Received: 25 July 2022 | Accepted: 23 September 2022

DOI: 10.1111/ene.15585

european journal of neurology
the official journal of the european academy of neurology

ORIGINAL ARTICLE

Clinical characteristics, treatments, outcome, and prognostic factors of severe autoimmune encephalitis in the intensive care unit: Standard treatment and the value of additional plasma cell–depleting escalation therapies for treatment-refractory patients

Lisa Schwarz[1] | Nilufar Akbari[2] | Harald Prüss[1,3] | Andreas Meisel[1,4] | Franziska Scheibe[1,4]

[1]Department of Neurology and Experimental Neurology, Charité – Universitätsmedizin Berlin, Berlin, Germany

[2]Institute of Biometry and Clinical Epidemiology, Charité – Universitätsmedizin Berlin, Berlin, Germany

[3]German Center for Neurodegenerative Diseases Berlin, Berlin, Germany

[4]Charité – Universitätsmedizin Berlin, NeuroCure Clinical Research Center, Berlin, Germany

Correspondence
Franziska Scheibe, Department of Neurology and Experimental Neurology, Charité - Universitätsmedizin Berlin, Charitéplatz 1, 10117 Berlin, Germany.
Email: franziska.scheibe@charite.de

Funding information
NeuroCure Clinical Research Center (NCRC), funded by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation), Grant/Award Number: EXC 2049-89829218

Abstract

Background and purpose: To investigate severe autoimmune encephalitis (AE) in the intensive care unit (ICU) with regard to standard treatment in responsive patients and additional escalation therapies for treatment-refractory cases.

Methods: This retrospective, single-center study analyzed medical records of ICU-dependent AE patients for clinical characteristics, treatments, prognostic factors, and neurological outcome as quantified by modified Rankin Scale (mRS) and Clinical Assessment Scale for Autoimmune Encephalitis (CASE).

Results: From 40 enrolled patients (median age = 52 years; range = 16–89 years) with AE mediated by neuronal surface antibodies (nsAb; 90%) and AE with onconeuronal antibodies (10%), 98% received first-line therapy. Of those, 62% obtained additional second-line therapy, and 33% received escalation therapy with bortezomib and/or daratumumab. Good neurological outcome, defined as mRS = 0–2, was observed in 47% of AE with nsAb (CASE = 5), 77% of anti-N-methyl D-aspartate receptor encephalitis patients (CASE = 1), whereas AE patients with onconeuronal antibodies had the poorest outcome (mRS = 6, 100%). Treatment-refractory AE patients with nsAb requiring escalation therapy achieved similarly good recovery (mRS = 0–2, 39%, CASE = 3) as patients improving without (mRS = 0–2, 54%, CASE = 4), although they presented a higher disease severity at disease maximum (mRS = 5 100% versus 68%, CASE = 24 versus 17; $p = 0.0036$), had longer ICU stays (97 versus 23 days; $p = 0.0002$), and a higher survival propability during follow-up ($p = 0.0203$). Prognostic factors for good recovery were younger age ($p = 0.025$) and lack of preexisting comorbidities ($p = 0.011$).

Conclusions: Our findings suggest that treatment-refractory AE patients with nsAb in the ICU can reach similarly good outcomes after plasma cell–depleting escalation therapy as patients already responding to standard first- and/or second-line therapies.

KEYWORDS
autoimmune encephalitis, bortezomib, daratumumab, intensive care unit, plasma cell depletion

INTRODUCTION

The clinical spectrum of autoimmune encephalitis (AE) consists of AE with neuronal surface antibodies (nsAb), in which autoreactive antibodies directly induce brain dysfunction, often with good response to immunotherapy [1, 2]. Classic AE with onconeuronal antibodies is accompanied by structural brain damage mediated by dysregulated T cells. Here, immunosuppression only prevents further disease progression, mostly without clinical improvement [3].

Treatment in the intensive care unit (ICU) is the major risk factor for an unfavorable long-term outcome of AE patients. It is required in about 55% of AE cases [4] and is linked with higher mortality (18.5%–40%) [5, 6]. Further risk factors for poor outcome include disease severity, missing treatment response to standard first- and/or second-line immunotherapies, length of ICU stay, frequency of ICU complications, time until treatment initiation, comorbidities, and age [7–9]. Especially in AE with nsAb, these factors are used to evaluate neurological prognosis at the acute disease stage and are considered in clinical end-of-life decisions of unresponsive patients with prolonged ICU stays. The reasons for treatment resistance in some AE patients with nsAb are not fully understood, but long-lived plasma cells are considered as crucial in maintaining chronic autoimmune processes because they cannot be reached by rituximab and cyclophosphamide [10, 11]. First case reports and small case series identified strategies with B-cell, short-lived, and long-lived plasma cell depletion by use of rituximab in combination with the proteasome inhibitor bortezomib or the anti-cluster of differentiation (CD38) antibody daratumumab, as promising treatment approaches to improve clinical outcome in treatment-refractory, antibody-mediated AE [10–13]. Similar results were observed in other autoimmune disorders like systemic lupus erythematosus [14, 15], neuromyelitis optica [16], or chronic inflammatory demyelinating polyneuropathy [17].

Thus, our study analyzed 40 patients with ICU-dependent AE for clinical characteristics, diagnostics, prognostic factors, and clinical outcomes regarding standard treatment in responsive patients versus additional escalation therapies for treatment-refractory cases.

METHODS

Patients, study design, and data collection

This retrospective study enrolled all patients treated in the neurological ICU at Charité–University Hospital Berlin, Germany between May 2008 and August 2020 who were diagnosed with AE with nsAb or AE with onconeuronal antibodies, fulfilling the diagnostic criteria by Graus et al. that distinguishes between possible, probable, and definitive AE [18]. Data were extracted from medical records and analyzed for demographic information, clinical symptoms, disease course, applied diagnostics like laboratory tests, radiological examinations (magnetic resonance imaging [MRI], positron-emission tomography-computed tomography [PET-CT]), electroencephalogram (EEG), and applied therapies with treatment responses. Known AE antibodies were determined by cell-based indirect immunofluorescence assays at Labor Berlin or Euroimmun, Germany. Antibodies against unknown epitopes were detected by indirect immunofluorescence on mouse brain slides as previously described [19].

Treatment protocols

Application of first-line therapies included 1 g methylprednisolone intravenously over 3–5 days, intravenous immunoglobulins of 1–2 g/kg, plasma exchange, and immunoadsorption. Second-line therapies comprised rituximab and cyclophosphamide. Rituximab was administered with 2 × 1000 mg intravenously within 14 days as treatment induction, and each further application counted as an additional cycle. Cyclophosphamide was induced as the first cycle with 350 mg/m^2 intravenously over 3 days and was continued with 600 mg/m^2 or 1000 mg absolute dose for each further cycle. Escalation therapies were applied with either one to eight cycles of 1–1.3 mg/m^2 bortezomib intravenously or subcutaneously at day 1, 4, 8, and 11 of each cycle and/or four to 13 cycles of 16 mg/kg daratumumab intravenously in weekly intervals for the first eight cycles and thereafter in 2-week intervals according to previously published protocols [10–12].

Outcome evaluation

Common ICU scores such as the Simplified Acute Physiology Score (SAPS II), Acute Physiology and Chronic Health Classification System II (APACHE II), Sepsis-Related Organ Failure Assessment (SOFA) score, and Simplified Therapeutic Intervention Scoring System 28 (TISS-28) were used to objectify ICU disease severity of AE patients at ICU admission, disease maximum, and ICU discharge. Neurological disease severity was assessed by chart-based neurological status evaluation during ICU/hospital stay with retrospective scoring of modified Rankin Scale (mRS) and Clinical Assessment Scale for Autoimmune Encephalitis (CASE) [20, 21]. The CASE score ranging from 1 to 27 points indicated higher AE severity with increasing values [21]. Long-term follow-up with final neurological outcome was evaluated by review of hospital records from outpatient follow-up visits and/or readmission/discharge letters (75%, $n = 30$), by structured telephone interview of patients/legal guardians (25%, $n = 10$) with a questionnaire containing items of mRS and CASE score (Appendix S1), and inquiries of the date of death from state authorities. Good outcome was defined as mRS = 0–2 and unfavorable outcome as mRS = 3–6.

