% CIs (not corrected for multiplicity) and a significance level $\alpha = 0.05$ (2-sided). All statistical analyses were performed using the statistical language R 3.4.3. (Source: R Core Team [2014]. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL R-project.org/).

Data availability statement

The data used for this study can be supplied by the corresponding author upon request. The STROBE guidelines were used for reporting of this observational study.

Results

Patient characteristics

Of the 602 patients enrolled in the GENERATE database (until December 31, 2016), we included 120 patients in the ICU-CompoSE study. The median age at disease onset was 43 years (interquartile range [IQR] 24–62, range 9–82 years), and 70 patients (58%) were female (table 1). Ethnicity was Caucasian in 99% and Asian in 1%.

Clinically, consistent with the accounts of the treating physicians and the clinical charts, 63% of the 120 patients showed symptoms of limbic encephalitis, whereas 31% were judged to show a generalized form of encephalitis, and 8% exhibited brain stem encephalitis. Other specific clinical syndromes included cerebellitis and Rasmussen encephalitis (table 1).

Prodromal symptoms were found in 34%, and the median duration of these symptoms was 8 days (IQR: 5–34; range 1–1,000 days). Prodromal symptoms consisted of unspecific respiratory or gastrointestinal symptoms (50%), headache (47%), neurologic deficits (41%), psychiatric symptoms (26%), and cognitive impairment (15%). The median delay between first symptoms and hospital admission was 6 days (IQR: 0–32; range 0–3,485 days).

MRI was performed in 98% of patients, and a pathologic result was obtained in 70%. In detail, the main pathologic findings consisted of FLAIR lesions ($N = 88$), diffusion-weighted imaging lesions ($N = 25$), MRI-contrast enhancing lesions ($N = 15$), and limbic lesions ($N = 52$).

EEG showed pathologic findings in 84% (generalized slow activity in 85%, focal abnormalities in 60%, and epileptic discharges in 41% of patients).
CSF was analyzed in 97% of the patients; 60% had pleocytosis, and 50% showed an increased total protein content. Isolated oligoclonal bands in CSF were seen in 29%.

Neuronal autoantibodies were examined in 27/120 patients in serum only, 10/120 patients in CSF only, and 83/120 patients in CSF and serum. Autoantibody testing was performed by commercially available mosaic biochip (Euroimmun, Lübeck, Germany) according to the manufacturer’s procedures by certified laboratories and by scientific laboratories using immunohistochemistry. Well-characterized neuronal autoantibodies were detected in 85/120 patients (71% total, 57% in serum, 48% in CSF, and 47% both). Anti-NMDA-R antibodies were most common, followed by leucine-rich glioma-inactivated 1, CASPR2, and glutamic acid decarboxylase (table 1). A total of 93% of patients were screened for a tumor, which was found in 21% of the screened patients (table 1).

### ICU complications and management

Eighty-four percent of patients had a decreased level of consciousness, and 34% developed delirium. Impairment of...
Consciousness lasted more than 8 days in 70% and more than 30 days in 32% of patients.

Autonomic dysregulation (33% tachycardia, 19% bradycardia, 18% hypertensive crisis or hypotension, 18% hypoventilation, and 13% hyperthermia) was seen in 45% of patients. The therapeutic strategies including external and internal cooling and administration of IV dantrolene for fever treatment, pacemaker for bradycardia, mechanical ventilation for hypoventilation, and catecholamines/antihypertensives for blood pressure dysregulation are listed in Table 2.

Thirty-five percent of patients developed status epilepticus (SE) (43% generalized, 37% nonconvulsive, and 34% focal or complex-focal), and 34% of patients had a relapse SE. The duration of SE was less than 1 day in 36% and more than 7 days in 28% of patients. The median number of different AEDs per patient with SE used to treat epileptic status was 5.

Thirty-three percent of patients showed movement disorders, which were treated with benzodiazepines (74%), AEDs (53%), and propofol (31%). We cannot exclude that some of the movement disorders were actually epileptic events and vice versa, especially without EEG.

Other relevant complications: 26% of patients experienced severe sepsis with organ dysfunction and 7% septic shock. Ten percent underwent cardiopulmonary resuscitation. Eight percent had venous thrombosis.

