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Immunity and inflammation in status epilepticus and its sequelae: possibilities for therapeutic application

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Abstract

Status epilepticus (SE) is a life-threatening neurological emergency often refractory to available treatment options. It is a very heterogeneous condition in terms of clinical presentation and causes, which besides genetic, vascular and other structural causes also include CNS or severe systemic infections, sudden withdrawal from benzodiazepines or anticonvulsants and rare autoimmune etiologies. Treatment of SE is essentially based on expert opinions and antiepileptic drug treatment *per se* seems to have no major impact on prognosis. There is, therefore, urgent need of novel therapies that rely upon a better understanding of the basic mechanisms underlying this clinical condition. Accumulating evidence in animal models highlights that inflammation ensuing in the brain during SE may play a determinant role in ongoing seizures and their long-term detrimental consequences, independent of an infection or auto-immune cause; this evidence encourages reconsideration of the treatment flow in SE patients.

Keywords

animal models; anti-inflammatory treatments; blood–brain barrier; comorbidities; COX-2; cytokines; neurodegeneration; outcome; prognosis; refractory status epilepticus; seizures

Framing the problem from the clinical side

Definition & incidence

Status epilepticus (SE) is operationally defined as ongoing seizures, or repetitive seizures without recovery of baseline clinical conditions in between, lasting for at least 5 min [1]. It is the second most frequent life-threatening neurological emergency after stroke, with an annual incidence between 12 and 40 per 100,000 persons; higher numbers are observed in children and elderly, generating a ‘U-shaped’ curve [2–4]. SE is labeled as ‘refractory’ if resistant to the first two treatment lines (see below) [5]; this occurs in 25–45% of SE

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episodes [6–8]. More recently, the concept of ‘super-refractory SE’ has been proposed to characterize SE episodes persisting despite a first anesthetic treatment course; this may occur in at least 12–28% of SE (or 50% of refractory SE) [9,10].

Classification & etiologies

From a taxonomical point of view, SE is a very heterogeneous condition; there are many forms of SE and causes prove to be extremely varied. In terms of clinical presentation, the paramount dichotomous categorization occurs between forms with or without major motor signs, which are modulated, in parallel, by the occurrence of focal versus generalized clinical and electrographic features, as well as by the degree of consciousness impairment [11].

Etiologies are classically divided into acute symptomatic, which account for over the half of all cases, remote symptomatic, progressive symptomatic and idiopathic/unknown [12]. More recently, the concept of ‘potentially fatal etiologies’, including those causes that may *per se* lead to death if not specifically treated, has been proposed; this seems to better correlate with prognosis as compared with the International League Against Epilepsy classification [13]. While pediatric SE is more often caused by infections and genetic/congenital disorders [3], in adults antiepileptic drug (AED) withdrawal, cerebrovascular disorders (mostly hemorrhagic) and tumors predominate [3,14].

Focusing on inflammatory SE etiologies, CNS or severe systemic infections (viral, bacterial or parasitic) may account for 3–35% of cases; it is nevertheless important to recognize that these wide estimations vary according to the geographical location: patients presenting in developing countries are indeed clearly more prone to suffer from infections [15,16]. Conversely, autoimmune etiologies have received far less attention to date and globally seem rarer, accounting for only about 2–3% of all SE episodes [15]. Patients with autoimmune SE tend to be relatively young; most of the episodes are related to anti-NMDA-receptor antibodies, anti-glutamic acid decarboxylase antibodies or multiple sclerosis, while other antibodies, including those associated with paraneoplastic syndromes, as well as Rasmussen encephalitis seem rarer [15,17,18]. Outcome seems globally better for SE episodes triggered by antibodies with surface cellular targets (e.g., anti-NMDA-receptor, GABA B receptor, voltage-gated potassium channel complex including leucine-rich glioma-inactivated-1) than for those related to intracellular targets (e.g., paraneoplastic syndromes, anti-glutamic acid decarboxylase) [17].

One important caveat to the above incidence estimations is represented by the proportion of SE episodes with potentially, yet unproven, (para-)inflammatory origin, often presenting in the context of a febrile illness without any previous history of seizures. These cases account for about 5% of SE cohorts [3,14] and might, at least in part, encompass still unknown autoantibodies. In adults, such forms have been called ‘malignant’ [19] or ‘new-onset refractory SE’ [20], while in children the acronym ‘febrile infection-related epilepsy syndrome’ has been proposed [21,22]. The exact incidence of these entities is still unclear, as case series [17,23] lacks a denominator and often suffers from a publication bias; nevertheless, they may account for a significant proportion of super-refractory SE episodes.