Statistical analysis

All descriptive data are presented as median (minimum/maximum, interquartile range [IQR]) throughout the entire article. Due to the small sample size, nonparametric tests were used for continuous variables. Applied statistical tests included Kruskal-Wallis test, Mann-Whitney *U* test, Fisher exact test, and survival probabilities were analyzed with Kaplan-Meier curves using log-rank statistics with the Mantel-Cox method. Multivariable binary logistic regressions were performed to explore prognostic factors for a good outcome (mRS = 0–2). Each analysis included one explanatory variable (i.e., age) and treatment (only first- and/or second-line or escalation therapy) as the control variable. Statistical analysis was performed by GraphPad Prism version 9.3.1 and IBM SPSS 28. p values <0.05 were considered as statistically significant.

RESULTS

Demographic and clinical characteristics

Retrospective review of medical records identified 40 AE patients; of those, 90% (n = 36) had AE with nsAb and 10% (n = 4) AE with onconeuronal antibodies (Figure 1). Median age of all patients at disease onset was 52 years (range = 16–89 years, 55% female, n = 22) (Table 1). A paraneoplastic disease was present in 33% (n = 13, 77% female, n = 10), with ovarian teratoma (31%, n = 4), small cell lung cancer (31%, n = 4), non–small cell lung cancer (23%, n = 3), breast and tongue cancer (both 8%, n = 1) being the most common tumor entities. The latency from first symptoms to diagnosis lasted 24 days (range = 0–960, IQR = 12–71) and duration of ICU stay for all patients comprised 38 days (range = 6–378, IQR = 21–95). Nearly all patients (95%, n = 38) required mechanical ventilation (15% noninvasive, n = 6; 80% invasive, n = 32) for a duration of 24 days (range = 1–271, IQR = 5–70) (Table 1).

The most frequent AE symptoms were disturbance of consciousness (95%, n = 38), neuropsychiatric symptoms (73%, n = 29), movement disorders (60%, n = 24), autonomic dysregulation (55%, n = 22), and seizures/status epilepticus (55%, n = 22). Of those, 11 patients (50%) presented status epilepticus for a duration of 50 days (range = 14–272, IQR = 25–158) and were treated with several antiepileptic drugs and sedatives. Increased intracranial pressure was identified in 8% (n = 3; Table 2). Treatments of AE symptoms are depicted in Table S1 and most common ICU complications in Table S2.

Diagnostic results

Cerebrospinal fluid (CSF) analysis was performed in all AE patients (100%, n = 40) with pleocytosis in 60% (n = 24, median = 42/µl, range = 6–547/µl), elevated protein levels in 45% (n = 18, median = 761 mg/L, range = 460–2305 mg/L), and oligoclonal bands tested in 95% (n = 38) were found positive in 23% (n = 9) and intrathecal immunoglobulin synthesis was detected in 50% (n = 20). 58% (n = 7/12) of AE patients with nsAb against unknown epitopes revealed positive immunostaining of serum and CSF in indirect immunofluorescence on mouse brain sections, supporting the diagnosis of antibody-mediated AE (Table 3).

MRI was performed in 95% (n = 38) of patients with normal results or only unspecific changes in 53% (n = 20) and pathologic findings related to AE in 47% (n = 18) of cases (limbic encephalitis 26%, n = 10; basal ganglia abnormalities 21%, n = 8; cranial nerve abnormalities 5%, n = 2). A brain PET-CT was conducted in 58% (n = 23) and revealed normal findings in 30% (n = 7), an anterior–posterior gradient in 30% (n = 7), signs of limbic encephalitis in 17% (n = 4), and focal hypermetabolism corresponding to epileptic activity in 9% (n = 2). EEG monitoring was performed in 88% (n = 35) with abnormal results (diffuse slowing 94%, n = 33; extreme delta brush 9%, n = 3; discontinuous epileptic discharges 40%, n = 14; seizures 13%, n = 5; burst suppression pattern 15%, n = 6; status epilepticus 15%, n = 6) (Table 3).

Immunotherapy

Thirty-nine of 40 patients (98%) received immunotherapy, except one patient who died after bacterial meningitis before treatment initiation (Figure 1, Table 4). First-line immunotherapy was applied in 39 patients (98%) with methylprednisolone (79%, n = 31), intravenous immunoglobulins (62%, n = 24), plasma exchange (90%, n = 35), or immunoadsorption (15%, n = 6). Second-line therapy was administered in 24 patients (62%) with rituximab (62%, n = 24) and cyclophosphamide (13%, n = 5). Only first-line therapy was applied in 38% (n = 15; repetitive first-line therapy in n = 4; responders: n=10, nonresponders: n=5 died without improvement [AE with nsAb n = 2, AE with onconeuronal Ab n = 3]), and first- and second-line therapy was administered in 62% (n = 24). Of those, 8% (n = 3) improved sufficiently, whereas 54% (n = 21) showed little or no improvement. Repetition of first- and/or second-line therapy was performed in 49% (n = 19) and induced remission in 18% (n = 7), whereas one AE patient with onconeuronal antibodies died later without improvement. 33% (n = 13; of those n = 2 were not exposed to repetitive first- and/or second-line therapy) remained without treatment response, but sufficiently improved after escalation therapy with bortezomib (23%, n = 9) or daratumumab (13%, n = 5; one patient received bortezomib and daratumumab [11]) (Figure 1, Table 4).

The latency from first symptoms to treatment initiation lasted 27 days (range = 0–960, IQR = 11–62, n = 39). 85% (n = 33) of AE patients with nsAb were responsive to immunotherapy with beginning clinical improvement after 30 days of treatment (range = 2-546, IQR = 15–125). The time window between initiation of treatment and first responses varied between the different patient subgroups. Patients with only first- and second-line therapy (n = 20) exhibited relatively fast treatment responses after