Mechanical ventilation was necessary in 57% of all patients, with a median duration of 28 days (IQR: 10–54; range 1–350 days). Thirty-seven percent had to be reintubated, and 68% underwent tracheostomy during the course of ICU treatment. Fifty-four percent of the patients developed ventilator-associated pneumonia (Table 3).

**Outcome and potential prognostic factors**

The median duration of ICU stay was 24 days (IQR: 7–45), and the median duration of hospital stay was 49 days (IQR: 31–100). Ninety percent of patients showed a maximum mRS score of ≥4 (23% mRS score 4, 61% mRS score 5, and 7% mRS score 6). At the time of hospital discharge, 47% of patients showed a mRS score of ≥4 (28% mRS score 4, 15% mRS score 5, and 7.5% mRS score 6). However, 60 patients (50% of the total cohort) had improved mRS values compared with the maximum mRS value [mRS 1 (12 patients), 2 (21 patients), and 3 (27 patients)] (figure).

Fifty-five percent of patients were discharged from the ICU to regular hospital wards, and 38% were transferred to neurologic intensive care rehabilitation centers. In 18% of cases, an ethical conflict had to be resolved during the hospital stay.

Table 4 summarizes the results of the crude and the sex- and age-adjusted logistic regression analyses of the 19 potential

| Variable                                      | All n = 120 |
|-----------------------------------------------|-------------|
| Consciousness disorder, no. of patients (%)   | 101 (84)    |
| Manifestation                                 |             |
| Somnolence                                    | 40 (33)     |
| Sopor                                         | 30 (25)     |
| Coma                                          | 18 (15)     |
| Delirium                                      | 41 (34)     |
| Mutism                                        | 13 (11)     |
| Duration of consciousness disorder            |             |
| Median, d (IQR)                               | 20 (5–40)   |
| Minimum/maximum, d                            | 0–400       |
| <1 d                                          | 7           |
| 1–7 d                                        | 22          |
| 8–30 d                                        | 28          |
| >30 d                                         | 32          |
| Autonomic disorders, no. of patients (%)      | 54 (45)     |
| Manifestation                                 |             |
| Fever without infection                       | 15 (13)     |
| Hypoventilation                               | 22 (18)     |
| Hyperventilation                              | 12 (10)     |
| Tachycardia                                   | 40 (33)     |
| Bradycardia                                   | 23 (19)     |
| Other heart rhythm disorders                  | 11 (9)      |
| Blood pressure crises                         | 21 (18)     |
| Diarrhea                                      | 6 (5)       |
| Hypersalivation                               | 10 (8)      |
| Therapy, no. of patients                      |             |
| Dantrolene                                    | 3           |
| External cooling                              | 12          |
| Internal cooling                              | 7           |
| Pacemaker                                     | 11          |
| Status epileptics (SE), no. of patients (%)   | 42 (35)     |
| Manifestation                                 |             |
| Generalized SE                                | 18 (43)     |
| Focal SE                                      | 14 (33)     |
| Nonconvulsive SE                              | 15 (36)     |
| SE relapse                                    | 13 (31)     |

Table 2 AE-associated complications and clinical management

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Continued
### Table 2 AE-associated complications and clinical management (continued)

| Variable                                                                 | All n = 120 |
|--------------------------------------------------------------------------|-------------|
| **Cumulative duration of SE no. of patients (% of n = 42)**               |             |
| <1 d                                                                     | 8 (19)      |
| 1–7 d                                                                    | 15 (36)     |
| >7 d                                                                     | 7 (17)      |
| Unknown                                                                  | 12 (28)     |
| **SE detection, no. of patients (% of n = 42)**                          |             |
| Clinical                                                                 | 28 (67)     |
| EEG once                                                                 | 4 (10)      |
| EEG several times                                                        | 28 (67)     |
| EEG monitoring                                                           | 10 (23)     |
| **Therapy SE, no. of antiepileptic drugs (AEDs) used (% of n = 42)**     |             |
| AED, median no. of different AEDs                                         | 5           |
| AED ≤ 4, no. of patients (%)                                             | 21 (50)     |
| AED > 4, no. of patients (%)                                             | 21 (50)     |
| **Movement disorders, no. of patients (% of n = 120)**                   |             |
| Manifestation (% of n = 39)                                              |             |
| Generalized                                                              | 13 (39)     |
| Focal                                                                    | 23 (58)     |
| Othersa                                                                  | 22 (56)     |
| Complications of movement disorders                                      | 11 (28)     |
| **Therapy movement disorders (% of n = 39)**                             |             |
| Benzodiazepines                                                          | 29 (74)     |
| AED                                                                      | 21 (53)     |
| Isoflurane                                                               | 2 (5)       |
| Propofol                                                                 | 12 (31)     |
| Othersb                                                                  | 14 (36)     |
| Other complications, no. of patients (% of n = 120)                      | 63 (53)     |
| Severe sepsis                                                            | 31 (26)     |
| Septic shock                                                             | 8 (7)       |
| Cardiopulmonary resuscitation                                           | 12 (10)     |
| Surgical complications                                                   | 7 (6)       |
| Venous thrombosis                                                        | 10 (8)      |
| Othersc                                                                  | 49 (42)     |

