Proceedings of the "International Congress on Structural Epilepsy & Symptomatic Seizures" (STESS, Gothenburg, Sweden, 29-31 March, 2023) and Preface to the Special Issue on "Structural Epilepsy and Symptomatic Seizures"

Francesco Brigo*, Johan Zelano*, Laura Abraira, Carla Bentes, Christine T Ekdahl, Simona Lattanzi, Morten Ingvar Lossius, Petra Redfors, Rob P.W. Rouhl, Emilio Russo, Josemir W. Sander, Alberto Vogrig, Ronny Wickström

*Contributed equally as first authors. Other authors have been listed alphabetically

Introduction

In 2019, over 130 people from more than ten nations traveled to Gothenburg, Sweden for the Seizures and Stroke Congress, the first international conference entirely devoted to post-stroke epilepsy. A follow-up meeting was held virtually in 2021 owing to the COVID-19 pandemics. Ultimately, the congress was held again in Gothenburg (29-31 March 2023), with a widened focus that included all symptomatic and structural epilepsies. The choice of such a broader topic was reflected in the new name of the congress, the "International Congress on Structural Epilepsy & Symptomatic Seizures" (abbreviated as STESS), which was attended by more than 150 participants from all over the world. It provided a teaching course for novice scientists and clinicians combined with a three-day program of cutting-edge research and clinical presentations, along with poster and platform presentations.

This special issue of Epilepsy & Behavior covers the most relevant topics in the field of structural epilepsy and symptomatic seizures. It includes reviews and original studies presented during the STESS, as well as some excellent spontaneous contributions from international researchers active in this field.

The present article is meant to serve both as a general introduction to the topics discussed in the special issue and as conference proceedings of the STESS, as it includes a series of summaries of the key presentations that were given in Gothenburg. They convey a flavor of the depth and breadth of discussion that animated the congress, and offer up-to-date information on prediction and risk factors, management, prognosis, and prevention of seizures in the context of a structural brain lesion. The appendix includes the abstracts of studies discussed as posters or oral presentations during the congress.

We express our sincere gratitude to everyone who helped make this congress a reality, including participants, sponsors, speakers, and supporting organizations. We also thank all those who contributed their high-quality research articles to this special issue, and to the Editor-in-Chief of Epilepsy & Behavior, Dr. Marco Mula, for his generous hospitality and continuous support.

We sincerely hope that this special issue may spark some useful insights and debate among scientists and physicians who dedicate their lives to better understanding and treating structural epilepsy and acute symptomatic seizures. This special issue is dedicated to them and to all people affected by structural epilepsy around the world.

Francesco Brigo and Johan Zelano

Outline

- Mechanisms of epileptogenesis in preclinical studies (Emilio Russo)
- The immune system in epileptogenesis (Alberto Vogrig)
- The immune reaction as a potential biomarker in epilepsy (Christine T Ekdahl)
- The value of EEG as a biomarker of epileptogenesis and seizure recurrence in different acquired epilepsies (Carla Bentes)
- Serum biomarkers for the diagnosis of structural acquired epilepsy (Laura Abraira)
- "Is it structural epilepsy?" Critical appraisal of the ILAE definition of epilepsy (Francesco Brigo)
- Acute Symptomatic Seizures and subsequent Epilepsy after CNS Infections (Josemir W. Sander)
- Reperfusion therapies and post-stroke epilepsy (Petra Redfors)
- NORSE and FIRES in adults and children - Do we need to think differently? (Ronny Wickström)
- Tailored ASM selection based on big data (Johan Zelano)
- Predicting treatment resistance in acquired epilepsies (Simona Lattanzi)
- Prognosis of symptomatic epilepsy: the impact on survival (Rob P.W. Rouhl)
- Anti-seizure medication withdrawal in seizure-free patients with structural epilepsy (Morten Ingvar Lossius)

Mechanisms of epileptogenesis in preclinical studies (Emilio Russo)

Epileptogenesis refers to the development as well as structural and functional extension of brain tissue capable of generating spontaneous seizures, resulting in the development of a chronic epileptic condition and/or progression of epilepsy after the condition is established [1]. This definition encompasses several aspects and possibilities also including the definition of secondary epileptogenesis; namely, the observation that more than one epileptic focus may emerge in some patients as the disease progresses [2]. In this latter, similar mechanisms to the one currently known may be involved but they may be different from the one originally put in place for the initial epileptogenesis process in the same single patient. Indeed, several mechanisms have been proposed and summarized in several reviews [3]; accordingly, being intrinsic in the definition, the most relevant aspect is the generation of a brain network able to cause seizures which is both created from a not previously present phenomenon (e.g., traumatic brain injury) but also through an alteration of homeostatic plasticity contributing to this phenomenon [4]. We should consider as the first animal model of epileptogenesis the kindling protocol proposed by Goddard in the 1967 [5], in which a sub-threshold electrical stimulus repeated over time is leading to the development of spontaneous epileptic seizures in rats. The protocol has been then modified and studied in order to understand the epileptogenesis mechanisms and test the potential efficacy of interventions in preventing and modifying the epileptogenic process ([6, 7].

Most of the information we have on the epileptogenic process derive from studies in post insult models (e.g., post SE, traumatic brain injury) and several processes are involved and distinguished. Primary injuries (at the time of the insult) can be identified as meningeal and vascular damage, acute neuronal death and axonal injury; secondary injuries (up to months after the insult) may be represented by oedema, excitotoxicity and neuronal/glial cells delayed death, inflammation, hypoxia/ischemia accompanied by circuitry reorganization including neurogenesis, gliogenesis, angiogenesis and altered brain plasticity ([3, 6-8]. All these processes may be present both in the latency period (the time-window between the identified insult and the appearance of the first seizure) and after the occurrence of the first spontaneous seizure not linked to the initial insult (e.g., symptomatic acute seizures).

It is now clearer that some of these mechanisms and processes may be independent from the initial cause and therefore may be shared among different aetiologies [9]; therefore, they represent common therapeutic targets also in terms of the searched effects. We may consider targets to reverse/prevent epileptogenesis or reduce brain injury such as cells' death, cytokines, immune system, the mTOR or Jak/STAT pathways. On the other hand, there are mechanisms which may be specific to epileptogenesis aetiology; for example, in the case of brain tumour related epilepsy in which some genetic mutations are linked to seizures (e.g., BRAF, Isocitrate dehydrogenase, PIK3CA) or there are specific astrocytic and haemodynamic features [10]. Similarly, these can be applied also to other causing agents (e.g., viral infections), insults (e.g., stroke) or factors including genetics [11-13]. Some of the most important and emerging molecular targets (e.g., neurogenesis, astrogliosis, neuroinflammation) have been recently reviewed [14].

Along with this increasing understanding of the mechanisms and targets, several treatment approaches have been studied in animal models indicating the potential antiepileptogenic effects of several treatments both in post-insult and genetic models [6]. However, none of them is usually considered as a clinically proven treatment and therefore a suitable clinical approach. Some exceptions must be frankly considered, it is common practice to prescribe

levetiracetam after a potential epileptogenic insult (e.g. traumatic brain injury) for a not defined period and in variable dosages without any meaningful demonstration of a clinical impact on the prevention of spontaneous seizure development. Vigabatrin has been proven to modify the natural history of epilepsy in patients with tuberous sclerosis according to the earliest time of intervention [15]; its antiepileptogenic effects in preclinical models were already earlier demonstrated [16]. Similarly, everolimus and mTOR inhibitors may somehow be considered disease modifying [17]. Finally, the preclinical antiepileptogenic effects of ethosuximide against absence epilepsy/seizures development were demonstrated in two different animal models and by different research groups; although with some biases, this effect was also supported by a retrospective clinical study [18-21].

More recently, an already known but forgotten point of view arose from gut microbiota research. The microbiota gut brain axis has recently been a hot topic of research also for the brain and its involvement in epilepsy has just been identified a few years ago [17, 22, 23]. A recent article indicated that the development of spontaneous seizures after traumatic brain injury is dependent on the initial composition of the gut microbiota [24]; this result indicates that the gut microbiota may play a protective as much as predisposing factor in epileptogenesis. All and all, we have correctly investigated the causes and mechanisms of epileptogenesis looking for responsibilities and defining targets as well as testing therapeutic approaches. This is all meaningful, but we should also wonder why some of our patients do not develop epilepsy similarly to others which will instead have seizures under similar conditions. As much as in the case of this gut microbiota study just mentioned above, there may be protecting factors (e.g., genetic, epigenetic etc) in some subgroups of patients which should be studied and these may also be biomarkers, therapeutic targets and opportunities to improve our understanding and new clinical tools.

The immune system in epileptogenesis (Alberto Vogrig)

Seizures are a well-recognized manifestation of a wide range of immune-mediated disorders, including systemic conditions (e.g. lupus erythematosus), as well as many inflammatory brain disorders [25, 26]. Among the latter entities, autoimmune encephalitides (AE) and paraneoplastic neurologic syndromes (PNS) represent an interesting paradigm due to their association with a diverse spectrum of antineuronal antibodies (Abs), which are specific to different subtypes and serve as relevant biomarkers [25, 27]. Also, this allows to classify patients into groups with distinct clinical presentations, potentially underlying specific pathophysiological processes [28].

In particular, PNS are rare disorders (the incidence of which approximates 1/100,000 person-years [26] triggered by a systemic malignancy (especially lung, breast, or ovary cancer) that can affect any part of the nervous system, often presenting with a stereotyped clinical manifestation (e.g. limbic encephalitis) [29]. The reason why only a minority of patients with cancer (1 in every 334 [26]) develop a PNS is due to specific genetic signatures of their associated tumors, which can entail alterations (somatic mutation, gene amplification, protein overexpression) in the genes coding for onconeural proteins (i.e. proteins normally expressed by neurons, and ectopically by certain cancer cells) [30] or in genes coding for other relevant subunits functionally connected to the implicated antigen (such as KCTD16 in the case of anti-GABABR PNS [31]). The net result is a robust immune attack mostly mediated by T cells against both the tumor and the nervous system [27]. In this case, the associated neuronal Abs (so called onconeural or “high-risk” Abs [29]) are good biomarkers

of the underlying immune response, but they are not pathogenic as they cannot interact with their intracellular antigenic targets. Instead, the neuronal damage is mediated by cytotoxic T cells, which in turn explains the unsatisfactory response to immunotherapy and irreversible neuronal loss [3,4]. Notable examples in which seizures are a core symptom include anti-Hu, Ma2, and CV2/CRMP5 (mostly paraneoplastic) and anti-GAD65 (synaptic intracellular but usually not associated with cancer) [25, 32]. Intriguingly, syndromes clinically and immunologically similar to PNS can be triggered by cancer immunotherapy, in particular immune checkpoint inhibitors (ICIs), and more than 30% of them develop seizures [33].

At the other side of the spectrum, patients with AE typically harbor Abs targeting neuronal surface or synaptic proteins, in which the trigger is less frequently cancer (hence called "low" and "intermediate-risk" Abs) and more commonly represented by either preceding infections (e.g. herpes simplex encephalitis) or specific host-related factors (e.g. human leukocyte antigen, HLA) [28, 34, 35]. In this case, the Abs have access to the epitopes causing a functional damage which is therefore more amenable to treatment [27, 28]. The most frequent Abs in this group associated with seizures include anti-GABAAR and GABABR (both commonly associated with status epilepticus) as well as anti-NMDAR, LGI1, CASPR2, among others [25, 32]. Like PNS, AE are also rare disorders (approximately 2 per million person-years [26]) but they should not be missed as they often respond favorably to immunotherapy.

These different pathological mechanisms offer a clear explanation of the divergent evolution of the seizure disorder in patients with PNS and AE, which was nicely framed by the conceptual definitions proposed by The International League Against Epilepsy (ILAE) Autoimmunity and Inflammation Taskforce [36]. In particular, it was proposed that seizures resulting from brain autoimmunity are either acutely symptomatic in the context of AE with neural surface Abs, or they are indicative of an enduring predisposition to seizures (i.e. autoimmune encephalitis-associated epilepsy, AEAE) for patients harboring Abs targeting intracellular antigens, suggesting that the specific autoantigen location can predict long-term outcome [37]. Obviously, this distinction has also practical consequences: long-term treatment with anti-seizure medications (ASMs) is probably unnecessary in the majority of patients with anti-NMDAR, GABABR, and LGI after resolution of the encephalitis stage, while most patients with anti-GAD65 or high-risk Abs require prolonged treatment with ASMs [25, 32, 36-38]. Sodium channel blockers seem to be more effective [32] and some combination of ASMs appear to be of particular interest as a form of personalized medicine (e.g. cenobamate-clobazam in anti-GAD65-associated seizures [39]). However, in both scenarios it should be highlighted that the most effective ASM during the acute (active) encephalitic stage is probably represented by immunotherapy, which includes first-line (such as corticosteroids, intravenous immunoglobulin, and plasma exchange) or second-line medications (such as rituximab and cyclophosphamide, with the former usually adopted in AE with neuronal surface Abs, and the latter in PNS with Abs against intracellular antigens, after having completed oncological treatments, if needed) [32]. Conversely, AEAE is probably the result of tissue damage related to the encephalitic process and thereby mainly structurally mediated, accounting for the poor efficacy of immunotherapy [37].