Prognosis

SE is linked to a considerable risk of short-term mortality. The latter has been addressed in several population-based [2,3] and hospital-based [7,8,14] studies, and oscillates between 7 and 39%, while long-term mortality at 10 years appears to be increased by a factor of 3 as compared with controls in the general population [24]. The three most important mortality predictors are an acute or potentially fatal etiology (odds ratio [OR]: 6.0), increasing age (OR: 5.5 if >65 years) and a generalized convulsive or comatose SE presentation (OR: 5.8) [25]. The risk of an unfavorable functional outcome seems to correlate with the length of ICU treatment [26], as well as, again, age and etiology [8]. Furthermore, refractory SE is linked to a worse prognosis, both in terms of mortality and morbidity, in comparison with SE responding to the first treatment steps [8].

An inaugural SE portends a risk three-times higher to develop epilepsy as compared with a first self-limited seizure. There is a lively ongoing debate regarding the incidence of neuronal damage after SE [27,28]. While *de novo* hippocampal lesions have been described after SE [29], these findings are not always replicated [30]. In fact, it appears that the underlying etiology might play a predominant role: in an elegant observational study on patients already diagnosed with epilepsy who subsequently developed a SE episode, neuropsychological features did not worsen after the SE [31]. Therefore, it is tempting to assume that it is not always the SE *per se*, but rather the biological background (including the cause) that modulates neuronal damage. In this context, since generalized SE induces systemic changes and neuronal damage even after prevention of the clinical convulsions in primates [32], it seems reasonable to assume that generalized convulsive SE has a much higher risk of neurological sequelae than focal SE [33].

Treatment

Besides stabilization of airways and cardiac function, the therapeutic arsenal is currently subdivided into three subsequent treatment lines: the first is represented by benzodiazepines, the second by intravenously administered AEDs and the third by general anesthetics (FIGURE **1**) [34,35]. In view of the low level of evidence after the first line, a marked uncertainty still exists regarding the optimal use of specific agents, the best sequence of administration and the optimal use according to the patient situation. In particular, the treatment of refractory and super-refractory SE is essentially based on expert opinions [10], since to date only one randomized clinical trial (interrupted following insufficient recruitment) has been conducted in this setting [9]. Of note, there is currently no evidence that antiepileptic treatment *per se* has a major impact on SE prognosis [36,37], an observation that might be explained at least in part by the fact that AEDs provide a purely symptomatic treatment; furthermore, general anesthetics may even be related to a higher risk of complications and mortality, particularly in focal SE [38,39].

As about one-third of patients still continue seizing despite the first two treatment lines, thus evolving to refractory SE, and half of these subsequently develop super-refractory SE, it seems important to consider further treatment alternatives, such as other anesthetics and AEDs, vagal nerve stimulation, transcranial magnetic stimulation, electroconvulsive treatment, mild hypothermia or resective surgery [10,33,40]. In particular, there has been a

recent reappraisal of ketamine, an anesthetic with NMDA antagonist properties, which seems promising [41,42] in view of the GABA-resistance and glutamate hyperactivity in ongoing experimental SE [43,44]. In addition, the ketogenic diet appears also worthwhile in this clinical setting [45,46].

As inflammatory causes may go unrecognized, as discussed below, it is also common practice to administer intravenous corticosteroids after formally ruling out an infection, while more specific immunosuppressive/anti-inflammatory treatments, such as plasma exchange, intravenous immunoglobulins, rituximab or cyclophosphamide, are generally reserved for patients in whom an autoimmune cause is suspected [17,47–49]. These immunological approaches, which may be considered as corroborating the third-line of treatment (at the bottom of FIGURE **1**), are not evidence-based, but in current clinical practice rely on the assumption that inflammation is the direct cause of SE; their administration typically occurs after the start of the refractory SE episode. However, as we will see in the following sections, inflammation may also play a determinant role in ongoing seizures independently of an infection or auto-immune cause [50,51]; this may thus lead to reconsideration of the treatment flow in SE patients.