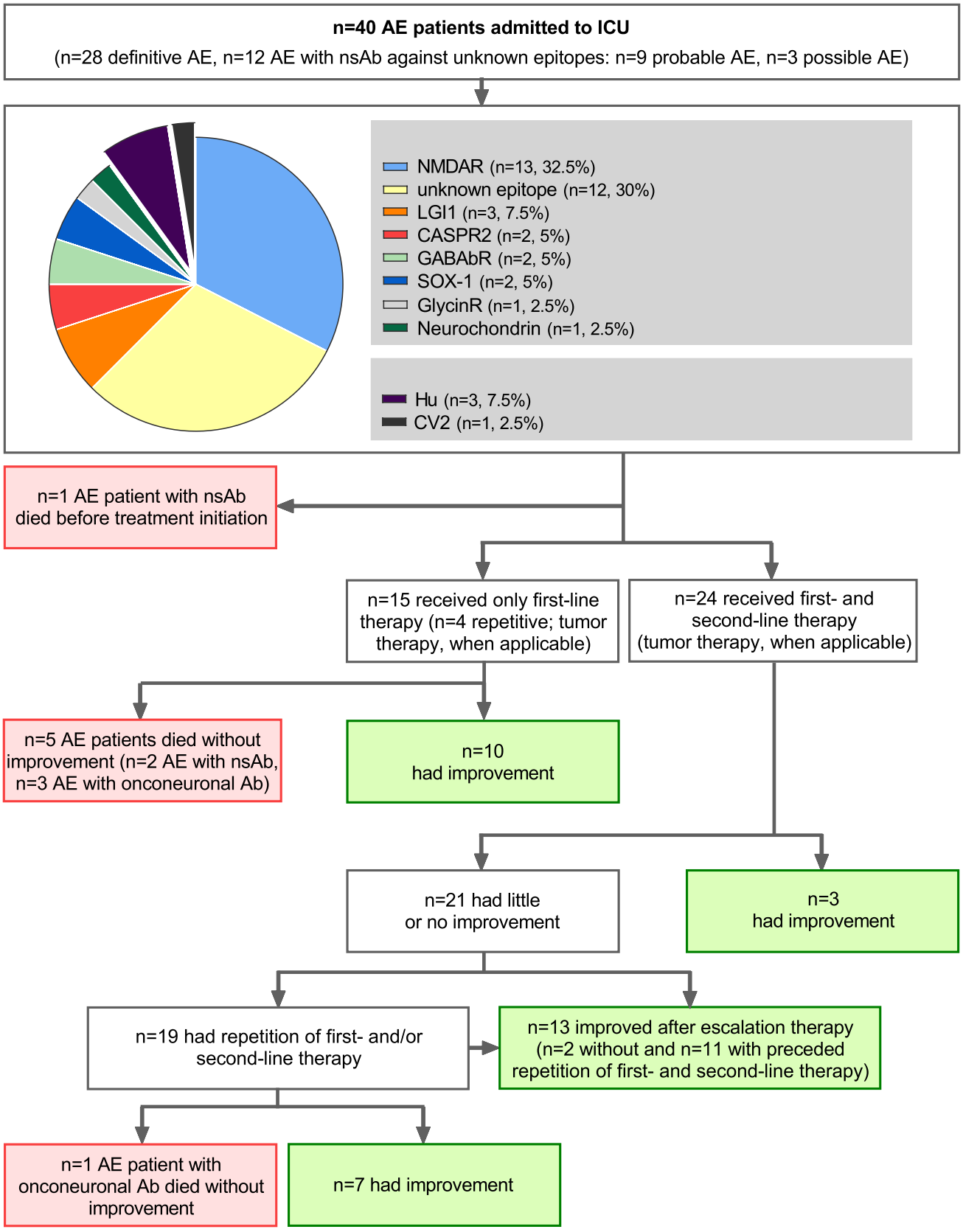


FIGURE 1 Overview of the study cohort with regard to autoimmune encephalitis (AE) disease spectrum, applied immunotherapies, and treatment responses. Ab, antibody; CASPR2, contactin-associated protein-like 2; CV2, collapsin response mediator protein (CRMP)5; GABAbR, gamma-aminobutyric acid-B-receptor; GlycinR, glycin-receptor; Hu, anti-neuronal nuclear antibody (ANNA-1); ICU, intensive care unit; LGI1, leucine-rich glioma-inactivated 1; NMDAR, anti-N-methyl D-aspartate receptor; nsAb, neuronal surface antibody; SOX-1, sry-like high mobility group box-1.

TABLE 1 Demographic and clinical characteristics of AE patients in the ICU

Variable	Value
Age (minimum/maximum, IQR), years, *n* = 40	52 (16/89, 30–68)
Female, *n* = 22	42 (18/81, 25–68)
Male, *n* = 18	58 (16/89, 41–69)
Ethnicity, *n* (%)	
Caucasian	35 (88)
Asian	4 (10)
African	1 (3)
Tumor association, *n* (% of all patients, *n* = 40)	13 (33)
Female (% of tumor patients)	10 (77)
Male (% of tumor patients)	3 (23)
Kind of tumor, *n* (% of all tumor patients)	
Ovarian teratoma	4 (31)
SCLC	4 (31)
NSCLC	3 (23)
Breast cancer	1 (8)
Tongue cancer	1 (8)
Latency first disease symptoms to hospital admission, median (minimum/maximum, IQR), days, *n* = 40	13 (0/942, 0–47)
Latency first symptoms to diagnosis, median (minimum/maximum, IQR), days, *n* = 40	24 (0/960, 12–71)
Duration of ICU stay, median (minimum/maximum, IQR), days	
All AE patients, *n* = 40	38 (6/378, 21–95)
AE patients with nsAb, *n* = 36	42 (6/378, 20–144)
With only first- and/or second-line therapy, *n* = 23	23 (6/378, 15–55), *p* = 0.0002
With escalation therapy, *n* = 13	97 (37/328, 55–240), *p* = 0.0002
NMDARE, *n* = 13	61 (8/378, 27–247)
AE patients with nsAb against unknown epitopes, *n* = 12	31 (6/160, 16–61)
AE patients with onconeuronal Ab, *n* = 4	33 (27/38, 28–38)
Mechanical ventilation, *n* (% of all patients, *n* = 40)	38 (95)
Noninvasive ventilation	6 (15)
Invasive ventilation	32 (80)
Tracheostomy	27 (68)
Duration of mechanical ventilation, median (minimum/maximum, IQR), days, *n* = 36[a]	24 (1/271, 5–70)
Duration of respirator weaning, median (minimum/maximum, IQR), days, *n* = 19[b]	19 (2/127, 7–37)
Follow-up time from disease onset until last follow-up, median (minimum/maximum, IQR), months[c]	
All AE patients, *n* = 38	24 (0.5/145, 9–67)
AE patients with nsAb, *n* = 34	29 (0.5/145, 10–67)
With only first- and/or second-line therapy, *n* = 21	18 (0.5/145, 7–61)
With escalation therapy, *n* = 13	47 (7/123, 17–68)
NMDARE, *n* = 12	41 (7/127, 10–117)
AE patients with nsAb against unknown epitopes, *n* = 11	47 (0.5/145, 10–67)
AE patients with onconeuronal Ab, *n* = 4	8 (2/25, 2–22)

Note: Statistical analysis for duration of ICU stay was performed by Mann-Whitney *U* test.

Abbreviations: Ab, antibody; AE, autoimmune encephalitis; ICU, intensive care unit; IQR, interquartile range; nsAb, neuronal surface antibody; NSCLC, non–small cell lung cancer; SCLC, small cell lung cancer.

[a]In two patients, ventilation data could not be quantified exactly, because mechanical ventilation was already started in an external hospital.

[b]Duration of respirator weaning could not be quantified in all patients, because patients died before weaning initiation, no weaning occurred in the ICU, and/or respirator weaning was continued in external rehabilitation centers.

[c]Follow-up data were not available in two patients.

19 days (range = 2–143, IQR = 8–24). In contrast, patients requiring escalation therapy showed first improvements after 119 days (range = 30–546, IQR = 53–223; $p < 0.0001$). The duration between start of first- and/or second-line therapy and beginning of escalation therapy lasted 57 days (range = 18–479, IQR = 28–175). Patients treated with escalation therapy presented the first signs of remission with regard to initiation of escalation therapy after 27 days (range = 4–146, IQR = 11–59, *n* = 13) with similar response times of bortezomib (27 days, range = 4–146, IQR = 27–66, *n* = 9), and daratumumab (34 days, range = 7–66, IQR = 7–59, *n* = 5) (Table 4). Patients with anti-N-methyl D-aspartate receptor encephalitis (NMDARE) showed first improvements after 81 days (range = 10–546, IQR = 23–167, *n* = 12). Although NMDARE patients receiving only first- and/or second-line therapy already improved after 24 days (range = 10–132, IQR = 12–108, *n* = 6), NMDARE patients requiring escalation therapy needed 149 days (range = 37–546, IQR = 56–335, *n* = 6; *p* = 0.041) for improvement. However, time of beginning treatment response with regard to initiation of escalation therapy was much shorter at 43 days (range = 15–146, IQR = 18–86, *n* = 6).

Immunosuppressive maintenance therapy after disease stabilization was applied in 60% (*n* = 24) of patients with oral steroids (33%, *n* = 13), methotrexate (18%, *n* = 7), azathioprine (13%, *n* = 5), rituximab (23%, *n* = 9), and cyclophosphamide (5%, *n* = 2).

In total, 33% (*n* = 13) suffered from paraneoplastic AE, of which 92% (*n* = 12) were exposed to tumor-specific therapy including tumor surgery (62%, *n* = 8), chemotherapy (38%, *n* = 5), radiation (23%, *n* = 3), and tumor-specific immunotherapy (8%, *n* = 1) (Table 4).

TABLE 2 Clinical characteristics of AE patients in the ICU

Variable	Value
Indication for ICU admission[a]	
Disturbance of consciousness	20 (50)
Seizures/SE	8 (20)
Neuropsychiatric symptoms	5 (13)
Hypoventilation/respiratory insufficiency	7 (18)
Prodromal symptoms[a]	20 (50)
Fever	9 (23)
Headache	11 (28)
Flu-like symptoms	6 (15)
Deterioration of general condition	15 (38)
Most frequent clinical symptoms[a]	
Disturbance of consciousness	38 (95)
Quantitative	32 (80)
Quantitative	23 (58)
Neuropsychiatric symptoms	29 (73)
Delusion	3 (8)
Hallucination	8 (20)
Behavioral changes	26 (65)
Movement disorder	24 (60)
Dystonia	6 (15)
Choreoathetosis	9 (23)
Myoclonus	20 (50)
Akinetic-rigid syndrome	2 (5)
Autonomic dysregulation	22 (55)
Dysarthria	18 (45)
Dysphagia	17 (43)
Central fever	12 (30)
Seizures/SE	22 (55)
Epileptic seizures,[a] no. of patients (% of $n = 11$)	11 (50)
Focal seizures	9 (81)
Complex focal seizures	3 (27)
Generalized epileptic seizures	8 (72)
SE, no. of patients (% of $n = 11$)	11 (28)
Generalized SE	6 (54)
Focal SE	1 (9)
SE relapse	4 (36)
Cumulative duration of SE (% of $n = 10$)[b]	10 (25)
>7 days	2 (20)
>30 days	8 (80)
Therapy of SE, median no. of sedatives and AEDs (% of $n = 10$)[b]	
1 or 2 sedatives	4 (40)
3 or 4 sedatives	6 (60)
1 or 2 AEDs	1 (10)
3 or 4 AEDs	9 (90)
Duration of SE, median (minimum/maximum, IQR), days, $n = 7$[c]	50 (14/272, 25–158)
Increased intracranial pressure[d]	3 (8)
Others[e]	20 (50)

Note: Values are presented as n (%) unless indicated otherwise.