The immune reaction as a potential biomarker in epilepsy (Christine T Ekdahl)

A PubMed search for the words “immune response” and “brain” generates 27 000 articles published over the last 20 years. About 20 000 of them were published during the last 10 years. In comparison, changing the word “immune response” to “neuronal response” generates more than 76 000 articles, but with a consistent publication rate during 20 years. The current exponential increase in articles about the immune response is acknowledged by the scientific community, even if we still publish several times more articles about neuronal responses. Most, if not all, neurological disorders show an immune response in the brain and the desire to use this finding as a biomarker for possibly diagnosis/progression/predictions of outcome is strong. However, the seemingly low specificity of the immune response in the brain is a struggle if the concept is not further dissected into its many components, as we do for neuronal responses.

During the last 20 years my research group has studied the immune response in the brain of rodents with epileptic seizures and lately we have started to translate the findings into explorative and hypothesis-driven clinical studies. We started out by describing the immune response in the electrically-induced rodent model of epileptic seizures. In this model, rats and mice are subjected to a stereotaxic implantation of stainless steel electrodes into the brain, in our case into the hippocampus, and one week later electrical stimulation to induce an initial seizure, followed by spontaneous seizures confirmed by videoEEG recordings. These rodents not only show neuronal responses in the brain but also microglial activation in terms of increased numbers and expression of phagocytic proteins for at least 6 months after the initial seizure [40-42] and even stronger reaction in animals that exhibited subsequent spontaneous seizures [43].

We have reduced microglial activation in the brain by administering a chemokine receptor antibody (CX3CR1 Ab) close to the hippocampus, which altered the neuronal response (Ali et al 2015, 2017). In mice lacking immune related factors such as tumor necrosis factor receptor 1 and 2 or interleukin 1 receptor 1 we have found altered microglial activation and seizure-induced neuronal damage [44, 45]. Since both epileptic seizures and a lipopolysaccharide (LPS)-induced immune response in the brain alter the electrophysiological properties of newborn neurons within the hippocampus [46, 47], we set out to describe where and for how long microglial processes may interact with neurons in ex vivo hippocampal tissue by using 2photon microscopy. We have shown how these live interactions differ in tissue from animals with epileptic seizures [48]. Furthermore, we have described seizure-induced changes in the expression of synaptic proteins within excitatory and inhibitory synapses in the electrically-induced model of epilepsy as well as in a genetic model of handling-induced seizures i.e. synapsin 2 knockout mice [49, 50]. We have found that the same synaptic proteins also react to administration of LPS into the brain [51] and that intraperitoneal treatment with antibodies against the synaptic protein N-cadherin together with levetiracetam decrease microglial activation [52]. Together these findings suggest a close interaction between neurons and immune-related cells and their signaling pathways [53].

The immune reaction is not only located within the epileptic focus from which the epileptic seizures originate, but involves cortical and subcortical brain structures, bilaterally, as well as being present in the blood [43, 54, 55]. Microglial activation is even present within the retina of epileptic rats and mice, though it may take several weeks after seizures before its clearly visible with histology [56] and partly detected with 7T MRI and 9.4T DTI [57].

Altering the immune reaction may interfer with the development of epilepsy. Intraperitonial administration of interleukin-6 receptor antibodies in synapsin 2 kockout mice promptly delays seizure onset and frequency. However, the effect was only evident when the treatment started one month before predicted seizure onset. No seizure reduction was observed when the treatment was initiated after seizure onset, suggesting a role for interleukin-6 signaling primarily during early epileptogenesis [58]. Knowing these experimental data we have pursued a clinical study on adult patients with videoEEG-verified temporal lobe epilepsy, frontal lobe epilepsy and psychogenic non-epileptic seizures. We have shown increased levels of interleukin-6 in blood from epilepsy patients compared to psychogenic non-epileptic seizures and age/gender-matched controls. In addition, a group of immune-related factors increased transiently directly after temporal lobe seizures, suggesting a possible fingerprint for acute diagnostic purposes when differentiating epileptic and non-epileptic seizures [59]. We are currently examining the immune profile in children with epilepsy and autism (Taylor et al, manuscript in preparation).

The quality of clinical epilepsy research is deeply depending on the verification of a large variety of epileptic seizures, their origins, and several comorbidities. This high variation may very well be the main reason for the sometimes contradicting results in current publications about the immune response in epilepsy. However, we believe that a defined immune profile in epilepsy may not be far away from diagnostic use in clinical practice and it is time for evaluating its prognostic value.

The value of EEG as a biomarker of epileptogenesis and seizure recurrence in different acquired epilepsies (Carla Bentes)

The electroencephalogram (EEG) is a neurophysiological technique with high temporal resolution and sensitivity in the evaluation of brain function in real-time. EEG does not have relevant contraindications and is a painless exam done at the patient's bedside, repeatedly or continuously, without increased risks. It is also a low-cost exam, available in most hospitals used in patients with seizures, *status epilepticus* and/or epilepsy, both for diagnosis and classification, as well as for treatment planning. Despite being considered the *gold standard* for identifying different epileptogenesis and ictogenesis biomarkers [60, 61], the clinical usefulness of the EEG in epilepsy prediction remains uncertain for most etiologies and in different types of clinical settings. Nevertheless, a great deal of new evidence has emerged in the last decade.

Epileptogenesis is the development and extension of tissue capable of generating spontaneous seizures, resulting in the development of an epileptic condition and/or progression of epilepsy after it is established [1]. Several studies have demonstrated specific changes in the EEG as potential biomarkers for the early development of epileptogenesis [62]. However, few of those refer to human epileptogenesis, and most of these were taken from Tuberous Sclerosis Complex and Acute Brain Injury (ABI) including post-traumatic and post-stroke clinical models [63-68]. Although scarce, this evidence has already changed our clinical practice [65, 69] and has a huge potential for the design of new anti-epileptogenesis drugs clinical trials [65, 70, 71].

Frequently, in acquired epilepsies, it is possible to identify a latent period after an ABI and before clinical epilepsy onset. During this period, epileptogenesis takes place at the

molecular, cellular level and brain networks. An early identification of this process is of utmost importance having clinical and research implications.

In 2008, Kim and collaborators showed that sporadic epileptiform discharges and focal polymorphic slowing were associated with post-traumatic epilepsy (PTE) development [67]. Their results also show that epileptiform activity occurs early (<5 days) after traumatic brain injury, suggesting early EEG a useful diagnostic tool for assessing PTE.

In a prospective cohort of anterior circulation ischemic stroke patients (16), 18% had interictal or ictal epileptiform activity in a short-duration EEG during hospitalization, and 25% had at least one seizure in the first year after stroke. In this cohort, an early post-stroke EEG helped to identify patients with a higher risk of post-stroke epilepsy (PSE) and an unfavourable stroke outcome, independently from clinical (NIHSS) and imaging (ASPECTS) severity of the infarct [68]. Interictal epileptiform activity and background activity asymmetry were the stronger predictors of PSE. In line with these results, using a case–control design study, Punia and collaborators [66] also found that acute epileptiform abnormalities on the EEG are associated with almost twelve times increased odds of PSE after adjusting for potential risk factors. When acute EEG findings are analysed alongside established clinical and neuroimaging predictors, only the former remained significantly associated with PSE.

Furthermore, in the first 7 days after stroke, Bentes and al. study (16) showed that more than 20% of acute symptomatic seizures were exclusively electrographic and more than 40% of patients with electrographic seizures had non-convulsive status epilepticus criteria or unprovoked seizures. In fact, more than one-fourth of acute symptomatic seizure patients having a vascular epilepsy diagnosis in 1-year time period would not have been identified without the EEG protocol that was used [68]. It is important to note that this study was performed in a Stroke Unit. Therefore, even with the best clinical care available, outside an intensive care unit, an important percentage of post-stroke seizures patients are not diagnosed, further increasing the value of the EEG in this context. In fact, early seizures are a strong predictor of PSE and are included in the available PSE prediction tools [72-74]. Additionally, the value of EEG is reinforced in the follow-up of Bentes and collaborators cohort [75], as one year after the cerebrovascular event, 1.7% of patients had clinical and neurophysiological criteria for *epilepsia partialis continua.*

In patients with different ABI (such as stroke, Intraparenchymal hemorrhage, subarachnoid hemorrhage, posterior reversible encephalopathy syndrome, infections and others) admitted to an intensive care unit and submitted to continuous EEG (cEEG), Punia and collaborators matched parallel control study [66] found, after adjusting for cEEG indication and follow-up duration, that the odd of cases developing epilepsy was almost fifteen times higher compared to the controls. This elevated risk was despite a ten times higher likelihood of cases to be taking AEDs at the last follow-up.

Evidence about the importance of neurophysiological biomarkers of epilepsy in acquired epilepsies is growing up, as shown in the study of Chen et al [76]. These authors found that 25.7% of patients with different types of ABI such as acute ischemic stroke, intracerebral hemorrhage, subarachnoid hemorrhage and traumatic brain injury, developed new-onset epilepsy during a median follow-up of 19.1 (16.2–24.3) months. In this study, EEG epileptiform abnormalities on an early cEEG were associated with a greater than three-fold increased risk of new-onset epilepsy.

In conclusion, EEG is a useful risk stratification tool for assessing the long-term risk of seizures and a biomarker for new-onset epilepsy in different acquired epilepsies. Although a short time window between ABI and EEG looks more effective for this purpose, the best technical modality, timing and duration of the EEG record is not yet established. Interictal epileptiform activity is a good biomarker candidate among others, but the best neurophysiological biomarker is yet to be established. Prospective, multicentric and validation studies of the EEG as a biomarker of epileptogenesis and seizure recurrence are needed. Furthermore, quantitative EEG and artificial intelligence algorithms are promising strategies on the search for epileptogenesis and seizure recurrence biomarkers.

Serum biomarkers for the diagnosis of structural acquired epilepsy (Laura Abraira)

Serum biomarkers for the diagnosis or prediction of epilepsy are becoming an interesting field of research in recent years. About 60% of epilepsies are secondary to structural causes, which means that a process of epileptogenesis may starts after the brain injury [77].

Epileptogenesis refers to the process whereby central nervous system tissue acquires the capability to generate the abnormal and spontaneous electrical activity that results in development of epilepsy or progression of this condition [1].

Immediately after the primary injury, there is a neuroinflammatory response necessary to repair the brain damage. However, when there is an excessive response or this process persist in time it may contribute to epileptogenesis and the development of epilepsy [78].

So far, we cannot identify which patients will develop epilepsy in the long term. The studies are heterogeneous, as they include different types of patients, which makes it difficult to interpret the results. Only 20% of patients will develop epilepsy after brain injury, which means that we need long time periods and high costs to design prospective studies [70] .

Biomarkers provide additional information to the clinical risk factors already described and may be useful in designing clinical trials for new-targeted drugs. The optimal biomarker should be epilepsy-specific, with high sensitivity and specificity. Furthermore, it should be translatable into clinical trials against epileptogenesis, non-invasive and have a long expression time window [6].

A biomarker is an objectively measurable characteristic of a biological process that reliably identifies the presence of development, severity, progression or location of an epileptogenic abnormality. They can be classified into different categories according to their function (susceptibility, diagnostic, monitoring, prognostic, predictive, response and safety) and different types, such as neurophysiological, neuroimaging or blood biomarkers [1].

Diagnostic or predictive categories include biomarkers related to epileptogenesis5. Molecular biomarkers include not only plasma and serum proteins, but also miRNAs. They have the advantage of being non-invasive, are related to the stage of the disease and can be linked to EEG and imaging biomarkers. However, we do not know the optimal time window for blood sampling, they are physically far from the site of pathology and the half-life can vary greatly. Thus, we are still far from their use in routine clinical practice [79].

Regarding protein biomarkers, Walker et al's group reported that increased levels of HMGB1 (high-mobility group box 1) protein identified animals that developed epilepsy after status epilepticus induced by unilateral electrical stimulation of the hippocampus [80]. Zelano's

group reviewed the most important blood biomarkers related to epilepsy and classified them into two groups according to their specificity (brain-derived biomarkers and biomarkers involved in the neuroinflammatory response). Brain biomarkers include proteins such as S100B and GFAP, which are released after brain damage and expressed by astrocytes; elevated levels of these proteins have been associated with the development of epilepsy. Other biomarkers such as NSE, NFL and UCHL-1 are neuronal proteins, so far the results are not specific for epilepsy. The second group of biomarkers includes a wide variety of cytokines (IL-1B, IL-6, IL-8, IL-10, IFNy, TNFa) that are involved in multiple inflammatory responses and can provide both proinflammatory and anti-inflammatory responses [80].

Most studies focus on post-traumatic and post-stroke epilepsy due to the high prevalence of both etiologies [74, 81, 82].

Pitkanen's group hypothesised a likely overlap between biomarkers present in traumatic brain injury and epilepsy, with the same biomarker being present in both processes. They proposed S100B, GFAP, IL-6, HMGB1, UCH-L1 as well as some proteins related to blood-brain barrier damage (vWF, VEGF, cFN)10 . In addition, an international research group (EpiBioS4Rx) composed of a multidisciplinary team aims to develop the first validated multimodal biomarker panel (EEG, neuroimaging, molecular and anatomopathology) for the design of anti-epileptogenesis clinical trials in post-traumatic epilepsy [83].

Regarding post-stroke epilepsy, Zelano's group evaluated acute symptomatic seizures and epilepsy in a group of 90 stroke patients undergoing thrombectomy [84]. They observed increased levels of TAU, NFL, GFAP, S100B and NSE. Abraira et al observed higher levels of endostatin and lower levels of S100B and Hsc70 in those patients at increased risk of developing epilepsy after stroke. In addition, lower levels of TNFR-1 and higher levels of NCAM were associated with the presence of acute symptomatic seizures [85, 86]. Finally, Tim von Orzten's group highlight the importance of the different role of each one depending on the phase of the process of epileptogenesis [87].