*Bruxism and axial rigor.  
Opoids, atypical neuroleptics, and L-dopa.  
Pneumothorax, ICU-acquired weakness, self-injury, pleural effusions, suicide attempt, pulmonary embolism, rhabdomyolysis, allergic reaction, lies, catheter infection, transfusion-dependent anemia, and severe electrolyte derangement.

### Table 3 ICU complications and outcome

| Variable                                                                 | All n = 120 |
|--------------------------------------------------------------------------|-------------|
| **Mechanical ventilation (MV), no. of patients (% of n = 120)**           |             |
| Duration of MV, median, d (IQR)                                          | 28 (10–54)  |
| Minimum/maximum, d                                                       | 0/350       |
| **Reasons for MV, no. of patients (% of n = 68)**                         |             |
| Consciousness disorder                                                  | 47 (69)     |
| Respiratory insufficiency                                                | 36 (53)     |
| Missing protection reflexes                                             | 29 (34)     |
| **Hypoventilation**                                                      | 6 (9)       |
| Pneumonia                                                                | 13 (19)     |
| Othersa                                                                  | 9 (13)      |
| **Intubation, no. of patients (% of n = 68)**                            | 63 (93)     |
| Reintubation                                                             | 25 (37)     |
| **Tracheal cannula (TC)**                                                | 46 (68)     |
| **Duration intubation to TC, median, d**                                 | 10          |
| **Complications of MV, no. of patients (% of n = 68)**                    |             |
| Pleura drainage                                                          | 5 (7)       |
| Acute respiratory distress syndrome                                      | 4 (6)       |
| Ventilator-associated pneumonia                                          | 37 (54)     |
| Othersb                                                                  | 19 (28)     |
| **Ethical consideration, no. of patients (% of n = 120)**                 | 21 (18)     |
| Change of therapy target                                                | 8 (7)       |
| DNR/DNI                                                                  | 2 (2)       |
| Treatment discontinuation                                                | 2 (2)       |
| Ethical counseling                                                       | 2 (2)       |
| Othersc                                                                  | 6 (5)       |
| **Outcome ICU stay, no. of patients (% of n = 120)**                      |             |
| Transfer to regular hospital ward                                        | 68 (57)     |
| Transfer to neurointensive care rehabilitation                           | 46 (38)     |
| Deceased                                                                 | 9 (7.5)     |
| **Duration ICU stay, median, d (IQR)**                                   | 24 (7–45)   |
| **Minimum/maximum, d**                                                  | 1/400       |
| **Duration hospital stay, median, d (IQR)**                              | 49 (31/100) |
| **Minimum/maximum, d**                                                  | 1/1978      |

Abbreviations: DNR = do-not-resuscitate order; DNI = do-not-intubate order; IQR = interquartile range.  
* Sedation in psychosis, status epilepticus, and severe sepsis.  
* Sedation in psychosis, status epilepticus, and severe sepsis.  
* Recurrent pneumonia, difficult airway, severe sepsis, intubation injury, and pneumothorax.  
* Dismissal against medical advice, personal risk, and extraneous endangering.
First, autonomic dysfunction, associated with worse outcome, is critical in a major subset of patients. It is an intrinsic aspect of AE, particularly NMDA receptor encephalitis (RE), which represents the largest patient group within our cohort.\(^5,7,10,11\)

Thus, autonomic dysfunction can be regarded as being a disease-specific risk factor or indicator for poor outcome. It can be hypothesized to be a causative trigger factor for further intensive care–associated complications, e.g., hypotension requiring vasopressors or respiratory dysfunction requiring mechanical ventilation resulting in ventilator-associated pneumonia.

