Diplomarbeit

Status Epilepticus from 0 to 100 Years

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Melbourne, July 15, 2014 Sara Mayrhuber

Abstract

Status Epilepticus (SE) is one of the most common neurological emergencies and is associated with high morbidity and mortality. A large number of research on specific topics with regards to SE were conducted, but despite various acquired knowledge, there is a lack of reviews and guidelines on the management of SE as a whole. This thesis is mainly based on literature research and aims to give an overview of the recent status of research on SE. It summarizes the outcomes of studies and reviews published in the last 15 years and listed in PubMed and Google Scholar. The primary focus lies on the age of the patient and thus the occurrent differences in etiology, the disease itself, diagnosis, and its treatment methods. All research yields *time is brain*. Studies conducted on the advances of SE research stated there is still room for improvements regarding treatment options and availability of medication of SE.

Kurzfassung

Der Status Epilepticus (SE) ist einer der häufigsten neurologischen Notfälle und ist assoziiert mit einer hohen Mortalitätsrate. Trotz des progressiven Wissenszuwachses gibt es kaum Reviews und Guidelines, die sich speziell auf das Management eines Status konzentrieren. Diese Diplomarbeit versucht, einen Überblick über die in den letzten 15 Jahren gewonnen Erkenntnisse zu schaffen. Dazu wurden hauptsächlich mithilfe von PubMed und Google Scholar gefundene Publikationen herangezogen. Der Fokus dieser Arbeit liegt besonders auf den Altersgruppen der Patienten und den damit verbundene Unterschieden in der Ätiologie, der Krankheit selbst, der Diagnose und den Behandlungsmöglichkeiten. Generell appelliert jede Studie, die sich mit SE beschäftigt, *time is brain*. Dies hebt hervor, wie wichtig eine rasche Diagnose und Therapie des SE ist. Je früher mit der Behandlung begonnen wird, desto besser sind die klinischen Ergebnisse. Nichtsdestotrotz, Studien, welche die Fortschritte der Forschung und den derzeitigen Wissensstand betrachten, bestätigen, dass Therapiemöglichkeiten und der Medikamentenzugang weit vom Optimum entfernt sind.

Contents

1. Introduction

In this chapter my motivation for this thesis is outlined and the structure and organization of the thesis is presented. Furthermore, the important terms for this thesis, i.e. epilepsy and status epilepticus (SE) are defined. Additionally a short insight into the historical background of SE is given.

1.1 Motivation

Status Epilepticus is one of the most common neurological emergencies that quickly turns out into a life-threatening condition if no intervention is taken. This disease affects not only adults, but also children and the elderly. Due to the aging population of these days, SE will be encountered more and more in emergency rooms. During the last decades definition, forms and treatment options of SE were constantly researched and modified. With improved technologies of modern neuroimaging, genomic technologies and molecular techniques there are a large number of studies available on SE. It is remarkable, that a lot of research on specific topics on SE is conducted. Despite this various achieved knowledge, there is a lack of reviews and guidelines on the management of SE as a whole. Particularly if it comes down to official medical treatment guidelines on SE. So far there is only one literature thesis on the current treatment options of the refractory SE at the Meduni Graz. The novelty of this work lies primarily in the entirety of this thesis, which provides an overview on published works over the last 15 years. With a focus on the differences between age groups, which is also the origin of the title of this thesis, it points out the need of improvement in particular parts of SE treatment. Moreover, it indicates trends such as the use of steroids in SE treatment, and presents new approaches of the pathomechanisms of SE. This thesis gives clinicians an overview on the current state of SE and serves as a reference book that is well linked with several up to date reviews on the latest achievements on SE.

1.2 Organization

This present work is organized as a literature research, primarily based on reviews and papers published in the last century, mainly found through PubMed [1] and Google Scholar [2].

It starts with this introduction and states important terms for this thesis, i.e. epilepsy and status epilepticus (SE). Additionally, a short insight into the historical background of SE is given.