Based on the evidence so far, predictive power is likely to require a combination of electrophysiological, neuroimaging and molecular biomarkers measured at different time points after injury. So far, incomplete statistical validation, lack of human studies, limited knowledge and high costs are some of the limitations to be improved [79].

“Is it structural epilepsy?” Critical appraisal of the ILAE definition of epilepsy (Francesco Brigo)

In 2014, the International League Against Epilepsy (ILAE) proposed a practical definition of epilepsy that could be applied in several contexts, including the setting of a first unprovoked seizure following an acquired static brain lesion [88]. Accordingly, it is possible to diagnose epilepsy with “one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years” [88]. The ILAE official report provided a series of case examples to provide clinical guidance. The case example n.2 describes “A 65-year-old man had a left middle cerebral artery stroke 6 weeks ago and now presented with an unprovoked seizure” [88]. According to the authors of the ILAE report, epilepsy can be diagnosed after a first unprovoked seizure following a stroke, a brain injury or a cerebral infection due to the “high (>70%) risk of another unprovoked seizure” [88]. This assertion was supported by the

findings of a single study published by Hesdorffer and colleagues in 2009 [Hesdorffer et al., 2009]. According to this study, the risk of long-term recurrence 10 years after a first unprovoked seizure was 71.5% (95% confidence intervals, CI: 59.7%-81.9%) after a stroke, 46.6% (95% CI: 30.4-66.3%) after traumatic brain injury, and 63.5% (95% CI: 21.2-98.6%) after central nervous system (CNS) infection [Hesdorffer et al., 2009].

In contrast to what is stated in the ILAE official report [88], the point estimate of the risk of seizure recurrence after a first unprovoked seizure is higher than 70% only for seizures following a stroke. Point estimates are values that have been directly observed in the study, whereas the CI represent the amount of uncertainty and imprecision associated with the sample taken, and depend on the sample size and the sampling variability. Of note, all values included within the range of CI are plausible. Hence, to conclude that a first unprovoked seizure has a risk of recurrence of ≥60%, all values in the CI should be above that threshold. This applies only to unprovoked seizures that occur after a stroke.

The application of the current practical definition of acquired structural epilepsy as reported in the ILAE official report is based on an incorrect interpretation of the findings of a single study, which makes it imprecise and potentially misleading. In some clinical scenarios, it carries the risk of overdiagnosing epilepsy, with possible negative psychosocial consequences and unnecessary use of antiseizure medications. The estimates for the risk of seizure recurrence after a first unprovoked seizure due to brain trauma, or cerebral infection are imprecise [89, 90], not invariably associated with a high risk (≥60%) of seizure recurrence, and do not automatically support a diagnosis of epilepsy. This most likely also applies to stroke, since different studies have found varying degrees of long-term recurrence following a first unprovoked post-stroke seizure [90]. This is not surprising, as stroke, brain trauma or brain infection (just as epilepsy!) are heterogeneous conditions that could result in wide, heterogeneous, and variable risks of seizure recurrence.

Further studies are needed to clarify the risk of seizure recurrence in various clinical situations and identify which factors (clinical characteristics, etiology, mechanism and severity of insult, and others) can modify the risk of seizure recurrence in various clinical situations.

Acute Symptomatic Seizures and subsequent Epilepsy after CNS Infections (Josemir W. Sander)

Epilepsy is just a tendency to have unprovoked seizures, resulting of an underlying problem of the brain or a system problem [91]. It is a symptom-complex, not a disease; a fair analogy would be anaemia. Indeed, anaemias are the seizures of blood and seizures are the anaemias of the brain.

Over 50 million people worldwide are affected by epilepsy, most of whom are in Low-and-Middle Income Countries (LMICs) with poor healthcare ecosystems. Most people with epilepsy in LMICs lack adequate treatment, and such settings have a vast diagnostic and treatment gap [92].

Epilepsy is mainly a condition of people with low incomes, and social determinants of health play a significant role in the risk of developing epilepsy. The incidence of epilepsy in LMICs is almost double that in high-income countries (HICs) [93]. There are several possible reasons why more people develop epilepsy in LMICs, and some of them may be methodological such

as case ascertainment methods, particularly the erroneous inclusion of people with acute symptomatic seizures (ASS) into epilepsy samples [94]. There is also evidence that people in the lower socioeconomic strata in HICs are more prone to develop epilepsy than people in wealthier settings in such countries5.

Social determinants, nonmedical factors influencing health outcomes, are known to be a significant player in the risk of ill health, and poverty is a major social determinant of health6. These determinants are the circumstances in which people are born, grow, work, live, and age and the broader forces and systems shaping daily life. Factors such as healthcare access and quality, social context, access to quality education, economic stability and the surrounding environment are essential in this consideration6.

Social-determined or poverty-related diseases are more prevalent in deprived populations, including infectious diseases, malnutrition-related diseases, respiratory diseases, cardiovascular diseases, cancers, poor oral health and traumatic brain injury. It is also common knowledge that inadequate health behaviour is more widespread among more impoverished members of society, particularly in epilepsy, CNS infections and parasitic infestations; genetic factors such as assertive mating and traumatic brain injury before, during or after birth play a significant role [92].

Disorders involving the cerebral cortex may trigger seizures, and brain infections or infestations are no exception and should be considered significant risk factors for epilepsy. Infections triggering seizures and epilepsy are probably more common than currently accepted [95]. Infections are the most common cause of “de novo” Status Epilepticus in children globally. Neurocysticercosis is the most common risk factor of newly diagnosed epilepsy in large areas of LMICs, and malaria is a common fever trigger in febrile convulsions in endemic regions [96]. In some series, over 3/4th of survivors of large temporal abscesses develop epilepsy in the aftermath, often after having had acute symptomatic seizures.

ASS often happens at the acute phase of a CNS infection and may occur in up to a third of all “known” cases of severe CNS infections. It is impossible to ascertain whether ASS are provoked or first spontaneous seizures, as there are still many unknowns, but these ASS likely differ mechanistically from subsequent consequential chronic epilepsy. Still, they are a significant risk factor for the subsequent development of epilepsy. However, not all people with ASS will develop subsequent epilepsy and not all those with subsequent epilepsy have ASS, and predictions are impossible as the exact mechanical risk factors for subsequent epilepsy after ASS are unknown7. The type of infection and presence of ASS influence the risks of subsequent epilepsy. For instance, the 20-year risk of developing epilepsy in survivors of viral encephalitis is around a quarter in those with ASS but only ten % without early seizures. In bacterial meningitis, the 20-year risk is 13% with ASS and 2.4% without. The attributable risk is not known in both cases, as it is the case in most cases of CNS infection,

All aetiological categories of CNS infections are associated with subsequent epilepsy in survivors. Bacterial infections resulting in acute bacterial meningitis, intracranial abscess or empyema, and CNS tuberculosis or neurosyphilis are linked with subsequent epilepsy. Coxsackie B, Arboviruses, SSPE, Herpes simplex, cytomegalovirus, Japanese encephalitis and HIV are particular culprits regarding viral infections associated with seizures and epilepsy. Protozoal diseases, particularly cerebral falciparum malaria, Toxoplasmosis and Trypanosomiasis, are associated with epilepsy. Seizures associated with fungal infections usually affect immunocompromised individuals. Helminthic infestations of the brain, particularly with Taenia solium, Onchocercus volvulus, Echinococcus granulosus and

Paragonimus westermani, are risk factors for epilepsy, with Taenia solium a significant contender for the biggest risk factor for seizures and epilepsy in the form of Neurocysticercosis.

The route of entry in the CNS for infective agents varies according to the nature of the agent. Bacterial and viral infections usually gain access from arteries through the blood-brain barrier or choroid plexus via passive venous transport through the spinal plexus, neuronal through olfactory routes or direct invasion through trauma or from cranial sinuses. The risk of invasion is often related to the immunological status of the individual.

Regarding pathophysiology, infective invasion may use different mechanisms, resulting in seizures, provoked or unprovoked [95, 96].

Bacterial and viral agents may lead to arteritis, followed by ischaemia and infarctions. Granulomas and abscess formation may also complicate such infection. Seizures due to direct neuronal damage may also result from HIV and the measle virus in Subacute sclerosing panencephalitis (SSPE) cases.

Protozoa excursions into the CNS may trigger seizures through various pathophysiological mechanisms, including arteritis leading to ischaemia and infarctions, abscess formation, and the development of granulomas [96]. Capillary thrombosis and astroglial reactions may also happen, often resulting in the formation of granulomas.

Helminthic brain infestation may lead to seizures via vasculitis, resulting in infarctions and granulomas. "Abscess" formation with mass effect is also noted. Helminths entering the brain may also serve as vectors for other infectious agents [95].

The burden of epilepsy could be substantially decreased if primary prevention strategies were available to decrease the risk of epilepsy following a brain infection or infestation. Primary prevention is currently the only viable approach to reduce the resulting epilepsy burden. Two parasitoses in which this would be possible are Neurocysticercosis and cerebral malaria. For instance, improving basic sanitation in Taenia solium endemic areas could substantially decrease the risk of Neurocysticercosis.

Despite infection-related epilepsy being an important disability factor and having a significant impact on the burden of the condition, there are still many unknowns, particularly in terms of the precise mechanism behind the risk and the attributable risk for each agent to trigger seizures and epilepsy. CNS infections and infestation are the most common preventable risk factors for epilepsy and should be targeted for primary prevention. Effective treatments for infection are parasites available, but the long-term impact on epilepsy risk is also not assessed.

Further research is needed to establish the attributable risk of CNS infection, ascertain the risk spectrum, and fine-tune the understanding of the mechanistic aspects of seizures and epilepsy triggered by CNS infections and infestation.

Reperfusion therapies and risk of post-stroke epilepsy (Petra Redfors)

The utilization of reperfusion therapies in the management of acute ischemic stroke has steadily increased over the years, both due to enhanced access to treatments worldwide and expanded indications.[97] Intravenous thrombolysis (IVT) has been approved for more than

20 years. Endovascular treatment (EVT) has become the standard care for eligible patients within 24 hours of symptom onset.[97] Recent studies have also demonstrated the efficacy of this treatment approach in selected patients with large vessel occlusion (LVO) and substantial infarct core.[97, 98] While these treatments are not equally available in all countries, efforts are being made globally to improve their accessibility and utilization as both treatments are cost-effective even in low and middle income countries.[99] Given this increasing trend in stroke patients receiving reperfusion treatments, it's important to investigate whether these treatments influence the risk of acute symptomatic seizures (ASS) or post-stroke epilepsy (PSE).

The potential ways in which reperfusion therapies might lead to seizures involve several routes.[100] These includes direct toxicity linked to Recombinant Tissue Plasminogen Activator (rtPA) and the initiation of an inflammatory cascade known as reperfusion syndrome.[101, 102] Hemorragic transformation is also more frequent after reperfusion therapies and has been pointed out as a risk factor of seizures after stroke.[103] On the other hand, reperfusion therapies have been found to reduce the size of the infarction, which might lead to fewer seizures.

The relationship between acute symptomatic seizures (ASS), occurring within 7 days of stroke onset and reperfusion therapies have been explored. A German retrospective study found no difference in ASS frequency after IVT or EVT compared to historical cases.[104] A meta-analysis by Liu et al reported a 3.6% ASS incidence but did not reveal any significant association between ASS and EVT.[105]

Various clinical factors that contribute to post-stroke seizures have been identified.[106] These factors include stroke location, cortical involvement, the severity of pre-treatment symptoms, and acute symptomatic seizures.[106, 107] However, whether risk factors for seizures following reperfusion therapies exhibit differences or if any risk factor holds greater significance in comparison to those associated with seizures without treatment are not clear. Thevathasan found an strong association between hemorrhagic transformation and seizures after endovascular treatment (EVT).[103] This association has also been observed following intravenous thrombolysis.[108] In a large population-based study conducted in Sweden, risk factors associated with PSE following EVT were markers of extensive infarction size, such as high post-treatment stroke severity and the presence of cerebral media infarction in follow-up CT scans.[109] In contrast, IVT before EVT and the lack of infarction on follow-up CT scans appeared to be protective factors.

Studies on PSE after thrombectomy are small and lack procedure-related details. In a meta-analysis encompassing four studies and 1500 EVT patients, a PSE occurrence rate of 5.8% was reported.[105] Endovascular treatment was not associated with the PSE. However, one of the studies incorporated in this meta-analysis conversely showed that individuals treated with reperfusion had a higher risk of developing poststroke seizures compared to controls.[110]

There are now indications that EVT might even protect against PSE, likely achieved by diminishing the infarct size. In the nationwide case-control study conducted in Sweden, involving 1500 patients who underwent IVT and an equal number who received EVT, individuals subjected to EVT exhibited a reduced risk when contrasted with untreated patients.[109]

NORSE and FIRES in adults and children- Do we need to think differently? (Ronny Wickström)

New-Onset Refractory Status Epilepticus (NORSE) with the subgroup of Febrile Infection Related Epilepsy Syndrome (FIRES) is a rare and acute condition with limited knowledge on pathophysiological mechanisms and a generally poor outcome with a significant mortality [111]. Early identification is therefore paramount to initiate appropriate investigations and management.