Second, similar to ICU patients with diseases other than AE, severe sepsis and septic shock were strongly related to worse neurologic outcome.\(^12\) Of interest, the proportion of patients who developed severe sepsis and septic shock that resulted in organ dysfunction (33%) was more than doubled in patients with severe AE compared with the general ICU population in Germany with a rate of 13% in 1 study.\(^13\) Treatment-induced immunosuppression, autonomic dysfunction, and a longer duration of mechanical ventilation most likely contributed to the increased proportion of sepsis and sepsis-induced organ dysfunction in our cohort.

Third, paraneoplastic origin (teratoma and other tumors in 21% of patients) was strongly associated with worse outcome as measured by the dichotomized mRS score. This is in accordance with previous reports focusing on NMDA-RE. Here, tumor removal led to faster improvement and fewer relapses.\(^5,14\)

In addition to the aforementioned disease-related factors, prolonged mechanical ventilation is associated with worse outcome. Here, similar results have been reported in acute encephalitis of all etiologies.\(^2,15\) A number of conditions are associated with the need for long-term respiratory support in this severely affected patient cohort including the increased risk of infection and pneumonia due to immunosuppression and the development of ICU-acquired weakness, which frequently affects critically ill patients and contributes to worse acute outcome and long-term mortality.\(^16\) Surprisingly, status epilepticus was not associated with a deterioration of neurologic outcome, although it was detected in a relevant subset of 35% of all patients. However, there was a slight tendency wherein pathologic EEG findings to be more frequently associated with a worse outcome. In clinical practice, seizure-related myoclonic activity may be difficult to differentiate from dyskinetic and stereotypic movements associated with certain AE subtypes. Therefore, the rate of status epilepticus in these patients may be overestimated, leading to decreased specificity in the evaluation of this factor in correlation with clinical outcome.

Paraclinical findings, e.g., pleocytosis and increased CSF protein levels, abnormal cerebral MRI, or FDG-PET are helpful for the diagnostic workup\(^17\) but are apparently not relevant for evaluating the risk of poor clinical outcome after ICU therapy. Although antineuronal autoantibodies were detected in 85 patients (71%), mostly NMDA-R antibodies (in 53 patients), these findings did not predict a negative or a positive neurologic outcome. This result is of relevance to

**Discussion**

The findings of our study provide a number of relevant insights regarding prognostic factors for outcome in severely affected patients with AE. These insights may increase awareness of the potential poor prognostic factors in patients with AE requiring ICU treatment.

First, autonomic dysfunction, associated with worse outcome, is critical in a major subset of patients. It is an intrinsic aspect
Disorders of consciousness such as delirium have recently been identified as a risk factor for developing long-term cognitive dysfunction after surviving sepsis in a large cohort of ICU patients. Our data showed no evidence for an association of altered consciousness with regard to the short-term outcome in our study. However, neurocognitive dysfunction is a major factor influencing the overall condition and is highly relevant for patients for managing their daily activities, it is therefore also relevant for evaluating in the patients’ mRS scores. The study design did not include a regular neuropsychological assessment at hospital discharge and no follow-up evaluation of patients. Because most patients exhibited mRS scores above 3, for which cognitive dysfunction is less significant, the relevance of consciousness disorders on overall outcome may be underestimated. It would be interesting to conduct a future study evaluating neurocognitive dysfunction in either this or a similar patient cohort as a long-term follow-up similar to what has already been undertaken in NMDA-RE-cohorts.²⁰

Our patients showed severe deficits: 90% of patients had a maximum mRS score 4–6 during their disease course. At the time of ICU discharge, however, this improved remarkably in 75% of the surviving patients, with only 48% of patients showing an mRS value of ≥4 (28% mRS 4 and 15% mRS 5). The hospital mortality rate of 7.5% in our cohort was almost identical with the recently published ICU NMDA-RE study. However, in other cohorts with AE, the reported mortality was much higher.²,¹¹–²³ The reasons for this low mortality might be the improved treatment and earlier recognition and diagnosis of AE. In addition, there might also be a bias attributable to the fact that relatives/spouses of deceased patients refused their informed consent.