The following chapter 2 - Classification describes the clinical forms of SE. Not only the common types, but also different forms affecting children and SE in the elder population are presented. New ideas of classification and influences to consider are summarized in the last section of this chapter.

In the next chapter 3 - Epidemiology, studies on the incidence in USA and Europe are presented. Also mortality rates of children, adults and elderly people are given.

In chapter 4 - Etiology, many different etiologies are presented and their corresponding mortalities are given. Frequency and mortality of SE of different etiologies are summarized and graphically shown.

In chapter 5 - Neurophysilogy and Neuropathology of SE, transformation of a single seizure into self-sustaining SE and the associated potential damages are discussed. Also the important possibility of studying SE in murine models is included. Furthermore, insight into the role of inflammation in SE is given. In the last section of this chapter, the influence to the brain due to duration and severity of seizures and a possible reduction of seizure time by a proper medication is reviewed.

The thesis also includes a short insight in the possibilities to diagnose SE with a focus on EEG, presented in chapter 6 - Diagnosis.

In the following chapter 7 - Treatment Options of SE, treatment options for SE are reviewed. Starting with a section dealing with pre-hospital treatment and pointing out the importance of time, also guidelines for the management of convulsive SE (CSE) and the management for seizures and SE in infancy are given. Different treatment options are discussed with a focus on new attempts in the treatment of SE with steroids. Practiced guidelines for the management of CSE and the management of seizures and SE in infancy are given. Furthermore, differences in medications for children and adults are discussed.

Finally, in the chapter 8 - Current Advances, Problems and Future Prospects, problems, future prospects, and recent advances in the understanding and treatment of SE, as well as new or still open questions are discussed. The first part of this chapter chapter is based on topics discussed in a Colloquium in Salzburg in 2013. In addition, the succeeding section discusses recently published results from the RAMPART (Rapid Anticonvulsant Medication Prior to Arrival Trial) study.

1.3 Definitions

1.3.1 Definition of Epilepsy

The World Health Organization (WHO) defines Epilepsy as a "chronic disorder of the brain" which is characterized by two or more recurrent, unprovoked seizures. In the form of short episodes of involuntary shaking, these seizures can affect either the whole body or only a part of the body. Their origin is an excessive electrical discharge. Further symptoms can include an impairment or loss of consciousness and time of seizures can vary from seconds to minutes, hours or even longer. Worldwide nearly 10% of people experience one seizure during their life. However, for the diagnosis of epilepsy, at least two seizures are required [3].

1.3.2 Definition and Historical Aspects of SE

Knowledge of status epilepticus (SE) dates back several thousand years in human history [4]. Although it was a widely known disease complication among physicians, it was not until 1967 that the first known scientific work on SE was published [5]. One of the authors of this work, Henri Gastaut, was also the first to give a clear definition of SE.

He defined SE

> *"as a prolonged seizure with as many forms as there were types of epileptic seizures."* (Trinka [6] 2012, *Epilepsia* **53**, p. 127)

In 1981 the International League Against Epilepsy revised the term SE [7]:

> *"... 'status epilepticus' is used whenever a seizure persists for a sufficient length of time or is repeated frequently enough that recovery between attacks does not occur."* (Commission on Classification and Terminology of the ILAE [7] 1981, *Epilepsia* **22**, p. 495)

As this "official" definition doesn't contain any lapse of time, Lowenstein came up with a new reasonable terminology [8]:

> *"Generalized, convulsive status epilepticus in adults and older children (>5 years old) refers to a 5min of (a) continuous seizures* ***or*** *(b) two or more discrete seizures between which there is incomplete recovery of consciousness."* (Lowenstein et al. [8] 1999, *Epilepsia* **40**, p. 120)

For children and infants with prolonged seizures, particularly associated with fever, Lowenstein advocated a time frame of more than 5 minutes. However as there is lack of verified information on seizure duration in children, a definition could not easily be applied [8].