The etiology for NORSE varies as it is a clinical presentation and not a specific diagnosis. In around 50% of cases, the etiology remains unexplained in spite of extensive evaluation [112]. This so-called "cryptogenic NORSE" [113] may differ mechanistically from other etiologies and thus require other forms of treatment. Although the pathopsyiological mechanisms are unknown, several lines of evidence point to inflammatory mechanisms including activation of innate immunity as at least part of the mechanisms. These include polymorphisms in cytokine-related genes [114, 115], increased cytokine levels in CSF and serum [116-118] [119] and reports of effects of therapies targeting interleukin (IL)-1 or IL-6 receptor-mediated signaling (reviewed in [120]). Following a rapid and extensive diagnostic work-up, NORSE treatment should therefore include aggressive escalation of anti-seizure medications followed by early initiation of ketogenic diet and the use of immunomodulation.

An international consensus guideline for diagnostic work-up, treatment and future directions for research was recently published [120, 121]. Initial testing should include a comprehensive infectious evaluation including cultures, and viral and bacterial serology relevant in the geographical region and season, a comprehensive rheumatologic evaluation, autoimmune and paraneoplastic antibody panels and evaluation for inborn errors of metabolism at least in young children [120]. Subsequent to status epilepticus treatment as per local protocols, first-line immunotherapy (including corticosteroids, intravenous immunoglobulins and possibly plasma exchange) should be initiated within 72 hours of seizure onset. In noninfectious NORSE with inadequate response to first-line immunological treatment in the initial week, ketogenic diet and second-line immunological treatment should be started within 7 days of seizure onset. Immunological treatment should be based on suspected etiology so that if a pathogenic antibody is identified or highly suspected, rituximab treatment should be initiated. In contrast, in cryptogenic NORSE without clinical features of autoimmune encephalitis, IL-1 blockers or IL-6 antagonists should be initiated. Risk–benefit discussions of these two agents should be conducted by a clinician comfortable with their usage.

In the postacute and chronic phase of NORSE, dietary treatment and immunomodulation should be continued if effective in the acute phase. Importantly, cognitive impairment and behavioural problems are a large and likely underreported problem in survivors of NORSE (reviewed in [122]). All patients who are able to do so should therefore undergo neuropsychological evaluation, be screened for mood and psychiatric disorders including sleep disorders and undergo an intensive program of motor and cognitive rehabilitation.

Recent consensus definitions and Delphi-based recommendations are available for clinical decision support and open International biobanks and registries are available for patient inclusion.

Tailored ASM selection based on big data (Johan Zelano)

A fundamental problem in epilepsy is predicting which ASMs will suit which patient. Observational studies suggest that only 50% become seizure-free on and tolerate their first ASM [123]. Age, concomitant drugs, and comorbidities are often stated as factors that need to be taken into account when clinicians select which ASM to use for initial monotherapy [124], but predicting which ASM will work for which patient is not yet possible. After a failed first attempt, the mode of action of the not-effective drug sometimes offers some insight into what ASMs to try or not to try next, but actual evidence is sparse.

Personalized medicine refers to a concept of treatment based on evidence from highly representative patient groups. Such evidence is unlikely to arise from traditional randomized trials in epilepsy, which aim to demonstrate an anti-seizure effect of a drug, but not to determine which drug is best for which patient. Trial populations are typically very heterogenous, including patients with epilepsies of all etiologies, ages, and sex. Many, including the ILAE task force on Epilepsy in the elderly, have wished for trials on more homogenous populations [125], but trials aimed at specific patient groups struggle to recruit, even if they target very prevalent etiologies like stroke. Small randomized trials have found lamotrigine and levetiracetam to be better tolerated than carbamazepine in poststroke epilepsy [126, 127]. Comparative trials in neurocysticercosis have failed to identify differences between treatment, but seem underpowered [128, 129]. With an increasing number of ASMs, multi-treatment RCTs that establish which drug works best for specific patient groups (for instance 40–50-year-old women with posttraumatic epilepsy) seem even less likely. Nonetheless, observational studies suggest that all epilepsies are not the same. In focal epilepsy, the etiology seems important for treatment responsiveness [130]. Sodium-channel blocking drugs have been suggested to be more effective in immune-medicated epilepsies [131].

It is against this background that big data becomes interesting. By using claims or prescription databases, several research groups have tried to use big data to identify which ASMs are most likely to be retained (an integrated measure of effect and tolerability) in specific patient groups. In contrast to typical clinical trials of up to a thousand patients, big data studies with population-wide inclusion can include tens of thousands of patients – allowing stratification of patients sufficiently to study for instance posttraumatic epilepsy in 40-50-year-old women. According to Swedish registers age-, sex-, and brain comorbidities influence which ASMs are retained; retention of the first ASM could potentially increase by 14-21% if patients with focal acquired epilepsies had given the most optimal ASM for them [132]. Interestingly, there is a high congruence of big data and expert opinion-based tools like Epipick [133] – the ASMs suggested by experts have a high retention rate [134]. Several groups have also tried to use machine-learning to derive the most optimal ASM for different patient groups in very large data sets.

The field is in its infancy, but big data studies seem able to provide information on which ASMs have been used and retained by specific patient groups. This is a step towards personalized medicine. Establishing which ASM is actually the best for each patient group will be more difficult, because of the intrinsically observational nature of register data. It is not known why a clinician decided on a particular ASM for a particular patient. Statistical matching procedures may overcome some of these barriers, but in the longer run randomized evidence would be preferable. A multistep approach could be to use big data for

distilling top ASM candidates for specific patient groups, which could then be evaluated in traditional multi-center trials.

Another important area of use for big data is safety – monitoring of adverse effects or poor outcomes linked to particular ASMs. Swedish patients with lamotrigine monotherapy and epilepsy after stroke had a lower hazard of death than patients on carbamazepine [135]. Claims data have been studied to detect negative effects of ASMs on child bone health [136]. Recently, Danish researchers found that lamotrigine was not linked to excess mortality in patients with heart conditions [137], providing important information in the discussion about the FDA warning regarding arrhythmogenicity. The detrimental effects of prenatal exposure of valproic acid could have been detected at least a decade earlier, had full advantage been taken of available registers [138]. Big data allows long-term follow-up and study of rare side effects. In the future, clinicians will hopefully be able to personalize ASM selection for retention as well as long-term safety.

Predicting treatment resistance in acquired epilepsies (Simona Lattanzi)

A variety of biological mechanisms underlies drug resistant epilepsy (DRE). A systematic review and meta-analysis identified symptomatic aetiology as a strong predictor of DRE, with little heterogeneity between studies [139]. Noteworthy, symptomatic epilepsies encompass a great variety of causes, and the question is whether the individual underlying aetiology may influence the risk of DRE. In a hospital-based observational survey in people with focal seizures, some lesions (e.g., post-stroke, vascular malformations, and tumours) were associated with a relatively high rate of seizure control and some others (e.g., hippocampal sclerosis, cerebral dysgenesis) with highly DRE [140]. The outcome was highly variable in adolescents and adults with localisation-related epilepsy who were followed up prospectively: people with mesial temporal sclerosis were less likely to be controlled than those with arteriovenous malformation, cerebral infarction, primary tumour, cortical gliosis, cerebral atrophy, and cortical dysplasia [141]. In a cohort of 591 subjects with focal epilepsy, ischemic stroke was the aetiology with the highest rate of 12-month terminal seizure freedom, and the better prognosis was achieved with the lowest antiseizure medication (ASM) load. People with hippocampal sclerosis and malformation of cortical development had the lowest rates of seizure freedom [130].

A splitting approach by individual aetiology looks reasonable to investigate the risk factors of drug-resistance. Nonetheless, aetiology-specific data about treatment response are surprisingly sparse. Limited evidence exists for stroke, traumatic brain injury, and immune-mediated disorders.

The occurrence of early seizures was an independent factor for the development of DRE after non-traumatic intra-cerebral hemorrhage [142]. A population-based, retrospective cohort study identified younger age and female sex as predictors of DRE in adults aged 67 and older who were hospitalized for stroke and were previously free from epilepsy [143]. In a retrospective analysis of a cohort of people with post-stroke epilepsy admitted at one epilepsy center in Italy, younger age at stroke onset, hemorrhagic stroke subtype, stroke severity, status epilepticus at epilepsy onset, and the latency from stroke to epilepsy onset were statistically significant predictors of DRE [144-146].

In a retrospective analysis of people with post-traumatic epilepsy, age at time of post-traumatic epilepsy, seizure type (generalized, focal, mixed onset), status epilepticus, and EEG findings (normal, abnormal background, epileptiform discharges) were independent predictors of DRE and were used to build a clinical nomogram [147].

Many subjects with encephalitis associated with autoantibodies against surface antigens (e.g., NMDAR, AMPAR, LGI1, GABAAR, GABABR) achieve complete seizure freedom after treatment, and ASMs can eventually be discontinued [36]. Seizures in the context of autoimmune encephalitis at initial or relapsing presentations can be best conceptualized as acute symptomatic seizures, despite seizures sometimes take weeks or even months to resolve [36]. The risk of epilepsy is, indeed, low (<5%-10%) for most types of encephalitides associated with autoantibodies against surface antigens, and low-moderate for those associated with antibodies against LGI1 and GABAAR. In contrast, some individuals with immune-mediated brain diseases have seizures that become chronic and prove resistant to both ASMs and immunotherapy. This may occur more frequently in subjects with encephalitis associated with onconeural antibodies (e.g., Hu, Ma2, CRMP5, amphiphysin) and antibodies targeting glutamic acid decarboxylase (GAD), who have a high (>60%) and very high risk (>80%) of autoimmune-associated epilepsy, respectively [36].

Putative risk factors of drug-resistant autoimmune-associated epilepsy include the presence of antibodies against intracellular antigens, immunotherapy delay, status epilepticus/NORSE, age, temporal lobe involvement, periodic discharge before immunotherapy, interictal epileptiform discharges, and generalized tonic-clonic seizures [148-150]. A clinical risk score for the prediction of DRE in people with autoimmune encephalitis has been recently developed [151].

The accurate prediction of DRE is a challenge. Drug resistance in epilepsy is a multifactorial phenomenon and the response to treatment is highly aetiology-specific [152]. Aetiology should be considered when counseling people about expected seizure outcome and when tailoring initial ASM doses [130].

Prognosis of symptomatic epilepsy: the impact on survival (Rob P.W. Rouhl)

Comorbidity has an impact on epilepsy survival, however vice versa, epilepsy (and its treatment) might also impact survival in specific brain diseases. This possibly reciprocal relation requires a thorough understanding of the pathophysiological mechanisms, but also of the potential biases in and limitations of epidemiological research. An important potential bias is the immortal time bias. In cohort studies a survival benefit may be found for patients with epilepsy and another brain disease. However, this might be due to immortal time bias. Patients with epilepsy (by definition) all have a longer outcome free follow-up, as all first aad to develop epilepsy, before potentially reaching the endpoint. This ‘artificial’ longer follow-up due to the classifying event (the development of epilepsy) is called the immortal time bias. Other pitfalls of the current epidemiological studies are the different definitions of epilepsy and seizures in the individual studies, the mode of follow-up (only few studies have epilepsy and seizures as a primary outcome measure) and the study design (most studies are retrospective).

In several brain diseases, epilepsy and seizures are related to a worse outcome. The first example is brain abscess, in a large study of 1179 patients with a large proportion of patients with epilepsy (323), the mortality risk ratio was 1.26 (1.01-1.57) [153]. In this cohort, patients were at risk for epilepsy when they had a history of a previous brain disease (stroke, trauma) or alcohol abuse; all relating to a more vulnerable brain.

The second example is traumatic brain injury: patients with epilepsy have a higher mortality risk, which varies between 27%-65% (versus patients without epilepsy 10-45%)[154, 155] depending on the length of follow-up. In one retrospective study, it seemed that early treatment with anti-epileptic drugs led to a survival benefit[156], however, the retrospective nature precludes such conclusions as patients with a worse prognosis might not be selected for anti-epileptic drug treatment.

In brain tumor patients, the relation between epilepsy and higher or lower mortality risks is not evident. After the first studies which showed that patients treated with valproic acid for their seizures in patients with glioblastoma multiforme [157], it appeared that epilepsy in general could have a survival benefit, though, this could be the consequence of the immortal time bias. Subsequent studies also failed to clearly show this benefit (independently), and also the potential positive effects of valproic acid could not be reproduced [158]. It now appears that epilepsy in patients with tumors with specific molecular profiles can react better to levetiracetam and may lead to somewhat lower mortality [159], though developments on insights in these molecular profiles are rapidly evolving, requiring ever more detailed epidemiologic studies.

Lastly, in patients with cerebrovascular disease, most studies did not find a relation between post-stroke epilepsy and (long-term) mortality, though in specific subgroups, mortality might be higher [160-162]. On the other hand, a large national register study in Sweden showed that the choice of treatment of epilepsy after stroke might have an impact on survival; authors found all-cause mortality hazard ratios for valproic acid of 1.40 (1.23-1.59, 95%-confidence interval) and for lamotrigine 0.72 (0.61-0.95) compared to carbamazepine (reference).[135] Of course, this is not a randomized study, so other factors in medication choices also influencing the outcome might have played a role.

In conclusion, the relation between comorbid epilepsy, or epilepsy with comorbidities and mortality is complex and still requires more epidemiological research taking into account all details we now know on the pathophysiological concepts, whilst not ignoring the possible biases and limitations of this type of research.