Influence of status epilepticus on brain & systemic inflammation

The long-term negative consequences of refractory SE in humans, which can include cognitive deficits, epilepsy or death, are likely to be caused in part not only by pre-existing neurologic impairment, but also by the molecular and cellular consequences of SE itself. Could inflammation play a role? If so, recognizing that the word ‘inflammation’ embodies a multidimensional assortment of pathways and cellular processes, does the evidence suggest any particular therapeutic options? In brief, mounting evidence indicates that inflammation is a consequence as well as a facilitator of seizures ([52] and references therein). We will consider the available information from both human experience and animal models of SE, emphasizing recent studies.

Clinical evidence

There is scarce information on pathology of brain tissue in patients after acute SE, but typical Ammon's Horn sclerosis has been reported [53–56]. Except for glia activation no inflammatory molecules were investigated in these studies. Moreover, it was impossible to formally rule out pre-existing pathology in these subjects that might have contributed to or caused SE. Convincing data exist, however, for a robust inflammatory environment in the sclerotic hippocampus removed during *en bloc* temporal lobe epilepsy (TLE) surgery, consisting of activation of microglia and astrogliosis, upregulation in these cells as well as in neurons of IL-1β, high mobility group box 1 (HMGB1), COX-2, the complement system and various downstream inflammatory mediators [52,57,58]. There is also evidence of albumin extravasation from nearby blood vessels denoting blood–brain barrier (BBB) damage, the presence of numerous $CD68^+$ macrophages and a few $CD3^+$ T-lymphocytes [59–62]. HMGB1 is a widespread nuclear protein that is rapidly translocated to the cytoplasm and released to the interstitial space upon neuronal injury or during seizures, then contributing to generate the inflammatory cascade. Indeed, in astrocytes, monocytes and microglia from hippocampus of TLE patients there is evidence of movement of HMGB1

from nucleus to cytoplasm [63]. A similarly complex inflammatory *milieu* was also described in surgical specimens from epilepsy patients with developmental cortical lesions, such as focal cortical dysplasia, tuberous sclerosis and brain tumors [64], and in Rasmussen's encephalitis, where a prominent leukocyte infiltration in cortical tissue is also observed [65,66]. Elevated cerebrospinal fluid (CSF) and serum levels of various cytokines and inflammatory molecules occur in the neonatal epileptic encephalopathy known as West Syndrome [67] and in adult TLE [68], which provides a putative link between epilepsy and systemic inflammation.

Although, as described above, a good deal of attention has been paid to inflammation in the brain of chronic epilepsy patients, less is known about inflammatory mediators that appear after acute SE in humans. When compared with children presenting with fever alone, those with febrile seizures have elevated serum levels of IL-1β, IL-6 and, for those in febrile SE, HMGB1 [69]. Extensive extravasation of albumin into the brain of patients who died in SE has been reported [70], indicative of massive opening of the BBB. Analysis of temporal cortex resected from a patient with new onset focal seizures that progressed to refractory SE showed intense gliosis (both astroglia and microglia) and strong IL-1β expression but sparse lymphocytic infiltration, all consistent with a pronounced focal inflammation [71]. Finally, an extensive comparison of cytokine levels in CSF of refractory SE patients with febrile infection-related epilepsy syndrome revealed increases in IL-6, IL-8 and CXCL10 when compared with CSF from patients with other inflammatory neurological diseases [72].

These findings focus the attention mainly on responses of the innate immune system to seizures and SE. However, it is not possible from any of the clinical studies to know whether the observed inflammatory changes precede or are caused by seizures. For that we turn to studies in animal models of SE.

Evidence from the bench

Studies in a multitude of animal models demonstrate that SE induced either by chemoconvulsant drugs or electrical stimulation of various brain areas causes a rapid and intense inflammatory cascade in the forebrain involving interactions among neurons, reactive astrocytes, activated microglia, vascular endothelial cells and, eventually, infiltrating neutrophils and monocytes from the blood [73]. The pathophysiological interactions among the various inflammatory molecules, and the sequence of events leading to their induction, have not yet been dissected out due to the complexity of the inflammatory cascade; recent review articles describe in detail the available knowledge [58,64,73–77]. Briefly, within 30–60 min of the onset of SE in adult mouse and rat, elevated IL-1β, TNF-α, IL-6 transcript levels are found in the hippocampus or forebrain concomitant with a rise in neuronal COX-2 protein [78–83]. These changes are followed shortly by morphological evidence of activation of microglia, reactive gliosis and infiltrating monocytes [59,82,84,85].