Abbreviations: AE, autoimmune encephalitis; AEDs, antiepileptic drugs; ICU, intensive care unit; IQR, interquartile range; SE, status epilepticus.

[a]Multiple selections possible.

[b]SE of one patient in external hospital with no available data about SE duration/treatment.

[c]In three patients there was insufficient documentation about SE duration/treatment; one patient died before SE termination.

[d]N-methyl-D-aspartate receptor encephalitis $n = 1$, AE with unknown neuronal surface antibody $n = 2$.

[e]Others: paresthesia $n = 5$, hemianopsia $n = 1$, hemiparesis $n = 2$, diplopia $n = 2$, catatonia $n = 2$, endocrine disorder $n = 1$, tremor $n = 1$, hypacusis $n = 1$, photo- and phonophobia $n = 1$, meningismus $n = 1$, permanent singultus $n = 1$, vertigo $n = 2$, ptosis $n = 3$, dyspnea due to spasms of vocal cords $n = 1$, fasciculations $n = 1$.

Outcome evaluation

Follow-up time from disease onset until last follow-up comprised 24 months for all AE patients (range = 0.5–145, IQR = 9–67, $n = 38$; two patients were lost to follow-up) (Table 1).

Evaluation of ICU disease severity by different scores showed no relevant differences for all AE patients and patient subgroups of AE with nsAb, NMDARE, AE with nsAb against unknown epitopes, and AE with onconeuronal antibodies as quantified by SAPS II score, APACHE II score, SOFA score, and TISS-28 score at the different time points of ICU admission, disease maximum, and ICU discharge (Figure S1a–d).

Neurological outcome was assessed by mRS and CASE score at hospital admission, disease maximum, and hospital discharge as best neurological outcome and at last follow-up (Figure 2a–d). Data revealed that 43% of all AE patients reached a favorable outcome with mRS = 0–2 ($n = 17/40$; CASE = 5) as the best outcome. Differences between the subgroups were remarkable. Whereas best neurological outcome was mRS = 0–2 in 47% of AE patients with nsAb ($n = 17/36$; CASE = 4), all AE patients with onconeuronal antibodies had a poor outcome, with mRS = 5 (100%, $n = 4$) and consecutive death of all patients at later disease course. A favorable outcome with mRS = 0–2 had only 20% of AE patients with nsAb against unknown epitopes ($n = 2/10$; CASE = 7), but 77% of NMDARE patients ($n = 10/13$; CASE = 1).

Of note, comparison of AE patients with nsAb improving after first- and/or second-line therapy ($n = 22$) versus treatment-refractory patients requiring escalation therapy ($n = 13$) revealed that patients with escalation therapy presented higher disease severity at disease maximum (mRS = 5 100% versus 68%, $p = 0.0312$; CASE = 24 versus 17, $p = 0.0036$). Best neurological outcome between both groups did

TABLE 3 Diagnostics in AE patients in the ICU

Diagnostic	Value
CSF, *n* (% of *n* = 40)	40 (100)
Pleocytosis, µl, *n* (%), median (minimum/maximum, IQR)	24 (60), 42 (6/547, 13–216)
Protein level, mg/L, *n* (%), median (minimum/maximum, IQR)	18 (45), 761 (460/2305, 517–1329)
Oligoclonal bands positive, *n* (% tested patients in *n* = 38)	9 (23)
Intrathecal Ig-synthesis	20 (50)
AE with Ab against unknown epitopes, *n* = 12	
IFT performed, positive in CSF, *n* (% of *n* = 12)	7 (58)
IFT performed, positive in serum, *n* (% of *n* = 12)	7 (58)
IFT not performed in CSF/serum, *n* (% of *n* = 12)	5 (42)
MRI, *n* (% of *n* = 40)	38 (95)
Normal or unspecific changes, *n* (% of *n* = 38)	20 (53)
Pathologic,[a] *n* (% of *n* = 38)	18 (47)
Limbic encephalitis	10 (26)
Basal ganglia abnormalities	8 (21)
Cranial nerve abnormalities	2 (5)
Fluid-attenuated inversion recovery lesions	14 (37)
Diffusion-weighted imaging lesions	15 (39)
MRI contrast-enhancing lesions	5 (13)
T1 signal alterations	6 (16)
T2 signal alterations	11 (29)
Brain PET, *n* (% of *n* = 40)	23 (58)
Normal nuclide distribution, *n* (% of *n* = 23)	7 (30)
Anterior–posterior gradient, *n* (% of *n* = 23)	7 (30)
Limbic encephalitis, *n* (% of *n* = 23)	4 (17)
Focal hypermetabolism by epileptogenic focus, *n* (% of *n* = 23)	2 (9)
EEG performed, *n* (% of *n* = 40)	35 (88)
Pathologic,[a] *n* (% of *n* = 35)	
Diffuse slowing	33 (94)
Delta brush	3 (9)
Discontinuous epileptic discharges	14 (40)
Seizure	5 (13)
Burst suppression pattern	6 (15)
Status epilepticus	6 (15)

Note: Values are presented as *n* (%) unless indicated otherwise.

Abbreviations: Ab, antibody; AE, autoimmune encephalitis; CSF, cerebrospinal fluid; EEG, electroencephalogram; ICU, intensive care unit; IFT, indirect immunofluorescence testing; Ig-synthesis, immunoglobulin synthesis; IQR, interquartile range; MRI, magnetic resonance imaging; PET, positron emission tomography.

[a]Multiple selections possible.

not differ significantly (with escalation therapy: mRS = 0–2, 39%, CASE = 3; without escalation therapy: mRS = 0–2, 54%, CASE = 4; subgroup analysis of patients without escalation therapy and mRS = 5 at disease maximum: mRS = 0–2, 40%, CASE = 4, *n* = 6/15). Comparison of patients with versus without escalation therapy showed longer ICU stays (97 days versus 23 days; $p = 0.0002$), longer durations until treatment response (119 days versus 19 days; $p < 0.0001$) and higher survival rates ($p = 0.0203$) for patients with escalation therapy, also indicated by mortality of 8% (*n* = 1/13) versus 50% (*n* = 10/20) during follow-up time of 47 and 18 months, respectively (Tables 1 and 4, Figure 2a–d, f).

Moreover, consistent with comparable grade of clinical remission in patients with and without escalation therapy, autoreactive serum and CSF autoantibody titers dropped after immunotherapy in both groups in a similar extent. Although responsive patients reached low antibody titers already after first- and/or second-line therapy, treatment-resistant cases achieved comparable low antibody levels only after escalation therapy (Figure 2e).