Neuro-ICU management in patients with AE frequently involves a long period of care. Therefore, complications, sometimes severe, occur in a majority of patients. More detailed knowledge of the individual prognosis based on well-

### Table 4

Potential prognostic factors of the neurologic outcome at hospital discharge according to the dichotomized modified Rankin Scale (mRS)

| Potential prognostic factor | Crude OR (95% CI) | p-value (2-sided) | Adjusted OR (95% CI) | p-value (2-sided) |
|-----------------------------|------------------|-------------------|----------------------|-------------------|
| S Prodromal symptoms [absent] | 1.03 (0.44–2.41) | 0.95 | 1.28 (0.52–3.19) | 0.59 |
| Y Consciousness disorder [absent] | 1.80 (0.63–5.57) | 0.28 | 2.39 (0.8–7.84) | 0.13 |
| M Somnolence [absent] | 1.41 (0.64–3.09) | 0.39 | 1.36 (0.61–3.05) | 0.45 |
| P Autonomic dysfunction [absent] | 1.69 (0.8–3.59) | 0.17 | 2.91 (1.24–7.3) | 0.02 |
| T Status epilepticus [absent] | 0.90 (0.42–1.92) | 0.78 | 0.95 (0.43–2.09) | 0.91 |
| O Other complications [absent] | 4.21 (1.95–9.42) | 3.3 × 10⁻⁴ | 4.45 (1.99–10.43) | 3.9 × 10⁻⁴ |
| M Sepsis/septic shock [absent] | 3.97 (1.67–10.11) | 2.4 × 10⁻³ | 4.54 (1.84–12.11) | 1.5 × 10⁻³ |
| W Pathologic CSF [absent] | 0.76 (0.21–2.71) | 0.67 | 0.94 (0.25–3.5) | 0.92 |
| O Pathologic MRI brain imaging [absent] | 0.91 (0.41–2.03) | 0.82 | 0.79 (0.34–1.81) | 0.57 |
| R Pathologic EEG [absent] | 0.35 (0.12–0.90) | 0.04 | 0.40 (0.14–1.09) | 0.08 |
| K Pathologic PET brain imaging [absent] | 0.76 (0.32–1.73) | 0.51 | 0.53 (0.21–1.28) | 0.17 |
| U Tumor [absent] | 3.82 (1.43–11.49) | 0.01 | 3.73 (1.35–11.57) | 0.01 |
| P Autoantibody [absent] | 0.84 (0.38–1.85) | 0.66 | 1.01 (0.44–2.33) | 0.98 |
| Autoantibody in CSF [absent] | 1.11 (0.53–2.35) | 0.78 | 1.46 (0.66–3.31) | 0.35 |
| Autoantibody in serum [absent] | 0.78 (0.37–1.66) | 0.53 | 0.90 (0.41–1.98) | 0.80 |
| T Mechanical ventilation [absent] | 5.78 (2.60–13.61) | 3.0 × 10⁻⁵ | 6.28 (2.71–15.61) | 3.5 × 10⁻⁵ |
| H Duration of ventilation [days] | 1.03 (1.02–1.05) | 3.8 × 10⁻¹⁴ | 1.03 (1.02–1.06) | 2.1 × 10⁻⁴ |
| E Tracheostomy [absent] | 4.98 (2.24–11.57) | 1.2 × 10⁻⁴ | 6.26 (2.68–15.73) | 4.5 × 10⁻⁵ |
| R Ethical considerations [absent] | 1.3 (0.48–3.55) | 0.61 | 1.52 (0.54–4.39) | 0.43 |

Effect size estimates (with 95% CI) are provided such that ORs > 1 indicate a correlation with a worse outcome (usually with the presence of a pathologic finding). The reference category or unit is provided in square brackets. Adjusted ORs were adjusted only for sex and age (linear) because of the limited number of patients. Left column: SYMPTOM—main symptoms and ICU complications; WORKUP—diagnostic findings; THER—therapeutic management and ethical considerations.
defined risk factors will aid decision making by both physicians and family members/spouses with regard to ICU treatment in supposedly treatment-resistant cases. Consequently, ethical decisions will have to be addressed. For example, 10 women underwent ovariectomy and were confronted with a lifelong challenge regarding family planning after surviving their acute illness. The discussion on the necessity of explorative or even prophylactic ovariectomy has increased recently as evidenced in 2 case reports of postencephalitic ovary removal 1 year after initial NMDA-RE in adolescent patients without symptoms.24 Issues resulting in lifelong consequences for patients need to be further addressed, in particular, because data, for example, on tumor incidence in different age groups11 and ethnicities10 show differential results.