Anti-seizure medication withdrawal in seizure-free patients with structural epilepsy (Morten Ingvar Lossius)

The question of the propriety of discontinuing medicines in epilepsy patients who have been seizure-free for a long time is a difficult one. Unfortunately, in this field of epileptology there are few robust studies that can guide clinicians. A thorough knowledge of the patient's epilepsy and a careful discussion of pros and cons is required.

It has been carried out two randomized controlled trials (RCTs) on discontinuing anti-seizure medicines (ASMs) in patients with epilepsy in general [163, 164], but there are no such studies specifically aimed at those with structural (lesional) epilepsy. However, retrospective

multi-centre studies have been conducted on ASM withdrawal in seizure-free patients after epilepsy surgery [165, 166]. The majority of these patients has structural epilepsy.

What speaks for discontinuing the drugs is that either patients experience annoying side effects, or they fear long-term side effects. According to Perucca et al.[167], nine out of ten patients experience at least one side effect when using ASMs. For many, regular intake of drugs is associated with having a patient role, and when ASMs are no longer required, many patients consider themselves to be cured [168].

Both old and new ASMs may have a negative impact on cognitive functions [169, 170]. In children, ASM side effects may interfere with normal brain development [171, 172], and chronic ASM exposure during critical stages of brain development can negatively influence academic achievements [173].

What speaks against discontinuing the drugs is the risk of seizure recurrence with all that entails, i.e. risk of seizure-related injuries, loss of employment and driving license, and in the worst case sudden death. The two mentioned randomized ASM withdrawal studies, including some patients with structural epilepsy, showed a doubled risk for seizure recurrence in the withdrawal group compared to those who continued to take the drugs, after one and two years, respectively [163, 164]. A meta-analysis, including 45 studies of 7082 patients, found a cumulative recurrence rate after ASM withdrawal about 34%, 3-4 years after drug withdrawal [174].

In a systematic review, the following independent predictors of seizure recurrence were identified: Duration before seizure remission, seizure-free interval before ASM withdrawal, age at epilepsy onset, history of febrile seizures, number of seizures before remission, absence of a self-limiting epilepsy syndrome, developmental delay, and epileptiform activity on EEG before ASM withdrawal [174].

A recent study showed that those with epilepsy-related low-grade brain tumors had the best chance of being seizure-free and off medication 5 years after epilepsy surgery, while those with epilepsy due to malformations of cortical development (MCD) had the worst chance [165].

The policy for postoperative ASM withdrawal has evolved over time. A worldwide electronic survey conducted among neurologists and pediatricians in 53 countries addressed the issue among 446 clinicians [175]. The authors concluded that, when compared to neurologists treating adults, pediatricians tapered the ASMs after a shorter seizure-free interval (1 year or less) after temporal lobe surgery.

Thus, whether to discontinue ASM or not in seizure-free patients with epilepsy should be individualized, taking into account the patient's epilepsy, the tolerability of the drug, and the patient's own preference. After 2-5 year of seizure freedom in adults, and even earlier in children and after successful epilepsy surgery, this question should be addressed. The decision must be made after a careful risk-benefit analysis.

References

[1] Pitkanen A, Engel J, Jr. Past and present definitions of epileptogenesis and its biomarkers. Neurotherapeutics 2014;11: 231-41.
[2] Shen Y, Gong Y, Ruan Y, Chen Z, Xu C. Secondary Epileptogenesis: Common to See, but Possible to Treat? Front Neurol 2021;12: 747372.
[3] Pitkanen A, Lukasiuk K. Mechanisms of epileptogenesis and potential treatment targets. Lancet Neurol 2011;10: 173-86.
[4] Issa NP, Nunn KC, Wu S, Haider HA, Tao JX. Putative roles for homeostatic plasticity in epileptogenesis. Epilepsia 2023;64: 539-552.
[5] Goddard GV. Development of epileptic seizures through brain stimulation at low intensity. Nature 1967;214: 1020-1.
[6] Engel J, Jr., Pitkanen A. Biomarkers for epileptogenesis and its treatment. Neuropharmacology 2020;167: 107735.
[7] White HS, Loscher W. Searching for the ideal antiepileptogenic agent in experimental models: single treatment versus combinatorial treatment strategies. Neurotherapeutics 2014;11: 373-84.
[8] Goldberg EM, Coulter DA. Mechanisms of epileptogenesis: a convergence on neural circuit dysfunction. Nat Rev Neurosci 2013;14: 337-49.
[9] Dulla CG, Pitkanen A. Novel Approaches to Prevent Epileptogenesis After Traumatic Brain Injury. Neurotherapeutics 2021;18: 1582-1601.
[10] Aronica E, Ciusani E, Coppola A, Costa C, Russo E, Salmaggi A, Perversi F, Maschio M. Epilepsy and brain tumors: Two sides of the same coin. J Neurol Sci 2023;446: 120584.
[11] Leo A, De Caro C, Nesci V, Tallarico M, De Sarro G, Russo E, Citraro R. Modeling poststroke epilepsy and preclinical development of drugs for poststroke epilepsy. Epilepsy Behav 2020;104: 106472.
[12] Loscher W, Howe CL. Molecular Mechanisms in the Genesis of Seizures and Epilepsy Associated With Viral Infection. Front Mol Neurosci 2022;15: 870868.
[13] Russo E, Citraro R, Constanti A, Leo A, Luttjohann A, van Luijtelaar G, De Sarro G. Upholding WAG/Rij rats as a model of absence epileptogenesis: Hidden mechanisms and a new theory on seizure development. Neurosci Biobehav Rev 2016;71: 388-408.
[14] Lukasiuk K, Lason W. Emerging Molecular Targets for Anti-Epileptogenic and Epilepsy Modifying Drugs. Int J Mol Sci 2023;24.
[15] Kotulska K, Kwiatkowski DJ, Curatolo P, Weschke B, Riney K, Jansen F, Feucht M, Krsek P, Nabbout R, Jansen AC, Wojdan K, Sijko K, Glowacka-Walas J, Borkowska J, Sadowski K, Domanska-Pakiela D, Moavero R, Hertzberg C, Hulshof H, Scholl T, Benova B, Aronica E, de Ridder J, Lagae L, Jozwiak S, Investigators E. Prevention of Epilepsy in Infants with Tuberous Sclerosis Complex in the EPISTOP Trial. Ann Neurol 2021;89: 304-314.
[16] Russo E, Citraro R, Scicchitano F, Urzino A, Marra R, Rispoli V, De Sarro G. Vigabatrin has antiepileptogenic and antidepressant effects in an animal model of epilepsy and depression comorbidity. Behav Brain Res 2011;225: 373-6.
[17] Citraro R, Leo A, Constanti A, Russo E, De Sarro G. mTOR pathway inhibition as a new therapeutic strategy in epilepsy and epileptogenesis. Pharmacol Res 2016;107: 333-343.
[18] Berg AT, Levy SR, Testa FM, Blumenfeld H. Long-term seizure remission in childhood absence epilepsy: might initial treatment matter? Epilepsia 2014;55: 551-7.
[19] Blumenfeld H, Klein JP, Schridde U, Vestal M, Rice T, Khera DS, Bashyal C, Giblin K, Paul-Laughinghouse C, Wang F, Phadke A, Mission J, Agarwal RK, Englot DJ, Motelow J, Nersesyan H, Waxman SG, Levin AR. Early treatment suppresses the development of spike-wave epilepsy in a rat model. Epilepsia 2008;49: 400-9.

[20] Dezsi G, Ozturk E, Stanic D, Powell KL, Blumenfeld H, O'Brien TJ, Jones NC. Ethosuximide reduces epileptogenesis and behavioral comorbidity in the GAERS model of genetic generalized epilepsy. Epilepsia 2013;54: 635-43.
[21] Russo E, Citraro R, Scicchitano F, De Fazio S, Di Paola ED, Constanti A, De Sarro G. Comparison of the antiepileptogenic effects of an early long-term treatment with ethosuximide or levetiracetam in a genetic animal model of absence epilepsy. Epilepsia 2010;51: 1560-9.
[22] Olson CA, Vuong HE, Yano JM, Liang QY, Nusbaum DJ, Hsiao EY. The Gut Microbiota Mediates the Anti-Seizure Effects of the Ketogenic Diet. Cell 2018;174: 497.
[23] Russo E. The gut microbiota as a biomarker in epilepsy. Neurobiol Dis 2022;163: 105598.
[24] Medel-Matus JS, Lagishetty V, Santana-Gomez C, Shin D, Mowrey W, Staba RJ, Galanopoulou AS, Sankar R, Jacobs JP, Mazarati AM. Susceptibility to epilepsy after traumatic brain injury is associated with preexistent gut microbiome profile. Epilepsia 2022;63: 1835-1848.
[25] Vogrig A, Joubert B, Andre-Obadia N, Gigli GL, Rheims S, Honnorat J. Seizure specificities in patients with antibody-mediated autoimmune encephalitis. Epilepsia 2019;60: 1508-1525.
[26] Vogrig A, Gigli GL, Segatti S, Corazza E, Marini A, Bernardini A, Valent F, Fabris M, Curcio F, Brigo F, Iacono D, Passadore P, Rana M, Honnorat J, Valente M. Epidemiology of paraneoplastic neurological syndromes: a population-based study. J Neurol 2020;267: 26-35.
[27] Dalmau J, Graus F. Antibody-Mediated Encephalitis. N Engl J Med 2018;378: 840-851.
[28] Vogrig A, Muniz-Castrillo S, Desestret V, Joubert B, Honnorat J. Pathophysiology of paraneoplastic and autoimmune encephalitis: genes, infections, and checkpoint inhibitors. Ther Adv Neurol Disord 2020;13: 1756286420932797.
[29] Graus F, Vogrig A, Muniz-Castrillo S, Antoine JG, Desestret V, Dubey D, Giometto B, Irani SR, Joubert B, Leypoldt F, McKeon A, Pruss H, Psimaras D, Thomas L, Titulaer MJ, Vedeler CA, Verschuuren JJ, Dalmau J, Honnorat J. Updated Diagnostic Criteria for Paraneoplastic Neurologic Syndromes. Neurol Neuroimmunol Neuroinflamm 2021;8.
[30] Peter E, Treilleux I, Wucher V, Jougla E, Vogrig A, Pissaloux D, Paindavoine S, Berthet J, Picard G, Rogemond V, Villard M, Vincent C, Tonon L, Viari A, Honnorat J, Dubois B, Desestret V. Immune and Genetic Signatures of Breast Carcinomas Triggering Anti-Yo-Associated Paraneoplastic Cerebellar Degeneration. Neurol Neuroimmunol Neuroinflamm 2022;9.
[31] Vogrig A, Pegat A, Villagran-Garcia M, Wucher V, Attignon V, Sohier E, Brevet M, Rogemond V, Pinto AL, Muniz-Castrillo S, Peter E, Robert M, Picard G, Hopes L, Psimaras D, Terra A, Perrin C, Cogne D, Tabone-Eglinger S, Martinez S, Jury D, Valantin J, Gadot N, Auclair-Perrossier J, Viari A, Dubois B, Desestret V, Honnorat J. Different genetic signatures of small-cell lung cancer characterize anti-GABA(B) R and anti-Hu paraneoplastic neurological syndromes. Ann Neurol 2023.
[32] Vogrig A, Gigli GL, Nilo A, Pauletto G, Valente M. Seizures, Epilepsy, and NORSE Secondary to Autoimmune Encephalitis: A Practical Guide for Clinicians. Biomedicines 2022;11.
[33] Vogrig A, Muniz-Castrillo S, Joubert B, Picard G, Rogemond V, Marchal C, Chiappa AM, Chanson E, Skowron F, Leblanc A, Ducray F, Honnorat J. Central nervous system complications associated with immune checkpoint inhibitors. J Neurol Neurosurg Psychiatry 2020;91: 772-778.
[34] Muniz-Castrillo S, Haesebaert J, Thomas L, Vogrig A, Pinto AL, Picard G, Blanc C, Do LD, Joubert B, Berzero G, Psimaras D, Alentorn A, Rogemond V, Dubois V, Ambati A, Tamouza R, Mignot E, Honnorat J. Clinical and Prognostic Value of Immunogenetic Characteristics in Anti-LGI1 Encephalitis. Neurol Neuroimmunol Neuroinflamm 2021;8.
[35] Muniz-Castrillo S, Joubert B, Elsensohn MH, Pinto AL, Saint-Martin M, Vogrig A, Picard G, Rogemond V, Dubois V, Tamouza R, Maucort-Boulch D, Honnorat J. Anti-CASPR2 clinical phenotypes correlate with HLA and immunological features. J Neurol Neurosurg Psychiatry 2020;91: 1076-1084.
[36] Steriade C, Britton J, Dale RC, Gadoth A, Irani SR, Linnoila J, McKeon A, Shao XQ, Venegas V, Bien CG. Acute symptomatic seizures secondary to autoimmune encephalitis and autoimmune-associated epilepsy: Conceptual definitions. Epilepsia 2020;61: 1341-1351.
[37] Rada A, Bien CG. What is autoimmune encephalitis-associated epilepsy? Proposal of a practical definition. Epilepsia 2023.
[38] de Bruijn M, van Sonderen A, van Coevorden-Hameete MH, Bastiaansen AEM, Schreurs MWJ, Rouhl RPW, van Donselaar CA, Majoie M, Neuteboom RF, Sillevis Smitt PAE, Thijs RD, Titulaer MJ.