TABLE 4 Treatment of AE patients in the ICU

Variable	Value	
Immunotherapy of patients		
First-line therapy, *n* (% of *n* = 39)	39 (100)	
Methylprednisolone[a]	31 (79)	
IVIG[b]	24 (62)	
Plasma exchange	35 (90)	
Immunoadsorption	6 (15)	
Second-line therapy, *n* (% of *n* = 39)	24 (62)	
Rituximab[c]	24 (62)	
Cyclophosphamide	5 (13)	
	Value	No. of cycles (minimum/maximum)
Repeat of first- and/or second-line therapy, *n* (% of *n* = 39)	23 (59)	
Methylprednisolone	10 (26)	1 (1/2)
IVIG	12 (31)	2 (1/4)
Plasma exchange	15 (38)	1 (1/7)
Immunoadsorption	1 (3)	2
Rituximab	7 (18)	2 (1/3)
Cyclophosphamide	5 (13)	4 (3/5)
Escalation therapy[d]	13 (33)	
Bortezomib	9 (23)	2 (1/8)
Daratumumab	5 (13)	8 (4/13)
Latency symptom onset to treatment initiation, median (minimum/maximum, IQR), days, *n* = 39	27 (0/960, 11–62)	
Begin of treatment response with regard to treatment start, median (minimum/maximum, IQR), days		
All AE patients with nsAb, *n* = 33	30 (2/546, 15–125)	
With only first- and/or second-line therapy, *n* = 20	19 (2/143, 8–24), $p < 0.0001$	
With escalation therapy, *n* = 13	119 (30/546, 53–223)	
Begin of treatment response with regard to start of escalation therapy[d]	27 (4/146, 11–59)	
Bortezomib, *n* = 9	27 (4/146, 27–66)	
Daratumumab, *n* = 5	34 (7/66, 7–59)	
Duration between start of first- and/or second-line therapy and begin of escalation therapy	57 (18/479, 28–175)	
Bortezomib, *n* = 9	57 (18/479, 25–160)	
Daratumumab, *n* = 5	37 (22/204, 23–135)	
AE patients with nsAb against known epitopes, *n* = 22	49 (2/546, 20–135)	
AE patients with nsAb against unknown epitopes, *n* = 11	17 (2/181, 3–44)	
NMDARE, *n* = 12[e]	81 (10/546, 23–167)	
With only first-and/or second-line therapy, *n* = 6	24 (10/132, 12–108)	$p = 0.0411$
With escalation therapy, *n* = 6	149 (37/546, 56–335)	
Beginning treatment response with regard to initiation of escalation therapy, *n* = 6	43 (15/146, 18–86)	
Maintenance therapy after AE stabilization,[f,g] *n* (% of *n* = 40)	24 (60)	
Oral steroids	13 (33)	
Methotrexate	7 (18)	
Azathioprine	5 (13)	

(Continues)

TABLE 4 (Continued)

Variable	Value
Rituximab	9 (23)
Cyclophosphamide	2 (5)
Relapses of AE patients with nsAb, *n* (% of *n* = 36)	4 (11)
With only first- and/or second-line therapy, *n* (% of *n* = 22)[h]	4 (18)
With escalation therapy, *n* (% of *n* = 13)	0 (0)
Treatment of all patients with paraneoplastic AE, *n* = 13, *n* (% of *n* = 13)[f,i]	
Tumor surgery	8 (62)
Chemotherapy	5 (38)
Radiation	3 (23)
Tumor-specific immunotherapy	1 (8)

Note: Statistical analysis for time until treatment response was performed by Mann-Whitney *U* test.

Abbreviations: AE, autoimmune encephalitis; CASPR2, contactin-associated protein-like 2; ICU, intensive care unit; IVIG, intravenous immunoglobulins; IQR, interquartile range; LGI1, leucine-rich glioma-inactivated 1; NMDARE, anti-N-methyl D-aspartate receptor encephalitis; nsAb, neuronal surface antibodies; SOX-1, sry-like high mobility group box-1.

[a]One cycle corresponds to 3–5 g methylprednisolone intravenous.

[b]One cycle corresponds to 1–2 mg/kg body weight IVIG.

[c]One cycle corresponds to 2×1000 mg rituximab intravenous at treatment induction and each further application counts as an additional cycle.

[d]Escalation therapy was applied to NMDARE *n* = 6, AE with nsAb against unknown epitopes *n* = 4, LGI1 encephalitis *n* = 1, CASPR2 encephalitis *n* = 2; one patient with CASPR2 encephalitis received bortezomib and daratumumab.

[e]One NMDARE patient died before clinical improvement.

[f]Multiple selections possible.

[g]Deceased patients without maintenance therapy *n* = 9, deceased patients with maintenance therapy *n* = 7.

[h]AE with nsAb against unknown epitopes *n* = 1, glycin receptor encephalitis *n* = 1, neurochondrin encephalitis *n* = 1, SOX1 encephalitis *n* = 1.

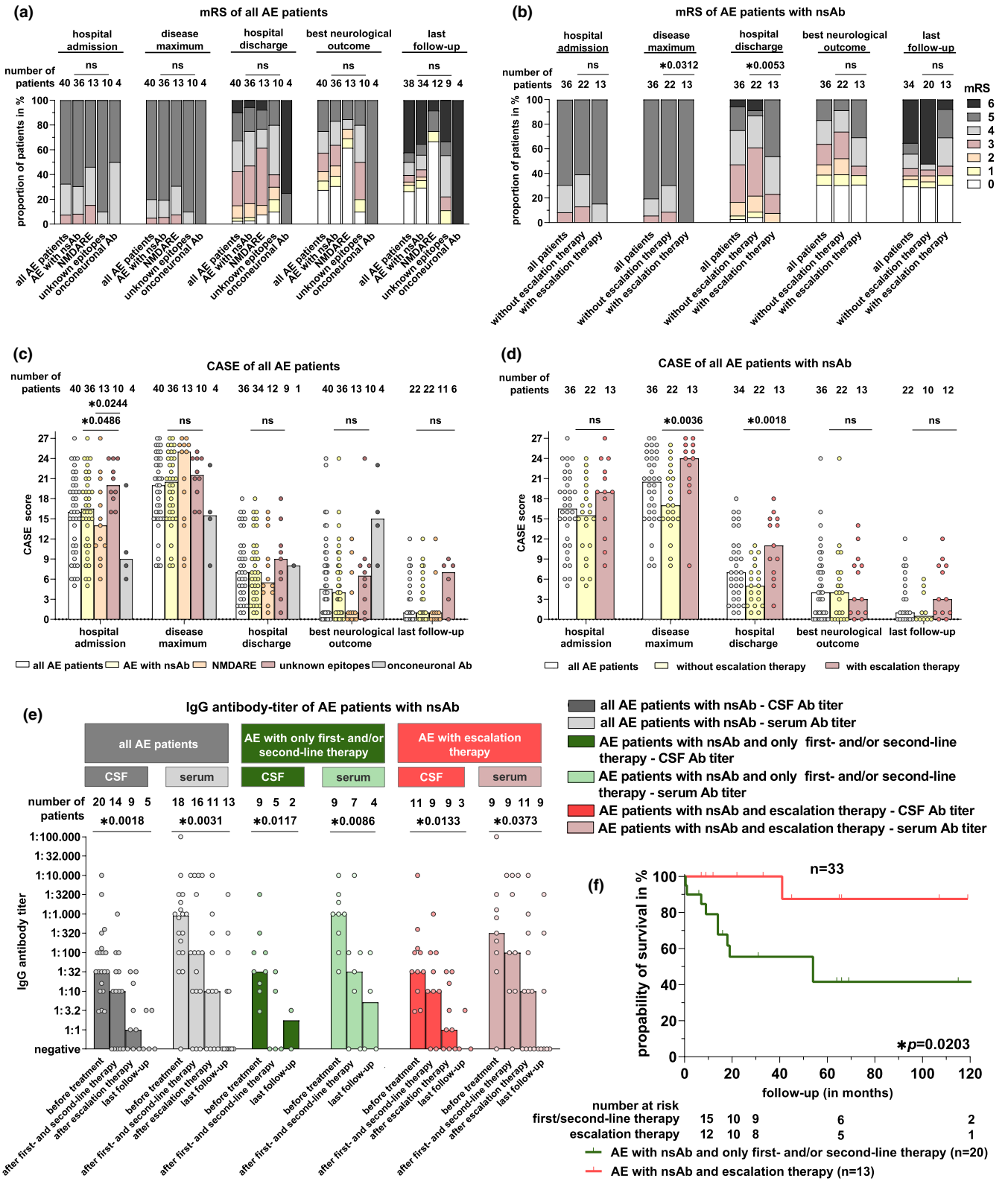
[i]One tumor patient died without tumor therapy.

AE patients with nsAb receiving only first- and/or second-line therapies presented relapses in 18% (*n* = 4/22) of cases, whereas no relapses were observed in patients with escalation therapy (*n* = 13; Table 4).