Previous definitions used a time limit of 30 minutes, based on experimental findings on cellular damage after this period. However this time frame seemed impractical as it was confirmed that a seizure which persists for more than 5 minutes, seldom comes to an end automatically. Furthermore there is damage in animals, even before the defined time of 30 minutes [9]. Therefore research suggests, the earlier treatment is initiated, the better the outcome [10].

2. Classification

In the first section of this chapter the clinical forms of SE are described. Not only are the common types presented, but also different forms affecting children and SE in the elder population. New ideas of classification and influences to consider were brought up in a review by Berg. They are summarized in the last section of this chapter.

2.1 Clinical Forms

2.1.1 Convulsive Status Epilepticus (CSE)

With an annual incidence of 17-23 episodes per 100 000 children, CSE is the most common presentation in pediatric clinics. As seizures, especially prolonged seizures have detrimental effects on the developing brain, the main concern is to identify and treat seizures effectively and as fast as possible [11]-[13].

CSE according to Martland is merely a symptom of a cerebral event, or in other words the response to a chronic neurological problem. Therefore it cannot be seen as a single disorder, but rather as a complication of several distinct disorders [11], [13].

Convulsive manifestations of SE, just as in self-limiting epileptic seizures, can be either tonic-clonic, tonic or just clonic, though the beginning might impress with a focal seizure which later on starts to generalize. In CSE with generalized tonic-clonic seizure (GTCS) seizures start first with a short stiffness of the limbs, which is called the tonic phase. Later on jerky movements of the limbs appear and persist throughout the SE [11], [13].

Normally GTCS stops within 2 to 3 minutes without any intervention needed. However, if the seizure lasts more than 5 minutes, GTCS self-termination becomes less likely. Moreover it becomes resistant to medical intervention too. This is why guidelines recommend starting treatment as early as possible, which means, it should be initiated once a GTCS lasts longer than 5 minutes [13].

2.1.2 Non-Convulsive Status Epilepticus (NCSE)

Per definition NCSE is described as an

> *"enduring epileptic condition with reduced or altered consciousness, behavioral and vegetative abnormalities, or merely subjective symptoms without major convulsive movements."* (Trinka [6] 2012, *Epilepsia* **53**, p. 129)

Up to now there is no general accepted definition. Many authors suggest a definition based on alterations in the clinical condition, in combination with pathological electroencephalographic (EEG) findings. Clinical changes as the only characteristic of NCSE is not considered sufficient, as there are several non-epileptic conditions with similar symptoms. Nonetheless, when clinical features are typical and the preconditions indicative, the presence of EEG changes is not compulsory. Additional confirmation of NCSE could be gained from an EEG documented positive response to anticonvulsants, but a lack of response should not exclude [14].

NCSE compared to CSE occurs less frequently and therefore became an entity which is commonly missed in differential diagnosis of impaired consciousness. This form of SE primarily presents non-motor signs and has a better prognosis than CSE [6], [15], [16].

Characteristic features of NCSE can be unusual eye movements, impaired consciousness, agitation but also aphasia and unusual limb posturing. NCSE includes many presentations such as absence status or mental change, as well as a coma with generalized epileptiform discharges, which can be a life-threatening condition [6], [15], [16].

2.1.3 Refractory Status Epilepticus (RSE)

In case the initiated therapy is not successful in stopping the seizure activity, the condition is called a refractory status epilepticus (RSE). It occurs in 23%-43% of the cases. RSE is defined as the most serious presentation of SE and relates to a seizure lasting longer than 60 minutes, despite first and second line anticonvulsant drugs (ACD) as well as intravenous benzodiazepines have been initiated [17], [18], [19].

RSE often has a poor outcome and the side effects of the medication must be taken into account. Therefore if first and second line medication cannot terminate this life-threatening condition, a higher dose of anticonvulsants should be administered until seizure freedom is achieved. Reaching drug concentrations much higher than normal, it becomes apparent that respiratory depression may result and intubation is unpreventable. Further there is a need for constant monitoring of blood pressure since relevant hypotonia will lead to a breakdown of the brain's blood supply, putting the patient in a particularly vulnerable phase [20].