Our analysis was performed using retrospectively collected patient data obtained from a subgroup of 120 patients who required ICU treatment. These patients were revealed from a nationwide cohort in Germany, which in the meantime consists of more than 750 patients with AE (GENERATE cohort; generate-net.de/). To our knowledge, this cohort of 120 patients represents the largest reported cohort of critically ill patients with AE who underwent ICU treatment compared with previous studies with patients with AE1,4,7,21,22 and mixed encephalitis cohorts including AE subgroups.2,15,25,26

This notwithstanding, some limitations need to be discussed herein:

First, the study is a noninterventional retrospective analysis and therefore not suitable for detecting cause and effect relationships.

Second, patients with a date of disease onset between 2004 and 2016 were enrolled in the study. During this time, awareness of AEs and antibody testing increased, reducing the time to treatment. Furthermore, while planning the study, the inclusion criteria were based on the encephalitis criteria as published by Granerod et al.1 Since then, the Graus criteria have been published in February 2016.8 According to the Graus criteria, the 35 patients without evidence of autoantibody in CSF or serum have been considered as possible AE rather than definite AE. Although, from a clinical standpoint, it still seems reasonable to include these patients in our cohort, although they were antibody negative. In addition, ICU management probably remained relatively unchanged. The continuing analysis of the present cohort will focus on the influence of (German) guidelines on AE management.27

Third, the 120 cases included in our study did not allow for a more profound analysis of rare or less frequent potential prognostic factors. Note that the statistical power for 120 patients is rather limited. Therefore, further adjustments or multiple testing corrections were not applied. In addition, a documentation bias should be mentioned. Clearly, extended clinical interpretations of our findings could only be justified on the basis of their confirmation in an independent dataset. Finally, the primary end point focused on outcome data at “hospital discharge” because it was not possible to obtain follow-up data of the patients, which might provide further important information, e.g., on long-term cognitive function.

Ultimately, our aim is that the data gathered within the tight network and close cooperation will provide evidence-based support with regard to ICU management and may be of advantage for counseling patients and relatives during a severe and threatening course of an autoimmune disease according to the relevant influencing factors.

The spectrum of ICU complications and the severity of the underlying disease reflect some general ICU- and specific AE-related features. Of interest, and despite early targeted immunotherapy,7 clinically highly threatening courses of AE still occur. Focusing on the earliest possible clinical diagnosis according to the Graus criteria8 may foster earlier immunotherapy. Moreover, these critical disease courses underscore the need for novel, target-specific treatment approaches beyond immunotherapy. Future studies should reveal whether such clinical rather than diagnostic-based approaches will result in less ICU complications in patients with AE. Cooperation and dialogue within a network such as GENERATE and IGNITE might be beneficial to AE-related ICU treatment because they could lead to an interdisciplinary evaluation of earlier and if necessary more aggressive management of AE resulting in better short- and long-term outcomes.

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served on the scientific advisory boards of Merck Serono, Sanofi-Aventis, and BARD and received travel funding and/or speaker honoraria from Merck Serono, Sanofi-Aventis, Teva, Biogen, Novartis, and Roche. C. Dohmen reports no disclosures. J. Bosel received travel funding and speaker honoraria from Bard, Zoll, Sedana Medical, Medtronic, and Boehringer Ingelheim; served on the editorial boards of *Neurocritical Care* and *Neurology Research and Practice*; receives publishing royalties from Thieme; and received research support from DGNI. J. Lewerenz received speaker honoraria and/or travel funding from Euroimmun, Teva, CHDI, and Movement Disorders Society and oversees a laboratory of a nonprofit hospital that offers testing for antineuronal and onconeuronal antibodies. F. Thaler, A. Kraft, and A. Juranek report no disclosures. M. Ringelstein received travel funding and/or speaker honoraria from Novartis, Ipsen, Bayer, Biogen, Genzyme, Teva, Merz, and Merck. K.-W. Suehs served on the scientific advisory board of Merck and received travel funding from Merck. C. Urbanek and A. Scherag report no disclosures. C. Geis received travel funding from Merck Serono; served as a guest editor of *Frontiers Neurology*; and received research support from the German Research Foundation and the German Ministry of Education. O.W. Witte served on the editorial boards of *Das Neurophysiologie-Labor* and *Zeitschrift für klinische Neurophysiologie* and received research support from the German Research Foundation, Thuringian Ministry for Education, Science and Culture, Federal Ministry for Research and Technology, and European Union. E. Kroner reports no disclosures. A. Guenther received travel funding and/or speaker honoraria from Merz, Ipsen, Boehringer Ingelheim, Pfizer, Daiichi Sankyo, and Bayer. Full disclosure form information provided by the authors is available with the full text of this article at Neurology.org/NN.