Prognostic factors for a good outcome

Multivariable binary logistic regression analysis with treatment as control variable (with or without escalation therapy) was used to analyze the association between explanatory variables and a good outcome (mRS = 0–2) in AE patients with nsAb. Identified variables for good outcome were younger age (odds ratio [OR] =0.955, 95% confidence interval [CI] =0.917–0.994, $p = 0.025$) and lack of preexisting comorbidities (OR = 0.093, 95% CI = 0.015–0.584, $p = 0.011$), whereas other factors did not reach statistical significance (e.g., time until treatment initiation, duration in the ICU, MRI abnormalities, number of ICU complications; Table 5). In contrast, direct group comparison of AE patients with nsAb treated with and without escalation therapy revealed that both groups

FIGURE 2 Outcome evaluation of autoimmune encephalitis (AE) patients and their subgroups by modified Rankin Scale (mRS) and Clinical Assessment Scale for Autoimmune Encephalitis (CASE) score at time points of hospital admission, disease maximum, hospital discharge, best neurological outcome, and last follow-up combined with autoreactive serum and cerebrospinal fluid (CSF) antibody (Ab) titer course and presentation of survival curves. (a) Graph depicts mRS of all patients with AE, AE with neuronal surface antibodies (nsAb), N-methyl-D-aspartate receptor encephalitis (NMDARE), AE with nsAb against unknown epitopes and AE with onconeuronal antibodies. (b) mRS of all AE patients with nsAb considering their treatment with and without escalation therapy. (c) Data present the CASE score of all patients with AE, AE with nsAb, NMDARE, AE with nsAb against unknown epitopes and AE with onconeuronal antibodies. (d) CASE score of all AE patients with nsAb considering applied immunotherapy with only first- and/or second-line or additional escalation therapy. (e) CSF and serum autoreactive immunoglobulin G (IgG) antibody titers of all AE patients with nsAb and their respective subgroups with and without escalation therapy at different time points of disease course (before treatment, after first- and/or second-line therapy, after escalation therapy [if indicated] and at last follow-up). (f) Survival curve of AE patients with nsAb (*n* = 33) treated with only first- and/or second-line or additional escalation therapy with the number at risk along the x-axis. Three patients within the cohort of AE with nsAb were excluded (*n* = 1 died before treatment initiation; *n* = 2 received immunotherapy, but had no follow-up data after hospital discharge). All data are presented as median. Statistical analysis for mRS, CASE score, and autoantibody titers were performed by Kruskal-Wallis test, and, if appropriate, by Mann-Whitney *U* test. Statistical analysis of mRS and CASE score did not include AE patients with onconeuronal antibodies because of the low patient number in this subgroup. Survival was analyzed by Kaplan-Meier curve using log-rank statistics with Mantel-Cox method. ns, not significant.



differed significantly; patients with escalation therapy presented longer durations in the ICU ($p = 0.0002$), had more ICU complications ($p = 0.024$), and had a higher mRS at disease maximum ($p = 0.0312$) (Table S3).

Mortality

At last follow-up, 40% ($n = 16$) had died at a median age of 69 years ($n = 8$, 50% female) during a follow-up time of 24 months. Of those,

TABLE 5 Summary of 10 individual multivariable analyses of potential prognostic factors for good outcome (mRS = 0–2) of AE patients with nsAb ($n = 33$)

Potential prognostic factor	Odds ratio	95% CI for odds ratio	*p*
Sex	1.599	0.386–6.618	0.517
Age	**0.955**	**0.917–0.994**	**0.025**
Time until treatment initiation in days	0.984	0.959–1.010	0.229
Duration in the ICU	1.001	0.994–1.008	0.777
Time of follow-up	1.000	1.000–1.001	0.145
Maximum mRS during disease course	0.421	0.100–1.767	0.237
MRI abnormalities	0.231	0.046–1.168	0.076
Preexisting comorbidities	**0.093**	**0.015–0.584**	**0.011**
No. of ICU complications	0.830	0.605–1.145	0.259

Note: The control variable in each logistic regression analysis is treatment: either only first- and second-line therapy or escalation therapy.

Abbreviations: AE, autoimmune encephalitis; CI, confidence interval; ICU, intensive care unit; mRS, modified Rankin Scale; nsAb, neuronal surface antibodies.

The bold indicates $p < 0.05$ was regarded as significant.

27.5% ($n = 11$) died after ICU discharge and 12.5% ($n = 5$) died in the ICU. From the latter, only 5% ($n = 2$) were AE patients with nsAb (NMDARE $n = 1$, AE with nsAb against unknown epitopes $n = 1$, both treated with first-line therapy) and 7.5% ($n = 3$) were AE patients with onconeuronal antibodies. Of the 16 deceased patients, 38% ($n = 7$) had underlying malignant tumor disease. Causes of death were related to severity of AE (31%, $n = 5$), tumor disease (19%, $n = 3$), infectious complications (25%, $n = 4$), or remained unknown (25%, $n = 4$). Three patients (7.5%) died in temporal context to multimodal immunotherapy (Table 6).

DISCUSSION

Our findings suggest that add-on treatment of plasma cell–depleting escalation therapies in treatment-refractory AE patients with nsAb induced similar neurological recovery with equivalent serum and CSF autoantibody titer decrease compared to patients already responding to standard first- and/or second-line treatments. This was even more surprising, because AE patients with escalation therapies presented a higher disease severity with more than sixfold longer times until treatment response and more than fourfold longer stays in the ICU. The main reason for these differences seemed to result from the high disease activity with missing treatment response to standard first- and second-line immunotherapies in treatment-refractory patients and was not related to increased mortality with shortened ICU stays of one treatment group. Presented data are remarkable, because treatment-resistant AE was previously thought to represent the major risk factor for a poor prognosis with high mortality. Our data suggest that application of escalation therapy might neutralize the relevance of previous predictors for poor outcome (e.g., time until treatment response, duration in the ICU, frequency of ICU complications), whereas only age and preexisting comorbidities remained as relevant prognostic factors. In addition, patients with escalation therapy showed no relapses and even lower mortality (8% versus 50%) compared to patients without escalation therapy despite longer follow-up times (47 versus 18 months). The reason for this difference might be caused by the escalation therapy itself, but other cofactors might have contributed to this observation (e.g., variable size and heterogeneity of treatment groups consisting of different types of AE, underlying malignant tumor disease). However, the patient cohort analyzed was too small to provide a reliable answer to this question.

NMDARE is known to have the best outcome of all AE types. Here, 46% of NMDARE patients required escalation therapy, resulting in a favorable outcome in 77%. Another study investigating the outcome in ICU-dependent NMDARE receiving only first- and/or second-line therapy revealed favorable recovery in only 57% of patients during the 6-month follow-up [9], whereas another published cohort found good outcome in 79% of NMDARE patients within 24 months, but with the restriction that pediatric and adult patients with lower disease severity, and ICU admission rates of only 75% were included [22].

Moreover, favorable outcome with mRS = 0–2 was reached in AE with nsAb in 47% and in AE with nsAb against unknown epitopes in only 20% of cases. Differences were not significant, but it remains uncertain whether they were related to small sample size or resulted in differences of disease pathophysiology with diverging responses to immunotherapy. The latter is supported by current literature indicating that various types of AE result in different outcomes [23]. AE with onconeuronal antibodies presented the poorest outcome (mRS = 6, 100%) emphasizing the importance of early diagnosis and treatment induction to stabilize disease courses in affected patients [24]. Because these disorders are usually mediated by dysregulated T cells, plasma-cell depleting escalation therapies are supposed to be ineffective for AE with onconeuronal antibodies, but development of novel treatment concepts for this disease entity is still missing.

Within our cohort, the observed total mortality of 40% with follow-up of 24 months might appear high, but only 12.5% of AE patients died in the ICU ($n = 5$), and of those, only 5% ($n = 2$) were AE patients with nsAb. Three patients (7.5%) died in timely context to multimodal immunotherapy. Our data are in line with other studies that observed mortality rates in the ICU between 7.5% and 24% [5, 7] and at later follow-up in between about 18.5% and 40% of cases [4–6]. However, these data are difficult to compare because of the heterogeneity of investigated patient groups with variable frequency of end-of-life decisions and follow-up times.