Evaluation of seizure treatment in anti-LGI1, anti-NMDAR, and anti-GABA(B)R encephalitis. Neurology 2019;92: e2185-e2196.
[39] Serrano-Castro PJ, Rodriguez-Uranga JJ, Cabezudo-Garcia P, Garcia-Martin G, Romero-Godoy J, Estivill-Torrus G, Ciano-Petersen NL, Oliver B, Ortega-Pinazo J, Lopez-Moreno Y, Aguilar-Castillo MJ, Gutierrez-Cardo AL, Ramirez-Garcia T, Sanchez-Godoy L, Carreno M. Cenobamate and Clobazam Combination as Personalized Medicine in Autoimmune-Associated Epilepsy With Anti-Gad65 Antibodies. Neurol Neuroimmunol Neuroinflamm 2023;10.
[40] Ekdahl CT, Claasen JH, Bonde S, Kokaia Z, Lindvall O. Inflammation is detrimental for neurogenesis in adult brain. Proc Natl Acad Sci U S A 2003;100: 13632-7.
[41] Mohapel P, Ekdahl CT, Lindvall O. Status epilepticus severity influences the long-term outcome of neurogenesis in the adult dentate gyrus. Neurobiol Dis 2004;15: 196-205.
[42] Bonde S, Ekdahl CT, Lindvall O. Long-term neuronal replacement in adult rat hippocampus after status epilepticus despite chronic inflammation. Eur J Neurosci 2006;23: 965-74.
[43] Avdic U, Ahl M, Chugh D, Ali I, Chary K, Sierra A, Ekdahl CT. Nonconvulsive status epilepticus in rats leads to brain pathology. Epilepsia 2018;59: 945-958.
[44] Iosif RE, Ekdahl CT, Ahlenius H, Pronk CJ, Bonde S, Kokaia Z, Jacobsen SE, Lindvall O. Tumor necrosis factor receptor 1 is a negative regulator of progenitor proliferation in adult hippocampal neurogenesis. J Neurosci 2006;26: 9703-12.
[45] Avdic U, Chugh D, Osman H, Chapman K, Jackson J, Ekdahl CT. Absence of interleukin-1 receptor 1 increases excitatory and inhibitory scaffolding protein expression and microglial activation in the adult mouse hippocampus. Cell Mol Immunol 2015;12: 645-7.
[46] Jakubs K, Nanobashvili A, Bonde S, Ekdahl CT, Kokaia Z, Kokaia M, Lindvall O. Environment matters: synaptic properties of neurons born in the epileptic adult brain develop to reduce excitability. Neuron 2006;52: 1047-59.
[47] Jakubs K, Bonde S, Iosif RE, Ekdahl CT, Kokaia Z, Kokaia M, Lindvall O. Inflammation regulates functional integration of neurons born in adult brain. J Neurosci 2008;28: 12477-88.
[48] Chugh D, Ekdahl CT. Interactions Between Microglia and Newly Formed Hippocampal Neurons in Physiological and Seizure-Induced Inflammatory Environment. Brain Plast 2016;1: 215-221.
[49] Jackson J, Chugh D, Nilsson P, Wood J, Carlstrom K, Lindvall O, Ekdahl CT. Altered synaptic properties during integration of adult-born hippocampal neurons following a seizure insult. PLoS One 2012;7: e35557.
[50] Chugh D, Ali I, Bakochi A, Bahonjic E, Etholm L, Ekdahl CT. Alterations in Brain Inflammation, Synaptic Proteins, and Adult Hippocampal Neurogenesis during Epileptogenesis in Mice Lacking Synapsin2. PLoS One 2015;10: e0132366.
[51] Chugh D, Nilsson P, Afjei SA, Bakochi A, Ekdahl CT. Brain inflammation induces post-synaptic changes during early synapse formation in adult-born hippocampal neurons. Exp Neurol 2013;250: 176-88.
[52] Avdic U, Ahl M, Andersson M, Ekdahl CT. Levetiracetam and N-Cadherin Antibody Alleviate Brain Pathology Without Reducing Early Epilepsy Development After Focal Non-convulsive Status Epilepticus in Rats. Front Neurol 2021;12: 630154.
[53] Ekdahl CT. Microglial activation - tuning and pruning adult neurogenesis. Front Pharmacol 2012;3: 41.
[54] Avdic U, Ahl M, Oberg M, Ekdahl CT. Immune Profile in Blood Following Non-convulsive Epileptic Seizures in Rats. Front Neurol 2019;10: 701.
[55] de Curtis M, Rossetti AO, Verde DV, van Vliet EA, Ekdahl CT. Brain pathology in focal status epilepticus: evidence from experimental models. Neurosci Biobehav Rev 2021;131: 834-846.
[56] Ahl M, Avdic U, Skoug C, Ali I, Chugh D, Johansson UE, Ekdahl CT. Immune response in the eye following epileptic seizures. J Neuroinflammation 2016;13: 155.
[57] Ahl M, Avdic U, Chary K, Shibata K, Chugh D, Mickelsson PL, Kettunen M, Strandberg MC, Johansson UE, Sierra A, Ekdahl CT. Inflammatory reaction in the retina after focal non-convulsive status epilepticus in mice investigated with high resolution magnetic resonance and diffusion tensor imaging. Epilepsy Res 2021;176: 106730.

[58] Backstrom F, Ahl M, Wickham J, Ekdahl CT. Reduced epilepsy development in synapsin 2 knockout mice with autistic behavior following early systemic treatment with interleukin-6 receptor antibody. Epilepsy Res 2023;191: 107114.
[59] Ahl M, Taylor MK, Avdic U, Lundin A, Andersson M, Amandusson A, Kumlien E, Compagno Strandberg M, Ekdahl CT. Immune response in blood before and after epileptic and psychogenic non-epileptic seizures. Heliyon 2023;9: e13938.
[60] Engel J, Jr., Pitkanen A, Loeb JA, Dudek FE, Bertram EH, 3rd, Cole AJ, Moshe SL, Wiebe S, Jensen FE, Mody I, Nehlig A, Vezzani A. Epilepsy biomarkers. Epilepsia 2013;54 Suppl 4: 61-9.
[61] Staba RJ, Stead M, Worrell GA. Electrophysiological biomarkers of epilepsy. Neurotherapeutics 2014;11: 334-46.
[62] Chen G, Zhang Z, Wang M, Geng Y, Jin B, Aung T. Update on the Neuroimaging and Electroencephalographic Biomarkers of Epileptogenesis: A Literature Review. Front Neurol 2021;12: 738658.
[63] Wu JY, Peters JM, Goyal M, Krueger D, Sahin M, Northrup H, Au KS, Cutter G, Bebin EM. Clinical Electroencephalographic Biomarker for Impending Epilepsy in Asymptomatic Tuberous Sclerosis Complex Infants. Pediatr Neurol 2016;54: 29-34.
[64] Wu JY, Goyal M, Peters JM, Krueger D, Sahin M, Northrup H, Au KS, O'Kelley S, Williams M, Pearson DA, Hanson E, Byars AW, Krefting J, Beasley M, Cutter G, Limdi N, Bebin EM. Scalp EEG spikes predict impending epilepsy in TSC infants: A longitudinal observational study. Epilepsia 2019;60: 2428-2436.
[65] van der Poest Clement E, Jansen FE, Braun KPJ, Peters JM. Update on Drug Management of Refractory Epilepsy in Tuberous Sclerosis Complex. Paediatr Drugs 2020;22: 73-84.
[66] Punia V, Fitzgerald Z, Zhang X, Huynh H, Bena J, Morrison S, Newey CR, Hantus S. Electroencephalographic biomarkers of epilepsy development in patients with acute brain injury: a matched, parallel cohort study. Ann Clin Transl Neurol 2019;6: 2230-2239.
[67] Kim JA, Boyle EJ, Wu AC, Cole AJ, Staley KJ, Zafar S, Cash SS, Westover MB. Epileptiform activity in traumatic brain injury predicts post-traumatic epilepsy. Ann Neurol 2018;83: 858-862.
[68] Bentes C, Martins H, Peralta AR, Morgado C, Casimiro C, Franco AC, Fonseca AC, Geraldes R, Canhao P, Pinho EMT, Paiva T, Ferro JM. Early EEG predicts poststroke epilepsy. Epilepsia Open 2018;3: 203-212.
[69] Slowinska M, Kotulska K, Szymanska S, Roberds SL, Fladrowski C, Jozwiak S. Approach to Preventive Epilepsy Treatment in Tuberous Sclerosis Complex and Current Clinical Practice in 23 Countries. Pediatr Neurol 2021;115: 21-27.
[70] Pitkanen A, Loscher W, Vezzani A, Becker AJ, Simonato M, Lukasiuk K, Grohn O, Bankstahl JP, Friedman A, Aronica E, Gorter JA, Ravizza T, Sisodiya SM, Kokaia M, Beck H. Advances in the development of biomarkers for epilepsy. Lancet Neurol 2016;15: 843-856.
[71] Koepp MJ, Trinka E, Mah YH, Bentes C, Knake S, Gigli GL, Serratosa JM, Zelano J, Magalhaes LM, Pereira A, Moreira J, Soares-da-Silva P. Antiepileptogenesis after stroke-trials and tribulations: Methodological challenges and recruitment results of a Phase II study with eslicarbazepine acetate. Epilepsia Open 2023.
[72] Strzelczyk A, Haag A, Raupach H, Herrendorf G, Hamer HM, Rosenow F. Prospective evaluation of a post-stroke epilepsy risk scale. J Neurol 2010;257: 1322-6.
[73] Haapaniemi E, Strbian D, Rossi C, Putaala J, Sipi T, Mustanoja S, Sairanen T, Curtze S, Satopaa J, Roivainen R, Kaste M, Cordonnier C, Tatlisumak T, Meretoja A. The CAVE score for predicting late seizures after intracerebral hemorrhage. Stroke 2014;45: 1971-6.
[74] Galovic M, Dohler N, Erdelyi-Canavese B, Felbecker A, Siebel P, Conrad J, Evers S, Winklehner M, von Oertzen TJ, Haring HP, Serafini A, Gregoraci G, Valente M, Janes F, Gigli GL, Keezer MR, Duncan JS, Sander JW, Koepp MJ, Tettenborn B. Prediction of late seizures after ischaemic stroke with a novel prognostic model (the SeLECT score): a multivariable prediction model development and validation study. Lancet Neurol 2018;17: 143-152.
[75] Bentes C, Franco AC, Peralta AR, Viana P, Martins H, Morgado C, Casimiro C, Fonseca C, Geraldes R, Canhao P, Pinho EMT, Paiva T, Ferro JM. Epilepsia partialis continua after an anterior circulation ischaemic stroke. Eur J Neurol 2017;24: 929-934.