The broad cytokine burst and gliosis following SE induced by pilocarpine is blunted in mice that have genetic ablations of COX-2 restricted to those principal forebrain neurons in which COX-2 is normally induced by SE [86], pointing to a role for COX-2 pathways in SE-induced inflammation. Further, major deleterious effects associated with induction of

inflammatory mediators after SE (i.e., neuronal injury, inflammatory cytokine burst, leakage of BBB) appear to involve the activation of IL-1 receptor type 1 (IL-1R1 for IL-1β), Toll-like receptor 4 and Receptor for Advanced Glycation End product (TLR4 and RAGE for HMGB1) and EP2 receptors (for PGE2) [74,82,87–89], pointing to these signaling pathways as major inflammatory mediators in the brain following SE. In addition, the extravasation of albumin into the hippocampus and cortex, normally observed several hours to days after SE [59,75,84] and indicative of breach of the BBB, was abolished in both the conditional COX-2 knockout and in wild-type mice treated with the EP2 antagonist [84,86] as well as by IL-1 receptor antagonist (IL-1ra, anakinra) [87,89], indicating a key role for the IL-1β/IL-1R1 and COX-2/EP2 system in controlling the BBB integrity after SE. The IL-1ra and EP2 receptor antagonists reduced neuroinflammation and were neuroprotective when first administered up to 3–4 h after SE onset [84,88], suggesting that IL-1R1 and EP2 inhibition, in concert, might be a useful adjunctive strategy to limit the neuropathology after SE.

Granulocytes (presumably mostly neutrophils) begin to infiltrate cortex and hippocampus a few hours after SE onset in rats and mice, and are commonly observed in different SE models [59,60,90]. Immunologic depletion of neutrophils and monocytes reduced neuronal injury caused by kainate in mice, and the infiltrating neutrophils appeared to be phagocytosed by resident microglia or monocyte-derived macrophages [60]. These observations are consistent with the well-recognized exacerbation of tissue injury by neutrophils in peripheral tissues [90].

SE-induced brain inflammation is developmentally regulated, and its age of onset and pathophysiological consequences depend on the precipitating event [91–94]. In 7- to 14-day-old mice (corresponding to perinatal/early infancy in humans [95]) exposed to hyperthermia for inducing febrile-like seizures, there is a rapid raise in forebrain IL-1β in astrocytes and HMGB1 nuclear-to-cytoplasm translocation in neurons [96,97]. Notably, the IL-1β increase lasts for 24–72 h and persists in mice later developing epilepsy (approximately 30% of animals exposed to hyperthermia-induced seizures). These changes were dependent on seizures and were not due to increased core or brain temperature [93]. Similarly, fever induced in 7- and 14-day-old mice by systemic lipopolysaccharide (LPS) mimicking Gram-negative bacteria infection, or by intracerebral injection of Poly I:C, mimicking viral infections, induced rapid and transient upregulation of both IL-1β and TNF-α in the hippocampus, hypothalamus and cortex [98,99].

The induction of brain inflammation during SE or acute self-remitting seizures occurs in naive animals without prior brain pathology, thus providing a straightforward demonstration that seizure activity *per se* is a triggering factor. There is evidence, however, that SE induction in a compromised brain, such as in rats with induced heterotopia, is associated with a more severe acute course and with worsening of the long-term neuropathological consequences [100]. The data from human tissue and animal models of SE are consistent with, and demonstrate, a multidimensional strong inflammatory response of the brain to SE. The following section describes efforts to identify which of the inflammatory pathways lend themselves to therapeutic opportunities.