In case all these actions fail, medication should be changed and the causes of SE should be reevaluated carefully. Valproic acid, even if its not approved yet, is known to be a potent medication to treat seizures in a wide range of patients. However patients who suffer from severe liver and pancreas diseases or in those with mitochondrial dysfunction, should not be exposed to Valproic acid. Valproic acid is also not recommended in females during pregnancy or in children under the age of 2. In addition, great care should be also taken in young patients [20].

2.1.4 Super-Refractory Status Epilepticus (SRSE)

Super-refractory SE is described as

> *"a stage of refractory SE characterized by unresponsiveness to initial anesthetic therapy. .... It is defined as `SE that continues or recurs 24 hours or more after the onset of anesthesia, including those cases in which SE recurs on the reduction or withdrawal of anesthesia.' It is encountered typically, but not exclusively, in two quite distinctive clinical situations: (1) in patients with severe acute brain injury, and (2) in patients with no history of epilepsy in whom status epilepticus develops out of the blue with no overt cause."* (Shorvon [21] 2011, *Epilepsia* **52**, p. 53)

The main problem in super-refractory SE is the choice of effective therapy. Due to the lack of randomized controlled studies, treatment in super-refractory SE is based on mere expert opinion. There are but a few publications on small case series and several case reports dealing with super-refractory SE so therapy recommendations should be treated with caution [21]. The different stages on the way towards super-refractory SE are shown in figure 2.1.