[76] Chen DF, Kumari P, Haider HA, Ruiz AR, Lega J, Dhakar MB. Association of Epileptiform Abnormality on Electroencephalography with Development of Epilepsy After Acute Brain Injury. Neurocrit Care 2021;35: 428-433.
[77] Vezzani A, Balosso S, Ravizza T. Neuroinflammatory pathways as treatment targets and biomarkers in epilepsy. Nat Rev Neurol 2019;15: 459-472.
[78] Klein P, Dingledine R, Aronica E, Bernard C, Blumcke I, Boison D, Brodie MJ, Brooks-Kayal AR, Engel J, Jr., Forcelli PA, Hirsch LJ, Kaminski RM, Klitgaard H, Kobow K, Lowenstein DH, Pearl PL, Pitkanen A, Puhakka N, Rogawski MA, Schmidt D, Sillanpaa M, Sloviter RS, Steinhauser C, Vezzani A, Walker MC, Loscher W. Commonalities in epileptogenic processes from different acute brain insults: Do they translate? Epilepsia 2018;59: 37-66.
[79] Simonato M, Agoston DV, Brooks-Kayal A, Dulla C, Fureman B, Henshall DC, Pitkanen A, Theodore WH, Twyman RE, Kobeissy FH, Wang KK, Whittemore V, Wilcox KS. Identification of clinically relevant biomarkers of epileptogenesis - a strategic roadmap. Nat Rev Neurol 2021;17: 231-242.
[80] Walker LE, Frigerio F, Ravizza T, Ricci E, Tse K, Jenkins RE, Sills GJ, Jorgensen A, Porcu L, Thippeswamy T, Alapirtti T, Peltola J, Brodie MJ, Park BK, Marson AG, Antoine DJ, Vezzani A, Pirmohamed M. Molecular isoforms of high-mobility group box 1 are mechanistic biomarkers for epilepsy. J Clin Invest 2019;129: 2166.
[81] Golub VM, Reddy DS. Post-Traumatic Epilepsy and Comorbidities: Advanced Models, Molecular Mechanisms, Biomarkers, and Novel Therapeutic Interventions. Pharmacol Rev 2022;74: 387-438.
[82] Pitkanen A, Paananen T, Kyyriainen J, Das Gupta S, Heiskanen M, Vuokila N, Banuelos-Cabrera I, Lapinlampi N, Kajevu N, Andrade P, Ciszek R, Lara-Valderrabano L, Ekolle Ndode-Ekane X, Puhakka N. Biomarkers for posttraumatic epilepsy. Epilepsy Behav 2021;121: 107080.
[83] Vespa PM, Shrestha V, Abend N, Agoston D, Au A, Bell MJ, Bleck TP, Blanco MB, Claassen J, Diaz-Arrastia R, Duncan D, Ellingson B, Foreman B, Gilmore EJ, Hirsch L, Hunn M, Kamnaksh A, McArthur D, Morokoff A, O'Brien T, O'Phelan K, Robertson CL, Rosenthal E, Staba R, Toga A, Willyerd FA, Zimmermann L, Yam E, Martinez S, Real C, Engel J, Jr. The epilepsy bioinformatics study for anti-epileptogenic therapy (EpiBioS4Rx) clinical biomarker: Study design and protocol. Neurobiol Dis 2019;123: 110-114.
[84] Eriksson H, Lowhagen Henden P, Rentzos A, Pujol-Calderon F, Karlsson JE, Hoglund K, Blennow K, Zetterberg H, Rosengren L, Zelano J. Acute symptomatic seizures and epilepsy after mechanical thrombectomy. Epilepsy Behav 2020;104: 106520.
[85] Abraira L, Giannini N, Santamarina E, Cazorla S, Bustamante A, Quintana M, Toledo M, Grau-Lopez L, Jimenez M, Ciurans J, Becerra JL, Millan M, Cardona P, Terceno M, Zaragoza J, Canovas D, Gasull T, Ustrell X, Rubiera M, Castellanos M, Davalos A, Montaner J, Alvarez-Sabin J. Correlation of blood biomarkers with early-onset seizures after an acute stroke event. Epilepsy Behav 2020;104: 106549.
[86] Abraira L, Santamarina E, Cazorla S, Bustamante A, Quintana M, Toledo M, Fonseca E, Grau-Lopez L, Jimenez M, Ciurans J, Luis Becerra J, Millan M, Hernandez-Perez M, Cardona P, Terceno M, Zaragoza J, Canovas D, Gasull T, Ustrell X, Rubiera M, Castellanos M, Montaner J, Alvarez-Sabin J. Blood biomarkers predictive of epilepsy after an acute stroke event. Epilepsia 2020;61: 2244-2253.
[87] Troscher AR, Gruber J, Wagner JN, Bohm V, Wahl AS, von Oertzen TJ. Inflammation Mediated Epileptogenesis as Possible Mechanism Underlying Ischemic Post-stroke Epilepsy. Front Aging Neurosci 2021;13: 781174.
[88] Fisher RS, Acevedo C, Arzimanoglou A, Bogacz A, Cross JH, Elger CE, Engel J, Jr., Forsgren L, French JA, Glynn M, Hesdorffer DC, Lee BI, Mathern GW, Moshe SL, Perucca E, Scheffer IE, Tomson T, Watanabe M, Wiebe S. ILAE official report: a practical clinical definition of epilepsy. Epilepsia 2014;55: 475-82.
[89] Hesdorffer DC, Benn EK, Cascino GD, Hauser WA. Is a first acute symptomatic seizure epilepsy? Mortality and risk for recurrent seizure. Epilepsia 2009;50: 1102-8.
[90] Zelano J. Recurrence risk after a first remote symptomatic seizure in adults: Epilepsy or not? Epilepsia Open 2021;6: 634-644.

[91] Shlobin NA, Sander JW. Current Principles in the Management of Drug-Resistant Epilepsy. CNS Drugs 2022;36: 555-568.
[92] Thijs RD, Surges R, O'Brien TJ, Sander JW. Epilepsy in adults. Lancet 2019;393: 689-701.
[93] Ngugi AK, Kariuki SM, Bottomley C, Kleinschmidt I, Sander JW, Newton CR. Incidence of epilepsy: a systematic review and meta-analysis. Neurology 2011;77: 1005-12.
[94] Bell GS, Neligan A, Sander JW. An unknown quantity--the worldwide prevalence of epilepsy. Epilepsia 2014;55: 958-62.
[95] Vezzani A, Fujinami RS, White HS, Preux PM, Blumcke I, Sander JW, Loscher W. Infections, inflammation and epilepsy. Acta Neuropathol 2016;131: 211-234.
[96] Singh G, Angwafor SA, Njamnshi AK, Fraimow H, Sander JW. Zoonotic and vector-borne parasites and epilepsy in low-income and middle-income countries. Nat Rev Neurol 2020;16: 333-345.
[97] Jadhav AP, Desai SM, Jovin TG. Indications for Mechanical Thrombectomy for Acute Ischemic Stroke: Current Guidelines and Beyond. Neurology 2021;97: S126-s136.
[98] Sarraj A, Hassan AE, Abraham MG, Ortega-Gutierrez S, Kasner SE, Hussain MS, Chen M, Blackburn S, Sitton CW, Churilov L, Sundararajan S, Hu YC, Herial NA, Jabbour P, Gibson D, Wallace AN, Arenillas JF, Tsai JP, Budzik RF, Hicks WJ, Kozak O, Yan B, Cordato DJ, Manning NW, Parsons MW, Hanel RA, Aghaebrahim AN, Wu TY, Cardona-Portela P, Pérez de la Ossa N, Schaafsma JD, Blasco J, Sangha N, Warach S, Gandhi CD, Kleinig TJ, Sahlein D, Elijovich L, Tekle W, Samaniego EA, Maali L, Abdulrazzak MA, Psychogios MN, Shuaib A, Pujara DK, Shaker F, Johns H, Sharma G, Yogendrakumar V, Ng FC, Rahbar MH, Cai C, Lavori P, Hamilton S, Nguyen T, Fifi JT, Davis S, Wechsler L, Pereira VM, Lansberg MG, Hill MD, Grotta JC, Ribo M, Campbell BC, Albers GW. Trial of Endovascular Thrombectomy for Large Ischemic Strokes. N Engl J Med 2023;388: 1259-1271.
[99] Saini V, Guada L, Yavagal DR. Global Epidemiology of Stroke and Access to Acute Ischemic Stroke Interventions. Neurology 2021;97: S6-s16.
[100] Bentes C, Brigo F, Zelano J, Ferro JM. Reperfusion therapies and poststroke seizures. Epilepsy Behav 2020;104: 106524.
[101] van Mook WN, Rennenberg RJ, Schurink GW, van Oostenbrugge RJ, Mess WH, Hofman PA, de Leeuw PW. Cerebral hyperperfusion syndrome. Lancet Neurol 2005;4: 877-88.
[102] Jean WC, Spellman SR, Nussbaum ES, Low WC. Reperfusion injury after focal cerebral ischemia: the role of inflammation and the therapeutic horizon. Neurosurgery 1998;43: 1382-96; discussion 1396-7.
[103] Thevathasan A, Naylor J, Churilov L, Mitchell PJ, Dowling RJ, Yan B, Kwan P. Association between hemorrhagic transformation after endovascular therapy and poststroke seizures. Epilepsia 2018;59: 403-409.
[104] Zöllner JP, Misselwitz B, Mauroschat T, Roth C, Steinmetz H, Rosenow F, Strzelczyk A. Intravenous thrombolysis or mechanical thrombectomy do not increase risk of acute symptomatic seizures in patients with ischemic stroke. Sci Rep 2020;10: 21083.
[105] Liu F, Chen D, Fu Y, Wang H, Liu L. Incidence and association of seizures in stroke patients following endovascular treatment: A systematic review and meta-analysis. Eur J Neurol 2023;30: 134-143.
[106] Zhang C, Wang X, Wang Y, Zhang JG, Hu W, Ge M, Zhang K, Shao X. Risk factors for post-stroke seizures: a systematic review and meta-analysis. Epilepsy Res 2014;108: 1806-16.
[107] Ferreira-Atuesta C, Döhler N, Erdélyi-Canavese B, Felbecker A, Siebel P, Scherrer N, Bicciato G, Schweizer J, Sinka L, Imbach LL, Katan M, Abraira L, Santamarina E, Álvarez-Sabín J, Winklehner M, von Oertzen TJ, Wagner JN, Gigli GL, Serafini A, Janes F, Merlino G, Valente M, Gregoraci G, Conrad J, Evers S, Lochner P, Roell F, Brigo F, Bentes C, Peralta AR, Melo TPE, Keezer MR, Duncan JS, Sander JW, Tettenborn B, Koepp MJ, Galovic M. Seizures after Ischemic Stroke: A Matched Multicenter Study. Ann Neurol 2021;90: 808-820.
[108] Brondani R, de Almeida AG, Cherubini PA, Secchi TL, de Oliveira MA, Martins SCO, Bianchin MM. Risk Factors for Epilepsy After Thrombolysis for Ischemic Stroke: A Cohort Study. Front Neurol 2019;10: 1256.

[109] Eriksson H, Nordanstig A, Rentzos A, Zelano J, Redfors P. Risk of poststroke epilepsy after reperfusion therapies: A national cohort study. Eur J Neurol 2023;30: 1303-1311.
[110] Naylor J, Thevathasan A, Churilov L, Guo R, Xiong Y, Koome M, Chen Z, Chen Z, Liu X, Kwan P, Campbell BCV. Association between different acute stroke therapies and development of post stroke seizures. BMC Neurol 2018;18: 61.
[111] Gaspard N, Foreman BP, Alvarez V, Cabrera Kang C, Probasco JC, Jongeling AC, Meyers E, Espinera A, Haas KF, Schmitt SE, Gerard EE, Gofton T, Kaplan PW, Lee JW, Legros B, Szaflarski JP, Westover BM, LaRoche SM, Hirsch LJ, Critical Care EEGMRC. New-onset refractory status epilepticus: Etiology, clinical features, and outcome. Neurology 2015;85: 1604-13.
[112] Lattanzi S, Leitinger M, Rocchi C, Salvemini S, Matricardi S, Brigo F, Meletti S, Trinka E. Unraveling the enigma of new-onset refractory status epilepticus: a systematic review of aetiologies. Eur J Neurol 2022;29: 626-647.
[113] Hirsch LJ, Gaspard N, van Baalen A, Nabbout R, Demeret S, Loddenkemper T, Navarro V, Specchio N, Lagae L, Rossetti AO, Hocker S, Gofton TE, Abend NS, Gilmore EJ, Hahn C, Khosravani H, Rosenow F, Trinka E. Proposed consensus definitions for new-onset refractory status epilepticus (NORSE), febrile infection-related epilepsy syndrome (FIRES), and related conditions. Epilepsia 2018;59: 739-744.
[114] Clarkson BDS, LaFrance-Corey RG, Kahoud RJ, Farias-Moeller R, Payne ET, Howe CL. Functional deficiency in endogenous interleukin-1 receptor antagonist in patients with febrile infection-related epilepsy syndrome. Ann Neurol 2019;85: 526-537.
[115] Saitoh M, Kobayashi K, Ohmori I, Tanaka Y, Tanaka K, Inoue T, Horino A, Ohmura K, Kumakura A, Takei Y, Hirabayashi S, Kajimoto M, Uchida T, Yamazaki S, Shiihara T, Kumagai T, Kasai M, Terashima H, Kubota M, Mizuguchi M. Cytokine-related and sodium channel polymorphism as candidate predisposing factors for childhood encephalopathy FIRES/AERRPS. J Neurol Sci 2016;368: 272-6.
[116] Sakuma H, Tanuma N, Kuki I, Takahashi Y, Shiomi M, Hayashi M. Intrathecal overproduction of proinflammatory cytokines and chemokines in febrile infection-related refractory status epilepticus. J Neurol Neurosurg Psychiatry 2015;86: 820-2.
[117] Kothur K, Bandodkar S, Wienholt L, Chu S, Pope A, Gill D, Dale RC. Etiology is the key determinant of neuroinflammation in epilepsy: Elevation of cerebrospinal fluid cytokines and chemokines in febrile infection-related epilepsy syndrome and febrile status epilepticus. Epilepsia 2019;60: 1678-1688.
[118] Wang D, Wu Y, Pan Y, Wang S, Liu G, Gao Y, Xu K. Multi-proteomic Analysis Revealed Distinct Protein Profiles in Cerebrospinal Fluid of Patients Between Anti-NMDAR Encephalitis NORSE and Cryptogenic NORSE. Mol Neurobiol 2023;60: 98-115.
[119] Hanin A, Cespedes J, Dorgham K, Pulluru Y, Gopaul M, Gorochov G, Hafler DA, Navarro V, Gaspard N, Hirsch LJ. Cytokines in New-Onset Refractory Status Epilepticus Predict Outcomes. Ann Neurol 2023;94: 75-90.
[120] Wickstrom R, Taraschenko O, Dilena R, Payne ET, Specchio N, Nabbout R, Koh S, Gaspard N, Hirsch LJ, International NCG. International consensus recommendations for management of New Onset Refractory Status Epilepticus (NORSE) incl. Febrile Infection-Related Epilepsy Syndrome (FIRES): Statements and Supporting Evidence. Epilepsia 2022;63: 2840-64.
[121] Wickstrom R, Taraschenko O, Dilena R, Payne ET, Specchio N, Nabbout R, Koh S, Gaspard N, Hirsch LJ, International NCG. International consensus recommendations for management of New Onset Refractory Status Epilepticus (NORSE) including Febrile Infection-Related Epilepsy Syndrome (FIRES): Summary and Clinical Tools. Epilepsia 2022;63: 2827-39.
[122] Taraschenko O, Pavuluri S, Schmidt CM, Pulluru YR, Gupta N. Seizure burden and neuropsychological outcomes of new-onset refractory status epilepticus: Systematic review. Front Neurol 2023;14: 1095061.
[123] Chen Z, Brodie MJ, Liew D, Kwan P. Treatment Outcomes in Patients With Newly Diagnosed Epilepsy Treated With Established and New Antiepileptic Drugs: A 30-Year Longitudinal Cohort Study. JAMA Neurol 2018;75: 279-286.