Influence of brain & systemic inflammation on status epilepticus

Inflammation is a prototypical response to infection or tissue injury, thus representing a key homeostatic endogenous mechanism for promoting tissue healing and repair. However, if the extent or duration of inflammation is not efficiently controlled by endogenous anti-inflammatory mechanisms apt to promote its fast resolution, then detrimental effects may occur. Indeed, there is evidence of inefficient endogenous anti-inflammatory control of brain inflammation both during chronic recurrent seizures, and in SE [101–103]. Unabated inflammation has been suggested to play a pathogenic role in several brain diseases, including epilepsy [52,104–106]. The crucial question of the pathophysiological consequences of brain inflammation triggered by SE prompted interventions in animal models for either promoting or interfering with this phenomenon, then studying how such interventions affect SE incidence or severity and its consequences on cell survival, mortality, behavioral deficits, seizure threshold and epilepsy development. The evidence provided by these studies highlights that specific inflammatory pathways and molecules may be putative targets for novel therapeutic interventions in SE.

The effect of anti-inflammatory treatments on experimental SE

Various pharmacological studies targeting IL-1β/IL-1R1, HMGB1/TLR4, COX-2/prostaglandins or the complement system have demonstrated that these inflammatory pathways significantly contribute to the onset and/or recurrence of acute brief seizures provoked by various convulsive stimuli in adult rodents [76,77,107–109]. This pharmacological evidence has been substantiated by changes in intrinsic seizure susceptibility of transgenic mice with functional alterations in these pathways [52,77,110]. However, differently from acute discrete seizures, interference with the same inflammatory pathways was in general not effective in reducing SE severity or its incidence, with a few notable exceptions. For example, the systemic injection in rats of the IL-1ra, a drug used in the clinic (Kineret) in autoimmune disorders, before the injection of pilocarpine, reduced the incidence of SE in rats. Moreover, the onset of SE was delayed, and its duration as well as the spiking activity was reduced in rats still developing SE [89]. In another study, a single bolus injection of anakinra 3 h after electrically induced SE provoked a drastic but transient decrease in spike frequency [88]. The most effective treatment on the acute course of SE to date remains the use of P2X7 receptor antagonists that drastically reduce its duration even after 1-h delay administration [111,112]. Co-administration of a P2X7 receptor antagonist with a benzodiazepine also provided SE suppression in a model of drug-refractory SE where either treatment alone was minimally effective. These drugs reduced microglia activation and IL-1β levels in forebrain, which is compatible with the evidence that P2X7 receptor activation is pivotal for the inflammasome induction and the consequent release of both IL-1β and HMGB1 [113,114]. Notably, even in the absence of effects on SE severity or its duration, these anti-inflammatory treatments, including COX-2 inhibitors and EP2 receptor antagonists, mediate significant neuroprotection in forebrain and decrease animal mortality. When the broad-spectrum anti-inflammatory drug dexamethasone was injected in rats prior to pilocarpine, the number of rats developing SE was reduced. When SE developed, the time-to-onset was significantly delayed and mortality was abolished. Dexamethasone also significantly reduced the BBB damage [115]. Different studies, however, reported evidence

of glucocorticoid-induced aggravation of brain inflammation [116], and exacerbation of cerebral edema and brain injury following dexamethasone in a model of pilocarpine-induced SE [117]. This contrasting result suggests that broad-spectrum anti-inflammatory interventions may not be the best therapeutic option in SE, and support the idea of more specific targeting of inflammatory pathways with a demonstrated pathologic role either in the acute phase of SE or its long-term consequences.

Finally, there is increasing evidence that anti-inflammatory treatments given either during SE, or shortly after SE has elapsed, significantly reduce the severity of the ensuing epilepsy in animals (TABLE **1**), as reflected by a drastic reduction in spontaneous seizure frequency and/or severity, prevention of seizure progression, decreased cell loss and comorbidities.

Specific inflammatory mediators contribute to decreasing seizure threshold in animal models either by activating their neuronal receptors, thereby rapidly affecting neuron excitability, or by slower onset effects related to the transcriptional activation of genes involved in synaptic and molecular plasticity [76,118].

Effects of inflammation on SE outcomes

This aspect has been mostly studied in developing rats or mice exposed to SE at post-natal days 7–14, representative of the perinatal/early infancy period in humans [95]. Inflammation evoked by seizures or SE in the developing brain is unique compared with the adult brain since inflammatory mediators play a role in normal development by regulating neurogenesis and synapse formation [119,120]. Moreover, the developmental timelines affect how brain will respond to seizures [95,121]. In principle, excess inflammatory signaling during brain development, either in response to seizures, or resulting from some infectious process, has the potential to interfere with normal developmental processes.