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### Appendix 1 Author contributions

| Name                        | Location                          | Role                  | Contribution                                                                 |
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| Julia Schubert, MD          | University of Jena, Jena, Germany  | Author                | Designed and conceptualized the study; analyzed the data; and drafted the manuscript for intellectual content |
| Dirk Brämer, MD             | University of Jena, Jena, Germany  | Author                | Designed and conceptualized the study; analyzed the data; and drafted the manuscript for intellectual content |
| Hagen B. Huttner, MD        | University of Erlangen, Erlangen, Germany | Author                | Major role in the acquisition of data and interpretation of data and revised the manuscript for intellectual content |
| Stefan T. Gerner, MD        | University of Erlangen, Erlangen, Germany | Author                | Major role in the acquisition of data and interpretation of data and revised the manuscript for intellectual content |
| Hannah Fuhrer, MD           | University of Freiburg, Freiburg, Germany | Author                | Major role in the acquisition of data and interpretation of data |
| Nico Melzer, MD             | University of Münster, Münster, Germany | Author                | Major role in the acquisition of data and interpretation of data and revised the manuscript for intellectual content |
| André Dik, MD               | University of Münster, Münster, Germany | Author                | Major role in the acquisition of data |
| Harald Prüss, MD            | Charité University Medicine, Berlin, Germany | Author                | Major role in the acquisition of data and interpretation of data |
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| Franziska Thaler, MD        | University of Munich, Munich, Germany | Author                | Major role in the acquisition of data |

Continued
### Appendix 1 (continued)

| Name                  | Location                                      | Role                                      | Contribution                                                   |
|-----------------------|-----------------------------------------------|-------------------------------------------|----------------------------------------------------------------|
| Andrea Kraft, MD      | Martha Maria Hospital, Halle, Germany         | Author                                   | Major role in the acquisition of data                         |
| Aleksandra Juranek, MD| Dortmund Hospital, Dortmund, Germany          | Author                                   | Major role in the acquisition of data                         |
| Marius Ringelstein, MD| University of Düsseldorf                      | Author                                   | Major role in the acquisition of data                         |
| Kurt-Wolfram Sühs, MD | University of Hannover, Hannover, Germany     | Author                                   | Major role in the acquisition of data                         |
| Christian Urbanek, MD | Hospital Ludwigshafen, Ludwigshafen, Germany   | Author                                   | Major role in the acquisition of data                         |
| André Scherag, PhD    | University of Jena, Jena, Germany              | Author                                   | Planned and performed biostatistical analyses and interpretation of data and revised the manuscript for intellectual content |
| Christian Geis, MD    | University of Jena, Jena, Germany              | Author                                   | Major role in the acquisition of data and revised the manuscript for intellectual content |
| Otto W. Witte, MD     | University of Jena, Jena, Germany              | Author                                   | Designed and conceptualized the study and revised the manuscript for intellectual content |
| Albrecht Günther, MD  | University of Jena, Jena, Germany              | Author                                   | Designed and conceptualized the study, performed acquisition of data, analyzed the data, and drafted the manuscript for intellectual content |