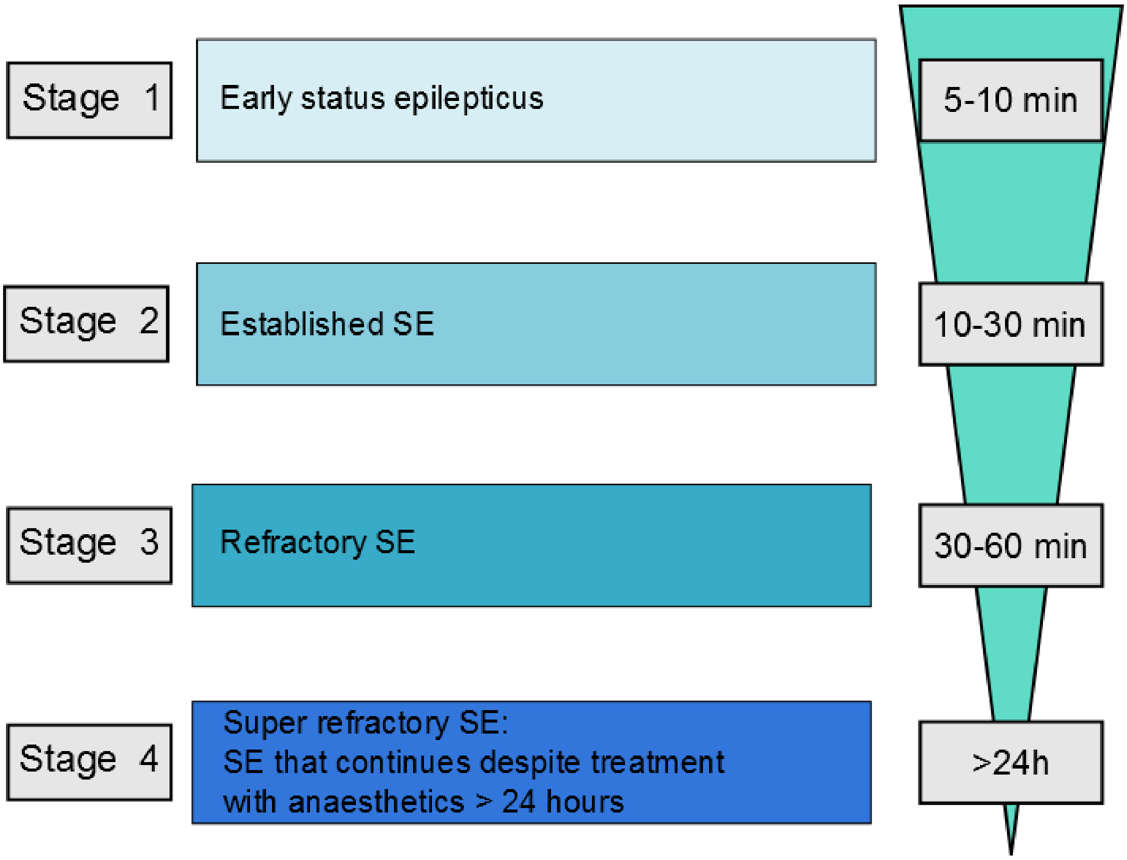

Figure 2.1.: Clinical course of convulsive status epilepticus. Modified according to Trinka [6].

2.1.5 Absence Status Epilepticus

Typical Absence SE

The main characteristic of absence SE is defined as an altered consciousness but changes in behavior have also been described. Usually, patients affected by the typical absence status epilepticus are capable of eating, drinking and reacting to commands in an ordinary manner [14].

This form usually occurs with an abrupt onset and can last minutes to days, or even weeks. Also it can be evoked, ended or interrupted by a generalized convulsive seizure. Regular spike wave discharges characterize the electroencephalogram with a frequency of around 3Hz, with time electroencephalogram becomes irregular and slow [14].

Patients are often misdiagnosed with idiopathic generalized epilepsy, in particular with a history of absence epilepsy or juvenile myoclonic epilepsy. Typical triggers are an inappropriate antiepileptic therapy, fatigue, excitement, fever, and hyperventilation. It can also be triggered by changes in the menstrual or the sleep-wake cycle [14].

Atypical Absence SE

In general, consciousness is more affected in atypical compared to the typical absence SE. Additional features such as eye-lid blinking and grimacing are common signs in atypical absence SE. To differentiate between typical and atypical absence status epilepticus at the bedside is often not easy due to lack of clear definitions often coupled with insufficient documentations of symptom development. Moreover, electroencephalogram does not provide approaches to distinguish between typical and atypical SE because of the unspecific morphology and frequency of recorded spike-waves [14].

This form of SE can be triggered by an alteration of antiepileptic drugs. Meierkord states that due to an increase of the anticonvulsant drug level or even the induction of the treatment, particularly of carbamazepine, gabapentin, phenytoin and vigabatrin, atypical absence SE might be elicited [14].

2.1.6 Status Epilepticus in Children

Infantile Spasms

Infantile Spasms, or the so called West Syndrome, named after William James West who first described this condition, are one of the most severe forms of childhood epilepsies generally having a poor outcome. This rare epileptic encephalopathy usually occurs age-related in the first year of life, with a peak around the fifth month of life. Often this pathology is related to a stagnation or decline of the "normal" early childhood development [22].

In some cases, a ``latent period" following a brain insult is the first clinical sign of the initiation of epileptogenesis. This state of epileptogenesis can last weeks to months and is usually followed by an onset of infantile spasms and hypsarrhythmia (see figure 2.2) [22].

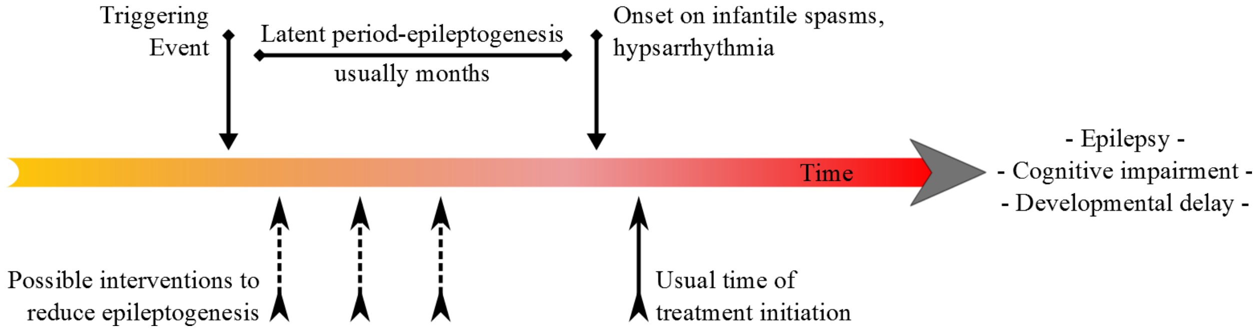

Figure 2.2.:This timeline shows a common sequence for the occurrence of epilepsy. Usual and possible points of intervention are depicted. Modified according to Stafstrom [22].