Currently, appropriate timing and dosing of escalation therapy at treatment induction are not specified. In our study, patients were exposed to escalation therapies after being unresponsive to first- and/or second-line treatment for a median duration of 57 days, but in several cases, it was applied as an ultima ratio decision to otherwise palliative care after unsuccessful pretreatment

TABLE 6 Clinical characteristics of deceased AE patients

Type of AE	Cause of death	Time point of death	Applied immunotherapy	Underlying tumor disease	MRI changes	ICU complications	Other comorbidities
AE with nsAb							
NMDARE	Septic shock with multiorgan failure	At ICU after 210 days of ICU treatment	IVIG, PE	None	None	Pneumonia, colitis, ileus, pulmonary embolism, CIP/CIM, pleural effusion, severe electrolyte derangement	None
LGI1	Bacterial meningitis	38 days after ICU discharge	None	None	Mild FLAIR lesions in hippocampus	Meningoencephalitis, Hashimoto thyroiditis, arterial hypertension	Urinary tract infection
LGI1	Unknown	30 days after ICU discharge	MP, IVIG, PE, RTX, OS	None	Mild FLAIR lesions in hippocampus	Hypotension, tracheal stenosis after tracheotomy	Arterial hypertonus, COPD, thrombopenia, renal insufficiency III°
$GABA_bR$	Tumor disease	259 days after ICU discharge in a nursing home	MP, IVIG, PE, RTX, OS	Yes (SCLC)	None	Pneumonia, thrombosis, catheter infection, HIT II, CIP/CIM	Arterial hypertension, chronic heart insufficiency, atrial flutter, insulin-dependent diabetes, renal insufficiency III°
$GABA_bR$	Tumor disease	515 days after ICU discharge	MP, PE	Yes (NSCLC)	Mild DWI lesions in hippocampus	Catheter infection, transfusion-dependent anemia	hypothyreodism, COPD, arterial hypertension
CASPR2	Septic shock	9 days after ICU discharge	MP, IVIG, PE, IA, RTX, BTZ, DARA, OS	Yes (tongue carcinoma)	Mild DWI/FLAIR/T2 lesions in hippocampus and cerebellum	Pneumonia, urinary tract infection, catheter infection, transfusion-dependent anemia	Arterial hypertension, diabetes, diabetic nephropathy, hypothyreodism
Neurochondrin	Unknown	270 days after ICU discharge	PE, RTX, CYCLO	None	None	CIP/CIM	Arterial hypertension
SOX1	Tumor disease	Very shortly after ICU discharge in rehabilitation center	MP, IVIG, PE, OS, AZA	Yes (SCLC)	None	Pneumonia, urinary tract infection, thrombosis, resuscitation, catheter infection, transfusion-dependent anemia, CIP/CIM	LEMS, arterial hypertension, diabetes, peripheral artery disease, hypercholesterolemia
SOX1	Pneumonia	21 days after ICU discharge	OS, PE, AZA	Yes (SCLC)	No MRI performed	CIP/CIM	LEMS, COPD, chronic kidney disease, cachexia
Ab against unknown epitope	Fulminant AE course, multiorgan failure, status epilepticus, intracranial pressure crisis, cardiac arrest	At ICU after 6 days of ICU treatment	PE	None	Basal ganglia lesions (DWI, FLAIR, T2)	Pneumonia, sepsis, thrombosis, renal failure with dialysis, PRIS, resuscitation	HIV, arterial hypertension
Ab against unknown epitope	Unknown	1631 days (~4.5 years) after ICU discharge	MP, PE	None	Mild lesions in hippocampus (FLAIR, DWI and T1 contrast enhancing lesions)	Pneumonia, bleeding of the gastrointestinal tract, renal insufficiency	Atrial flutter, arterial hypertension
Ab against unknown epitope	Unknown	216 days after ICU discharge in a rehabilitation center	MP, PE	None	Mild DWI lesions in hippocampus and amygdala	Pneumonia, urinary tract infection, sepsis, catheter infection, disseminated intravasal coagulation	Epilepsy, depression, anxiety disorder, glaucoma

TABLE 6 (Continued)

Type of AE	Cause of death	Time point of death	Applied immunotherapy	Underlying tumor disease	MRI changes	ICU complications	Other comorbidities
AE with onconeuronal Ab							
Hu	AE (treatment discontinuation)	At ICU after 38 days of ICU treatment	MP, IVIG, IA	Lung cancer suspected on CT, but not proven	None	Pneumonia, urinary tract infection, sepsis, pleural effusions	Intracranial hemorrhage
Hu	AE (treatment discontinuation)	At ICU after 27 days of ICU treatment	IVIG, PE, RTX, CYCLO, OS	Yes (NSCLC)	None	Urinary tract infection, pneumothorax, resuscitation, catheter infection, pleural effusion, colitis	COPD, hypothyreodism, vitamin B12 deficiency
Hu	AE	363 days	MP, IVIG, PE (~1 year) after ICU discharge	None	None	Pneumonia	Arterial hypertension, hyperlipidemia, coronary heart disease, diabetes
CV2	AE (treatment discontinuation)	At ICU after 37 days of ICU treatment	MP, IVIG	Yes (SCLC)	No MRI performed	Pneumonia, sepsis, catheter infection, pleural effusion	Diverticulitis

Abbreviations: Ab, antibody; AE, autoimmune encephalitis; AZA, azathioprine; BTZ, bortezomib; CASPR2, contactin-associated protein-like 2; CIP/CIM, critical illness polyneuropathy/myopathy; COPD, chronic obstructive pulmonary disease; CT, computed tomography; CV2, collapsin response mediator protein (CRMP)5; CYCLO, cyclophosphamide; DARA, daratumumab; DWI, diffusion-weighted imaging; FLAIR, fluid-attenuated inversion recovery; GABAbR, gamma-aminobutyric acid-B-receptor; HIT II, heparin-induced thrombocytopenia type II; HIV, human immunodeficiency virus; IA, immunoadsorption; Hu, anti-neuronal nuclear antibody (ANNA-1); ICU, intensive care unit; IVIG, intravenous immunoglobulins; LEMS, Lambert-Eaton myasthenic syndrome; LGI1, leucine-rich glioma-inactivated 1; MP, methylprednisolone; MRI, magnetic resonance imaging; nsAb, neuronal surface antibodies; NSCLC, non–small cell lung cancer; OS, oral steroids; PE, plasma exchange; PRIS, propofol infusion syndrome; RTX, rituximab; SCLC, small cell lung cancer; SOX-1, sry-like high mobility group box-1.

for many months. Longer observation periods can be useful to wait for responses from first- and/or second-line therapies, but early induction of escalation therapy appears attractive to accelerate clinical recovery and to shorten ICU stays. Unfortunately, there exist no biomarkers to identify treatment-refractory AE patients at early disease stage.

Despite the limited data, based on our clinical experience reported here, we recommend the following treatment regimen for application of plasma cell–depleting escalation therapies in AE patients with nsAb (Figure 3). Escalation therapy should be considered after consultation with an AE specialist and after treatment with repeated first- and second-line therapies that have been unsuccessful over a period of approximately 2 months, without evidence of clinical improvement (e.g., termination of status epilepticus, relevant reduction of sedation, progress in respirator weaning, objective improvement of other AE symptoms) and without relevant decrease in autoantibody levels as a biomarker of treatment response. The decision for escalation therapy should be individualized, considering disease severity, age, comorbidities, irreversible brain damage, as well as frequency and severity of infections during previous first- and/or second-line therapies [12]. Escalation therapy should be initiated after an appropriate interval from previous immunotherapies to minimize the