There is evidence that cytokines play a permissive role in experimental febrile SE since the threshold to both hyperthermic seizures and LPS-promoted seizures in febrile animals depends on the hippocampal levels of IL-1β and TNF-α [93,122,123]. Prolonged hyperthermic seizures in immature rats have been reported to lead to adult TLE [124] and this occurred only in animals having chronically elevated IL-1β in the hippocampus [96].

Differently from febrile SE, SE in the immature rats due to chemoconvulsants such as lithium/pilocarpine or kainate is associated with hippocampal injury that was enhanced if rats were exposed to systemic LPS at the time of SE induction [125]. Kainic acid-induced SE in post-natal day 14 and older rats also elicited increases in brain cytokines [91,126]. Moreover, in both SE models brain inflammation precedes the development of cell loss in the hippocampus supporting its potential role in SE-induced neurodegeneration.

Finally, there is compelling evidence that brain inflammation, either arising from an immune stimulus (mimicking bacterial or viral infections with LPS or Poly I:C, respectively) or from prolonged seizures, predisposes the immature brain to an increased risk of developing seizures in adulthood by chronically decreasing seizure threshold [98,99,126]. Notably, inflammation induced by LPS in 14-day-old rats results in more severe consequences of SE when induced in adulthood. This evidence suggests that systemic inflammation and the

mirrored brain inflammation are responsible for an enhancement of epileptogenesis [127]. The mechanisms underlying this long-lasting increase in brain excitability are not yet well understood, although there is evidence for the involvement of alterations in both glutamate and GABA receptor levels and their subunit composition, as well as the Na^+-K^+-Cl^- cotransporter in forebrain [128,129].

Brain inflammation has been also implicated in the pathophysiology of several neuropsychiatric conditions in epilepsy [130] such as depression, memory impairment and autism-like disorders. It is, therefore, conceivable that inflammatory mediators induced in the brain by SE may contribute to the development of neuropsychiatric abnormalities. In particular, brain IL-1β has been regarded as a key factor in the inflammation-associated depression and memory deficits [131,132], and excessive HMGB1 signaling in the brain may lead to selective memory deficits by activating both TLR4 and RAGE [133]. Among the inflammatory cytokines, IL-6 has been strongly associated with autistic impairments [134]; moreover, increased blood levels of HMGB1 [135,136], and enhanced TLR2 and TLR4 signaling in monocytes [137] have been measured in autistic patients. Immature rats exposed to LPS or Poly I:C develop cognitive impairments and anxiety-like behaviors in adulthood [129].

Expert commentary

There is clinical evidence that SE causes a broad inflammatory process that can be detected in the brain, in CSF and in serum. Likewise, the experimental data gathered in animal models of SE have shown that prolonged seizures induced by a variety of systemic or intracerebral stimuli lead to a rapid and long-lasting activation of specific inflammatory pathways in the brain regions of seizure origin and generalization. Since the induction of inflammatory mediators occurs in otherwise healthy animals, it indicates that SE *per se* can trigger this phenomenon, in the absence of any existing neuropathology or concomitant infectious process. Although instrumental for providing relevant information on the causative role of unremitting seizure activity *per se* on brain inflammation, the induction of SE in normal brain may also be viewed as a limitation since in the clinical setting pre-existing neuropathological conditions likely contribute to SE precipitation, and possibly to its refractoriness to treatment. Nevertheless, the pathologic consequences of brain inflammation caused by SE, likely due to lack of efficient resolution by endogenous anti-inflammatory mechanisms, suggest that SE might be controlled in the clinical setting by adjunctive therapy with specific anti-inflammatory drugs, independent of its etiology. Importantly, even anti-inflammatory treatments that fail to affect the acute course of SE provide long-term benefits by drastically ameliorating SE prognosis in animals. In particular, cell loss caused by SE is strongly reduced, as well as the mortality rate and the behavioral dysfunctions mimicking neuropsychiatric conditions. Moreover, various anti-inflammatory treatments in SE-exposed animals decrease the severity of ensuing epilepsy (TABLE **1**). In this context, it is intriguing to note that statins, which may exert anti-inflammatory properties [138–140], have been recently shown to be associated with improved SE prognosis in a retrospective clinical study if patients were taking them before the SE episode [141].