After several years spasms might stop but affected children may develop other forms of partial or generalized seizures. It is known that up to one fifth of Lennox-Gastaut cases had preceding infantile spasms. Typical symptoms of Lennox-Gastaut syndrome are developmental delay, behavioral and psychological abnormalities in addition to frequent seizures of different types [23].

With more than 200 etiologies registered, the most common etiology is brain dysfunction due to some prenatal, perinatal or postnatal hypoxic events. Also brain malformation, central nervous system infection or a hypoxic ischemic encephalopathy, accounts for the etiologies of infantile spasms. Genetic disposition also plays a role as families have been described where multiple siblings, in some cases only boys, were affected. However uncertain etiologies are steadily decreasing, as modern imaging, genetic testing and biochemical diagnostic methods constantly improve [22].

Infantile spasms emerge typically in clusters, often during a sleep-wake transition. Spasms can include intermittent spasm-like seizures with motion of the legs, arms or the trunk. Common clinical manifestations include movements with mixed flexion-extension of the body, isolated extension, or flexion of arms, legs or trunk [22].

Still the bio-chemical basis of West syndrome is unknown. There is a hypothesis that neurotransmitter functions are disturbed, namely derangement in GABA transmission as well as a hyper-production of the corticotropin-releasing hormone (CRH) [22].

Treatment of infantile spasm is generally based on cessation of spasms and restoration of a normal EEG pattern (no occurring hypsarrhythmia), although the mechanism of action is not exactly known. Usually 39-amino acid adrenocorticotropic hormone, referred to as ACTH, is used for therapy of infantile spasms according to the review article by Strafstrom. As ACTH administration is expensive, prone to notable side effects and ineffective in some cases, other options for treatment have to be considered [22].

For example, vigabatrin is the first choice medication in children with tuberous sclerosis and has proved to be highly effective. However advances in the understanding of infantile spasm remain modest due to limited access to experimental models. Furthermore, this disorder is based on a complex of interacting pathologies, rather than a single mechanism [22].

CSE in Children and Fever Induced Status

In children an important distinction between febrile and afebrile SE needs to be made. As a consequence of higher muscle activity during a SE, body temperature might increase. As a consequence body temperature should be interpreted cautiously. Febrile cases are considered when temperature rises above 39.0°C in children and 38.0°C in babies under 3 months of age. Measurements can be done by a thermometer used in the axilla or with an infra-red tympanic thermometer [11].

The febrile SE is known to be the most common neurological emergency in childhood. In most children prognosis is good and there are no further sequelea. However some children's febrile SE, particularly those affected with neurological dysfunctions, will develop full blown epilepsy [24].

Febrile Infection - Related Epilepsy Syndrome (FIRES)

The Febrile infection - related epilepsy syndrome emerges typically in children between three and fifteen years of age. What characterize FIRES are seizures that occur usually in healthy children, after or during an unspecific febrile infection. In FIRES, seizures might quickly transform into refractory SE, often accompanied by severe cognitive dysfunction [25].

Case reports show that nearly half of the patients are afebrile at the time the first seizure emerges. Seizures in FIRES are characterized by focal onset, chewing movements and clonic jerks of the mouth. Frequency of seizures varies from between several seizures to 100 per day, as has been reported in some cases. EEG is characterized by a slow wave pattern between seizures that looks similar to an encephalitis pattern. Though many investigations were conducted, no evidence for a viral or autoimmune involvement was found and neither was lymphocyte infiltration in postmortem examination. This points in the direction of an encephalopathy, rather than an infection of the brain [25].