### References

1. Graneros J, Ambrose HE, Davies NWS, et al. Causes of encephalitis and differences in their clinical presentations in England: a multicenter, populations-based prospective study. *Lancet Infect Dis* 2010;10:835–844.
2. Singh TD, Fugate JE, Rabinstein AA. The spectrum of acute encephalitis: causes, management, and predictors of outcome. *Neurology* 2015;84:359–366.
3. Davies G, Irani SR, Coltart C, et al. Anti-N-methyl-D-aspartate receptor antibodies: a potentially treatable cause of encephalitis in the intensive care unit. *Crit Care Med* 2010;38:679–682.
4. Mittal MK, Rabinstein AA, Hocker SE, Pittock SJ, Wijdicks EFM, McKeon A. Autoimmune encephalitis in the ICU: a analysis of phenotypes, serologic findings, and outcomes. *Neurocrit Care* 2016;24:240–250.
5. Titulaer MJ, McCracken L, Gab lidslo I, et al. Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. *Lancet Neurol* 2013;12:157–165.
6. Prüssl H, Dalmau J, Harms L, et al. Retrospective analysis of NMDA receptor antibodies in encephalitis of unknown origin. *Neurology* 2010;75:1735–1739.
7. de Montmollin E, Demeret S, Brulé N, et al. Anti-N-methyl-D-aspartate receptor encephalitis in adults requiring intensive care. *Am J Respir Crit Care Med* 2017;195:491–499.
8. Graus F, Titulaer MJ, Bale R, et al. A clinical approach to diagnosis of autoimmune encephalitis. *Lancet Neurol* 2015;15:391–404.
9. van Swieten JC, Koudstaal PJ, Visser MC, et al. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke* 1988;9:604–607.
10. Dalmau J, Lancaster E, Martinez-Hernandez E, Rosenfeld MR, Balice-Gordon R. Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. *Lancet Neurol* 2011;10:63–74.
11. Titulaer MJ, McCracken L, Gab lidslo I, et al. Late-onset anti-NMDA receptor encephalitis. *Neurology* 2013;81:1058–1063.
12. Vincent JL, Saxer P, Sprung CL, et al. Sepsis in European intensive care units: results of the SOAP study. *Crit Care Med* 2006;34:344–353.
13. SepNet Critical Care trials Group. Incidence of severe sepsis and septic shock in German intensive care units: the prospective, multicentre INSEP study. *Intensive Care Med* 2016;42:1980–1989.
14. Dalmau J, Gleichman AJ, Hughes EG, et al. Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. *Lancet Neurol* 2008;7:1091–1098.
15. Thalau KT, Motta M, Asemota AO, et al. Predictors of outcome in acute encephalitis. *Neurology* 2013;81:793–800.
16. Hermans G, Van den Berge G. Clinical review: intensive care acquired weakness. *Crit Care* 2015;19:274.
17. Tripathi M, Tripathi M, Roy SG, et al. Metabolic topography of autoimmune non-paraneoplastic encephalitis. *Neurodeontology* 2018;60:189–198.
18. Dalmau J, Geis C, Graus F. Autoantibodies to synaptic receptors and neuronal cell surface proteins in autoimmune diseases of the central nervous system. *Physiol Rev* 2017;97:839–887.
19. Iwashyna TJ, Ely EW, Smith DM, Langa KM. Long-term cognitive impairment and functional disability among survivors of severe sepsis. *JAMA* 2010;304:1787–1794.
20. Finke C, Kopp U, Prüss H, et al. Cognitive deficits following anti-NMDA receptor encephalitis. *J Neurol Neurosurg Psychiatry* 2012;83:195–198.
21. Harutyunyan G, Hauer L, Dünser MW, et al. Autoimmune encephalitis at the neurological intensive care unit: etiologies, reasons for admission and survival. *Neurocrit Care* 2017;27:82–89.
22. Harutyunyan G, Hauer L, Dünser MW, et al. Risk factors for intensive care unit admission in patients with autoimmune encephalitis. *Front Immunol* 2017;8:833.
23. Chi N, Wang W, Huang C, et al. Risk factors for mortality in patients with anti-NMDA receptor encephalitis. *Brain Dev* 2017;39:448–451.
24. Omata T, Kodama K, Watanabe Y, et al. Ovarian teratoma development after anti-NMDA receptor encephalitis. *Acta Neurol Scand* 2017;136:298–304.
25. Chen X, Li JM, Liu F, Wang Q, Zhou D, Lai X. Anti-N-methyl-D-aspartate receptor encephalitis: a common cause of encephalitis in the intensive care unit. *Neurosci Lett* 2016;57:1989–1993.
26. Sonneville R, Gault N, de Montmollin E, et al. Clinical spectrum and outcomes of their clinical presentations in England: a multicenter, populations-based prospective study. *Lancet Infect Dis* 2010;10:835–844.
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