The rapid induction of inflammatory mediators during SE calls for early intervention to increase the chances of therapeutic success; in the experimental setting, anti-inflammatory drugs have been shown to positively affect the long-term SE sequelae when injected within the first 3–4 h from SE induction. Animal models also provide evidence that systemic or brain inflammatory challenges in infant rodents at the time of SE induction worsen the long-term consequences of SE by increasing cell loss, reducing seizure threshold and promoting co-morbidities in adulthood.

These findings highlight the possibility to block the activation of specific detrimental inflammatory signaling pathways as potential new targets for therapeutic intervention to improve prognosis in patients with new onset SE or SE recurring in the context of a chronic disease condition.

Five-year view

As we have seen in the preceding sections, inflammation seems to act in a bi-directional way toward SE: on the one side it can participate in its triggering, and on the other side it can be induced by ongoing seizures. It appears straightforward that if inflammation is identified as a main cause of a SE episode, such as for the recently described autoimmune conditions, this has to be addressed specifically, as successful management of the etiology is the best predictor for a favorable clinical outcome. This constellation, admittedly, seems to be relatively rare in epidemiological terms, but it may apply more often in refractory SE.

Notably, inflammatory changes triggered by SE in the brain appear in fact to be a hallmark of experimentally induced SE, and may contribute to sustaining the ongoing seizures by lowering the neuronal excitability threshold. The term ‘inflammation’ addresses a multidimensional array of mediators and pathways, some of which are undoubtedly beneficial, others contribute to chronic pathology including perhaps epileptogenesis. Over the next 5 years, it will be important to determine which of the inflammatory pathways are specifically tied to pathology, the timing of their engagement *vis-à-vis* SE onset, and which have a wide enough therapeutic margin to present clinically useful targets.

In view of the consistent body of evidence from animal studies, and given the current low level of evidence of anticonvulsant approaches in patients with refractory SE, it seems reasonable for this group of patients to foresee randomized studies testing not only broad-spectrum anti-inflammatory agents, such as steroids, but also specific ones, such as IL-1β inhibitors, some of which are already in clinical use [142], also including a long-term follow-up. This is the only way to rationally determine the conditions under which these approaches will effectively prove successful acutely in humans, but also if they will exert an anti-epileptogenic action.

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Key issues

- Status epilepticus (SE) is linked to a considerable risk of short-term mortality, unfavorable functional outcome and epilepsy.
- Treatment of SE is essentially based on expert opinions.
- SE etiology and age are the main prognostic determinants.
- Anticonvulsant drug treatment *per se* seems to have no major impact on SE prognosis. Broad spectrum anti-inflammatory treatments are reserved to patients with a proven autoimmune cause.
- Inflammation appears to play a determinant role in ongoing seizures and their long-term consequences independently of infection or auto-immunity.
- This may lead to reconsideration of the treatment of SE to include adjunctive anti-inflammatory drugs targeted to specific pathogenic pathways.
- Randomized controlled trials are needed in this field.