As for therapy, application of general anesthetics might not only be ineffective but also aggravate outcome. A promising treatment option, even when it's applied late, is the ketogenic diet. In nearly half of the patients this diet has shown beneficial therapeutic effects [25].

If seizures remain refractory after 4-8 months of continued seizure activity, death may occur. In other cases seizures decline but patients often suffer from cognitive impairments weeks or even months later, primarily afflicting memory, speech and other frontal lobe functions [25].

2.1.7 Status Epilepticus in the Elder Population

As the aging population is often affected by disorders with symptoms very similar to NCSE, such as confusion, personality change or psychosis, diagnosis of NCSE is becoming a challenging task for physicians [26], [27].

This is an important concern as NCSE is the most prevalent form of SE in the elderly. In addition to diagnostic difficulties, all treatment in elder patients must be well adapted to the current state of general health. The problematic in the treatment lies obviously in its adverse effects. Especially in elder patients, it becomes apparent that there is a much higher risk of side effects, such as cardiac depression, hypotensive crisis or sedative effects. Pharmacokinetics change in the elderly and are characterized by reduced diminished protein binding, altered volume of distribution, dysfunctional hepatic metabolism, and reduced renal eliminations [26], [27].

Still this type can often be treated well by an initial dose of benzodiazepines but always with monitored blood pressure and cardiac rhythm. Compared to younger patients one can assume that prognosis is worse, especially because of comorbidities in old patients and the risk of hospital acquired infections [26], [27].

Moreover, it becomes evident that anesthesia used for the elderly suffering from SE, probably doesn't have a beneficial effect on the outcome. Furthermore, there is evidence that the outcome of seriously ill patients can be aggravated by anesthesia, especially in unstable patients. A higher mortality rate compared to younger patients has been reported in several studies. Therefore treatment initiation should always be done cautiously. Currently there is not enough data on SE in this specific population, which again poses a supplementary challenge for the attending physicians [26], [27].

The most common etiologies in the elderly are acute or remote stroke, but also low AED level, hypoxia, tumor, metabolic disturbance and trauma. Especially notable is that about 30% of acute seizures in elder patients turn out as an SE with a doubled incidence (86 cases per 100 000 population per year), compared to the general population. Looking at the ``very old" (>80 years) the incidence increases to 100 per 100 000 population per year [27].

2.2 Classification of Status Epilepticus: A New Approach

In 2011 the critical review with the title New concepts in classification of the epilepsies: Entering the 21st century, was published by Berg. Over the last few decades, many advances in epilepsy research were achieved, especially in the field of neuroimaging, neurophysiologic techniques, molecular cell biology, genetics and digitations. This has brought huge progress to the understanding of epilepsy but concepts and classification of epilepsies and seizures are still based on achievements and concepts proposed in the last centuries. Even if the old classification is familiar that changes are likely to provoke residence, new insights need to be integrated in order to guarantee a better understanding of research results and ensure better care of patients with epilepsy [28].

The comparison of major changes and the newly proposed terminology and concepts by Berg attempts to move away from an overall classification for epilepsies into which all epilepsies must fit. For example while it might be useful to categorize SE into focal and generalized SE, frequently both seizure types can appear within the same patient [28].

The new proposal also concerns the etiology in that idiopathic, symptomatic and cryptogenic should be replaced through the terms genetic, structural/metabolic and unknown etiology, see also table 2.1. Genetic defects result directly in the propensity to develop epileptic seizure. In this category it is primarily important to identify the affected gene [28].

Table 2.1: Classification of Status Epilepticus - currently used and recently proposed categories.

Categories of SE	
old	new
idiopathic	genetic
symptomatic	structural/metabolic
cryptogenic	unknown

In structural/metabolic epilepsy, epilepsy is secondary to a metabolic or structural condition. However, as critics point out several metabolic disorders also have genetic origin which makes the classification difficult in individual cases [28].