[124] Tomson T, Zelano J, Dang YL, Perucca P. The pharmacological treatment of epilepsy in adults. Epileptic Disord 2023.
[125] Piccenna L, O'Dwyer R, Leppik I, Beghi E, Giussani G, Costa C, DiFrancesco JC, Dhakar MB, Akamatsu N, Cretin B, Kramer G, Faught E, Kwan P. Management of epilepsy in older adults: A critical review by the ILAE Task Force on Epilepsy in the elderly. Epilepsia 2023;64: 567-585.
[126] Consoli D, Bosco D, Postorino P, Galati F, Plastino M, Perticoni GF, Ottonello GA, Passarella B, Ricci S, Neri G, Toni D, Study E. Levetiracetam versus carbamazepine in patients with late poststroke seizures: a multicenter prospective randomized open-label study (EpIC Project). Cerebrovasc Dis 2012;34: 282-9.
[127] Gilad R, Sadeh M, Rapoport A, Dabby R, Boaz M, Lampl Y. Monotherapy of lamotrigine versus carbamazepine in patients with poststroke seizure. Clin Neuropharmacol 2007;30: 189-95.
[128] Kaushal S, Rani A, Chopra SC, Singh G. Safety and efficacy of clobazam versus phenytoin-sodium in the antiepileptic drug treatment of solitary cysticercus granulomas. Neurol India 2006;54: 157-60.
[129] Santhosh AP, Kumar Goyal M, Modi M, Kharbanda PS, Ahuja CK, Tandyala N, Prabhat N, Singh R, Mehta S, Vinay Mahesh K. Carbamazepine versus levetiracetam in epilepsy due to neurocysticercosis. Acta Neurol Scand 2021;143: 242-247.
[130] Doerrfuss JI, Kowski AB, Holtkamp M. Etiology-specific response to antiseizure medication in focal epilepsy. Epilepsia 2021;62: 2133-2141.
[131] Feyissa AM, Lopez Chiriboga AS, Britton JW. Antiepileptic drug therapy in patients with autoimmune epilepsy. Neurol Neuroimmunol Neuroinflamm 2017;4: e353.
[132] Hakansson S, Karlander M, Larsson D, Mahamud Z, Garcia-Ptacek S, Zelezniak A, Zelano J. Potential for improved retention rate by personalized antiseizure medication selection: A register-based analysis. Epilepsia 2021;62: 2123-2132.
[133] Asadi-Pooya AA, Beniczky S, Rubboli G, Sperling MR, Rampp S, Perucca E. The EpiPick algorithm to select appropriate antiseizure medications in patients with epilepsy: Validation studies and updates. Epilepsia 2021.
[134] Hakansson S, Zelano J. Big data analysis of ASM retention rates and expert ASM algorithm: A comparative study. Epilepsia 2022;63: 1553-1562.
[135] Larsson D, Baftiu A, Johannessen Landmark C, von Euler M, Kumlien E, Asberg S, Zelano J. Association Between Antiseizure Drug Monotherapy and Mortality for Patients With Poststroke Epilepsy. JAMA Neurol 2022;79: 169-175.
[136] Whitney DG, Caird MS, Hurvitz EA, Rajapakse CS, Fedak Romanowski EM. Effect of levetiracetam and oxcarbazepine on 4-year fragility fracture risk among prepubertal and pubertal children with epilepsy. Epilepsia 2021;62: 2180-2189.
[137] Christensen J, Trabjerg BB, Dreier JW. Cardiac morbidity and mortality associated with the use of lamotrigine. Epilepsia 2022;63: 2371-2380.
[138] Christensen J, Trabjerg BB, Sun Y, Gilhus NE, Bjork MH, Tomson T, Dreier JW. Prenatal exposure to valproate and risk of congenital malformations-Could we have known earlier?-A population-based cohort study. Epilepsia 2021;62: 2981-2993.
[139] Xue-Ping W, Hai-Jiao W, Li-Na Z, Xu D, Ling L. Risk factors for drug-resistant epilepsy: A systematic review and meta-analysis. Medicine (Baltimore) 2019;98: e16402.
[140] Semah F, Picot MC, Adam C, Broglin D, Arzimanoglou A, Bazin B, Cavalcanti D, Baulac M. Is the underlying cause of epilepsy a major prognostic factor for recurrence? Neurology 1998;51: 1256-62.
[141] Stephen LJ, Kwan P, Brodie MJ. Does the cause of localisation-related epilepsy influence the response to antiepileptic drug treatment? Epilepsia 2001;42: 357-62.
[142] de Greef BT, Schreuder FH, Vlooswijk MC, Schreuder AH, Rooyer FA, van Oostenbrugge RJ, Rouhl RP. Early seizures after intracerebral hemorrhage predict drug-resistant epilepsy. J Neurol 2015;262: 541-6.
[143] Burneo JG, Antaya TC, Allen BN, Belisle A, Shariff SZ, Saposnik G. The risk of new-onset epilepsy and refractory epilepsy in older adult stroke survivors. Neurology 2019;93: e568-e577.

[144] Lattanzi S, Trinka E, Turcato G, Rinaldi C, Cagnetti C, Foschi N, Broggi S, Norata D, Brigo F, Silvestrini M. Latency of poststroke epilepsy can predict drug resistance. Eur J Neurol 2022.
[145] Lattanzi S, Rinaldi C, Cagnetti C, Foschi N, Norata D, Broggi S, Rocchi C, Silvestrini M. Predictors of Pharmaco-Resistance in Patients with Post-Stroke Epilepsy. Brain Sci 2021;11.
[146] Lattanzi S, Meletti S, Trinka E, Brigo F, Turcato G, Rinaldi C, Cagnetti C, Foschi N, Broggi S, Norata D, Silvestrini M. Individualized Prediction of Drug Resistance in People with Post-Stroke Epilepsy: A Retrospective Study. J Clin Med 2023;12.
[147] Yu T, Liu X, Sun L, Lv R, Wu J, Wang Q. Risk factors for Drug-resistant Epilepsy (DRE) and a nomogram model to predict DRE development in post-traumatic epilepsy patients. CNS Neurosci Ther 2022;28: 1557-1567.
[148] Steriade C, Moosa ANV, Hantus S, Prayson RA, Alexopoulos A, Rae-Grant A. Electroclinical features of seizures associated with autoimmune encephalitis. Seizure 2018;60: 198-204.
[149] Huang Q, Ma M, Wei X, Liao Y, Qi H, Wu Y, Wu Y. Characteristics of Seizure and Antiepileptic Drug Utilization in Outpatients With Autoimmune Encephalitis. Front Neurol 2018;9: 1136.
[150] Matricardi S, Casciato S, Bozzetti S, Mariotto S, Stabile A, Freri E, Deleo F, Sartori S, Nosadini M, Pappalardo I, Meletti S, Giovannini G, Zucchi E, Di Bonaventura C, Di Gennaro G, Ferrari S, Zuliani L, Zoccarato M, Vogrig A, Lattanzi S, Michelucci R, Gambardella A, Ferlazzo E, Fusco L, Granata T, Villani F, Immune Epilepsies Study Group of the Italian League Against E. Epileptic phenotypes in autoimmune encephalitis: from acute symptomatic seizures to autoimmune-associated epilepsy. J Neurol Neurosurg Psychiatry 2022.
[151] Wesselingh R, Broadley J, Buzzard K, Tarlinton D, Seneviratne U, Kyndt C, Stankovich J, Sanfilippo P, Nesbitt C, D'Souza W, Macdonell R, Butzkueven H, O'Brien TJ, Monif M. Prevalence, risk factors, and prognosis of drug-resistant epilepsy in autoimmune encephalitis. Epilepsy Behav 2022;132: 108729.
[152] Asadi-Pooya AA, Brigo F, Lattanzi S, Blumcke I. Adult epilepsy. Lancet 2023;402: 412-424.
[153] Bodilsen J, Duerlund LS, Mariager T, Brandt CT, Wiese L, Petersen PT, Larsen L, Hansen BR, Omland LH, Tetens MM, Jorgensen RL, Leth S, Nielsen H, for D. Risk Factors and Prognosis of Epilepsy Following Brain Abscess: A Nationwide Population-Based Cohort Study. Neurology 2023;100: e1611-e1620.
[154] Englander J, Bushnik T, Wright JM, Jamison L, Duong TT. Mortality in late post-traumatic seizures. J Neurotrauma 2009;26: 1471-7.
[155] Uski J, Lamusuo S, Teperi S, Loyttyniemi E, Tenovuo O. Mortality after traumatic brain injury and the effect of posttraumatic epilepsy. Neurology 2018;91: e878-e883.
[156] Glaser AC, Kanter JH, Martinez-Camblor P, Taenzer A, Anderson MV, Buhl L, Shaefi S, Pannu A, Boone MD. The Effect of Antiseizure Medication Administration on Mortality and Early Posttraumatic Seizures in Critically Ill Older Adults with Traumatic Brain Injury. Neurocrit Care 2022;37: 538-546.
[157] Kerkhof M, Dielemans JC, van Breemen MS, Zwinkels H, Walchenbach R, Taphoorn MJ, Vecht CJ. Effect of valproic acid on seizure control and on survival in patients with glioblastoma multiforme. Neuro Oncol 2013;15: 961-7.
[158] Happold C, Gorlia T, Chinot O, Gilbert MR, Nabors LB, Wick W, Pugh SL, Hegi M, Cloughesy T, Roth P, Reardon DA, Perry JR, Mehta MP, Stupp R, Weller M. Does Valproic Acid or Levetiracetam Improve Survival in Glioblastoma? A Pooled Analysis of Prospective Clinical Trials in Newly Diagnosed Glioblastoma. J Clin Oncol 2016;34: 731-9.
[159] Chen JS, Clarke R, Haddad AF, Wang EJ, Lacroix M, Sarkar IN, Zand R, Chen ES, Toms SA. The effect of levetiracetam treatment on survival in patients with glioblastoma: a systematic review and meta-analysis. J Neurooncol 2022;156: 257-267.
[160] van Tuijl JH, van Raak EPM, van Oostenbrugge RJ, Aldenkamp AP, Rouhl RPW. The occurrence of seizures after ischemic stroke does not influence long-term mortality; a 26-year follow-up study. J Neurol 2018;265: 1780-1788.
[161] Zelano J, Redfors P, Asberg S, Kumlien E. Association between poststroke epilepsy and death: A nationwide cohort study. Eur Stroke J 2016;1: 272-278.

[162] Claessens D, Bekelaar K, Schreuder F, de Greef BTA, Vlooswijk MCG, Staals J, van Oostenbrugge RJ, Rouhl RPW. Mortality after primary intracerebral hemorrhage in relation to post-stroke seizures. J Neurol 2017;264: 1885-1891.
[163] Randomised study of antiepileptic drug withdrawal in patients in remission. Medical Research Council Antiepileptic Drug Withdrawal Study Group. Lancet 1991;337: 1175-80.
[164] Lossius MI, Hessen E, Mowinckel P, Stavem K, Erikssen J, Gulbrandsen P, Gjerstad L. Consequences of antiepileptic drug withdrawal: a randomized, double-blind study (Akershus Study). Epilepsia 2008;49: 455-63.
[165] Lamberink HJ, Otte WM, Blumcke I, Braun KPJ, European Epilepsy Brain Bank writing g, study g, European Reference Network Epi C. Seizure outcome and use of antiepileptic drugs after epilepsy surgery according to histopathological diagnosis: a retrospective multicentre cohort study. Lancet Neurol 2020;19: 748-757.
[166] Lamberink HJ, Boshuisen K, Otte WM, Geleijns K, Braun KPJ, TimeToStop Study G. Individualized prediction of seizure relapse and outcomes following antiepileptic drug withdrawal after pediatric epilepsy surgery. Epilepsia 2018;59: e28-e33.
[167] Perucca P, Carter J, Vahle V, Gilliam FG. Adverse antiepileptic drug effects: toward a clinically and neurobiologically relevant taxonomy. Neurology 2009;72: 1223-9.
[168] Cole AJ, Wiebe S. Debate: Should antiepileptic drugs be stopped after successful epilepsy surgery? Epilepsia 2008;49 Suppl 9: 29-34.
[169] Ortinski P, Meador KJ. Cognitive side effects of antiepileptic drugs. Epilepsy Behav 2004;5 Suppl 1: S60-5.
[170] Sarco DP, Bourgeois BF. The safety and tolerability of newer antiepileptic drugs in children and adolescents. CNS Drugs 2010;24: 399-430.
[171] Guerrini R, Zaccara G, la Marca G, Rosati A. Safety and tolerability of antiepileptic drug treatment in children with epilepsy. Drug Saf 2012;35: 519-33.
[172] Ikonomidou C, Turski L. Antiepileptic drugs and brain development. Epilepsy Res 2010;88: 11-22.
[173] Mula M, Trimble MR. Antiepileptic drug-induced cognitive adverse effects: potential mechanisms and contributing factors. CNS Drugs 2009;23: 121-37.
[174] Lamberink HJ, Otte WM, Geleijns K, Braun KP. Antiepileptic drug withdrawal in medically and surgically treated patients: a meta-analysis of seizure recurrence and systematic review of its predictors. Epileptic Disord 2015;17: 211-28.
[175] Bartolini L, Majidi S, Koubeissi MZ. Uncertainties from a worldwide survey on antiepileptic drug withdrawal after seizure remission. Neurol Clin Pract 2018;8: 108-115.