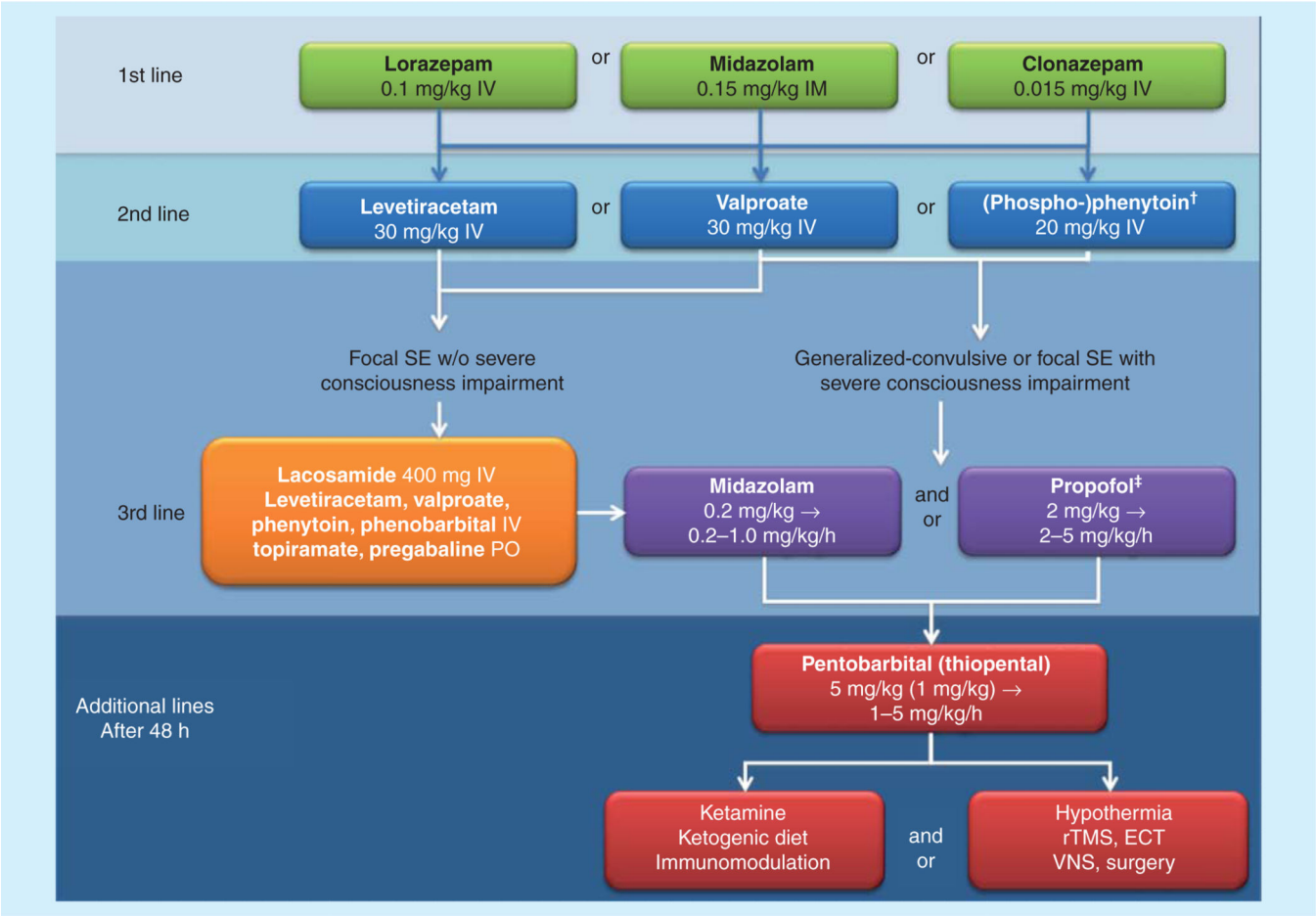

Figure 1. Antiepileptic treatment of status epilepticus (modified from [40])

The principal treatment lines along with the suggested dosages (based mostly on adult literature) are illustrated. Refractory SE episodes without marked consciousness impairment may be managed initially without general anesthetics.

†Cardiac monitoring is mandatory.

‡In order to prevent 'propofol infusion syndrome', regular check of lactate and creatine kinase is mandatory.

ECT: Electroconvulsive treatment; IV: Intravenously; PO: Orally; rTMS: Repetitive transcranial magnetic stimulation; SE: Status epilepticus; VNS: Vagal nerve stimulation.

Table 1

Anti-inflammatory treatments improving status epilepticus outcomes in experimental models.

Drugs	Targets	Ref.
Celecoxib, parecoxib	COX-2 inhibition	[143,144]
Aspirin	COX-1 & 2 inhibition	[145]
α4-Integrin-specific Ab	Adhesion molecules	[146]
Erythropoietin	Broad spectrum	[147]
Fingolimod	SP1 receptor/astrocytes	[148]
Minocyclin	↓Cytokines/Microglia	[149]
Anakinra (Kineret)	IL-1β receptor (IL-1R1)	[89]
Anakinra + COX-2 antagonist	IL-1R1 + COX-2 inhibition	[150]
Anakinra + TLR4 antagonist	IL-1R1 + HMGB1 inhibition	Personal communication
Nrf2 gene therapy	↓Oxidative stress/cytokines	[151]
miRNA-146a	IL-1β/TLR4	Personal communication
EP2 antagonists	EP2 receptors	[74]
Dexamethasone	Broad spectrum	[115–117]
Statins	Broad spectrum	[138,141,152] but see [139]