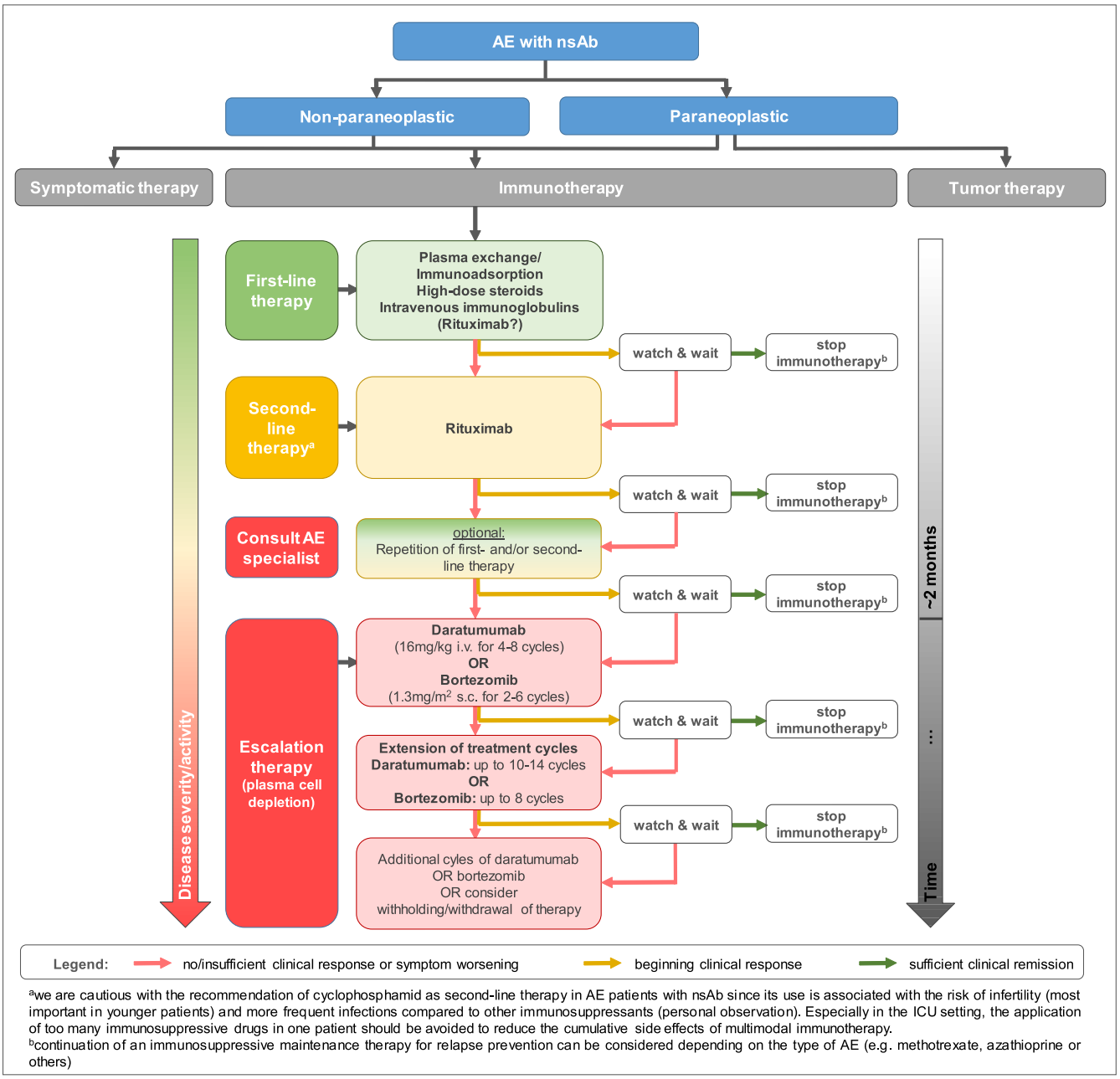


FIGURE 3 Treatment recommendation for autoimmune encephalitis (AE) with neuronal surface antibodies (nsAb) including therapy-refractory disease courses (based on our single-center experience). ICU, intensive care unit; i.v., intravenous; s.c., subcutaneous.

risk of life-threatening infections [12]. Moreover, we suggest a combination of rituximab with a plasma cell–depleting agent to allow depletion of B cells, and short-lived and long-lived plasma cells. Given the paucity of data, a clear recommendation for bortezomib instead of daratumumab or vice versa is not possible. Studies comparing the efficacy and safety of both plasma cell–depleting agents in treatment-resistant AE patients are not yet available. However, the first prospective, multicenter, randomized controlled phase II trial, Generate-Boost, is now ongoing to investigate efficacy and safety of bortezomib in patients with severe AE [25]. Based on our experience, we prefer daratumumab because it seems to induce a stronger plasma cell depletion as bortezomib (50%–80% versus 30%) as indicated by a decrease of laboratory surrogate markers of plasma cell depletion such as antibody titers, immunoglobulin levels, and long-lived vaccine titers [10–12, 15]. A superior efficacy for daratumumab was also suspected by two case reports that observed clinical improvements to daratumumab in two AE patients unresponsive to previous immunotherapy including bortezomib [11, 13]. Noteworthy, we are cautious to apply bortezomib in patients with contrast-enhancing lesions in MRI because we observed severe global atrophy suspected to be bortezomib-induced neurotoxicity in one NMDARE patient with disturbed blood–brain barrier (personal unpublished observation). From our single-center experience, most patients sufficiently respond to two to six cycles of 1.3 mg/m^2 bortezomib subcutaneously or four to eight cycles of 16 mg/kg daratumumab intravenously. Some patients with very high disease activity can present apparently insufficient response to applied escalation therapy. These patients might require a longer and individualized treatment scheme with more therapy cycles (up to 8 cycles for bortezomib and up to approximately 10–14 cycles for daratumumab). Decision for the number of applied treatment cycles can orientate on the degree of symptom remission and decline of the above-mentioned laboratory markers of plasma cell depletion during immunotherapy [10–12, 15].

Limitations of our study include the retrospective, single-center study design with distinct durations in follow-up, disease heterogeneity of different AE types varying in pathophysiology, pretreatments and treatment responses, use of two plasma cell-depleting drugs with different mode of action, and unequal numbers of applied treatment cycles. Lack of standardized criteria for initiation of escalation therapy might have favored induction of escalation therapy, although failure of first- and/or second-line therapy was not certain. The coapplied immunotherapies were confounders when attributing clinical improvements and antibody titer decrease to effects of escalation therapy that can be further overestimated, because a subgroup of treatment-refractory AE patients can improve at least in part spontaneously. The retrospective scoring of outcome parameters affected the accuracy of outcome measures. The small sample sizes contributed to limited statistical power, complicating identification of significant subgroup differences and making it impossible to control for confounding, to include non-linear functional forms for continuous variables or interactions in multivariable analysis. Thus, applied statistical tests have only an explorative character and require confirmation in large-scale observational studies.

In conclusion, our data suggest that plasma cell–depleting escalation therapies can disrupt chronic autoimmune responses in treatment-refractory AE patients with nsAb and relativize the magnitude of ICU treatment as an important outcome risk factor. However, further prospective, randomized clinical trials comparing treatment-refractory AE patients with and without escalation therapy are needed to investigate these drugs for their efficacy and safety, but also to clarify timing and dosing at treatment induction.

AUTHOR CONTRIBUTIONS

All authors contributed to the study conception and design. Material preparation and data collection and analysis were performed by Lisa Schwarz and Franziska Scheibe. Statistical analysis was performed by Lisa Schwarz, Franziska Scheibe, and Nilufar Akbari. The first draft of the article was written by Lisa Schwarz and Franziska Scheibe. All authors were involved in data interpretation, commented on previous versions of the article, and all authors read and approved the final version of the article.

ACKNOWLEDGMENTS

Open Access funding enabled and organized by Projekt DEAL.

FUNDING INFORMATION

The study was funded by NeuroCure Clinical Research Center, funded by the German Research Foundation under Germany's Excellence Strategy EXC 2049–89829218.

CONFLICT OF INTEREST

The authors have no competing interests to declare that are relevant to the content of this article.

DATA AVAILABILITY STATEMENT

Anonymized data will be made available on request from any qualified investigator.

ETHICAL APPROVAL

The study was approved by the institutional ethics committee of Charité–Universitätsmedizin Berlin, Germany (EA2/096/21) and was performed in accordance with the Declaration of Helsinki.

ORCID

Lisa Schwarz https://orcid.org/0000-0002-1283-3478
Nilufar Akbari https://orcid.org/0000-0002-3481-4956
Harald Prüss https://orcid.org/0000-0002-8283-7976
Andreas Meisel https://orcid.org/0000-0001-7233-5342
Franziska Scheibe https://orcid.org/0000-0002-8773-6090

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Schwarz L, Akbari N, Prüss H, Meisel A, Scheibe F. Clinical characteristics, treatments, outcome, and prognostic factors of severe autoimmune encephalitis in the intensive care unit: Standard treatment and the value of additional plasma cell–depleting escalation therapies for treatment-refractory patients. *Eur J Neurol*. 2023;30:474-489. doi: 10.1111/ene.15585