3. Epidemiology

3.1 Incidence

Presenting prolonged, self-sustaining seizures, SE is the second most frequent neurological emergency. With an incidence of 10-41 per 100 000 per year, about 287 000 people in Europe are concerned by SE anually [6], [29].

In the last few years three population-based prospective studies were conducted to examine the epidemiology of SE. The investigations found that the incidence around Richmond, USA was 41 per 100 000 individuals per year. The incidence in adolescents was 27 per 100 000 per year. In comparison to this, the incidence rate in the elderly was as high as 86 per 100 000 per year. This distribution illustrates clearly that in an aging society the clinical presentation of SE will become more and more common in the emergency rooms [20].

Two prospective studies conducted in Europe found similar incidence results with 17.1 in Germany [30] and 10.3 per 100 000 individuals concerned per year in the French speaking part of Switzerland [31].

Also a retrospective study conducted in Minnesota with an incidence of 18.1 per 100 000 proved similar findings [32].

According to the review article by Rosenow analyzing data of nine population based studies conducted in the USA and Europe between 1997 and 2006, the incidence of SE in the Caucasian population in developed countries is at least 20/100 000 per year. However due to a lack of a generally accepted definition for non-convulsive SE (NCSE), the author stated that it is likely that the estimated number of unknown cases is much higher. This stresses the importance of a consensus in the diagnosis of NCSE [33].

3.2 Mortality

During the last twenty years mortality and morbidity from SE have decreased throughout the general population [34]. The article by Martland on the management of SE reports a decline in mortality and morbidity in children within the last few years, predominantly due to the consequence of the wider use and accessibility of anticonvulsants [13].

Chin documented mortality rates of 3% in 91 children suffering from SE, whereas in the 1970's mortality rates of up to 11% were reported. The explanation for this decrease in mortality he thought lay in the change in definition for CSE. CSE used to be defined in the 1970's by a seizure duration of one hour but recently this was reduced to 30min [34].

In a study conducted by DeLorenzo in Richmond Virginia, the mortality rate of SE was an average of 22% across all age groups. Whereas among children the rate accounted for 3%, in adults it was 26%. With 38%, he demonstrated the highest mortality in the elderly. Reasons being that age at onset, duration of the seizure and etiology play an important role for the outcome of SE. Independent of any variables, patients who suffered from stroke or anoxia showed a high mortality rate. In contrast, patients who underwent alcohol withdrawal and simultaneously suffered from SE, or patients with low antiepileptic drug levels saw relatively low mortality rates [29].

Trinka, in his article on the causes of SE and several other studies, argued that an increased risk of mortality and morbidity, linked with SE, occurs in three cases [6]:

1. specific etiologies,
2. age > 60 years and
3. long duration of SE

In the review *Prognostic Factors, Morbidity and Mortality in Tonic-Clonic Status Epilepticus* Neligan also emphasized that outcome is worse with advanced age. Also the review by Neligan reported a mean mortality rate of 3% in children. In adults mortality of 14% was reported and accounted 38% in patients over 60 years [35].

In RSE the short-term fatality rate ranges between 16%-39%, therefore the mortality rate compared to non-refractory SE is three times higher. It is also important to be aware that death occurs in general after a persisting SE and not during a SE, usually associated with the underlying disease [19].

4. Etiology

In this chapter the many different etiologies are presented and their corresponding mortality is given. The main part of this chapter is based on a study by Neligan [36]. Frequency and mortality of SE of different etiologies are summarized and graphically shown in figure 4.1.

4.1 General Aspects

Even if the underlying etiology has no direct impact on first-line therapy in SE, knowing the cause is important, not only to adapt future treatment, but also for assessment of prognosis and outcome [11].

Focusing on the differences in etiology, there is a great variation depending on the setting, the age as well as the population [37]. But also the duration of a seizure and the cause for SE play an important role to foresee the outcome [20].

In 2010, the review Frequency and Prognosis of Convulsive Status Epilepticus of Different Causes was published. This focused on causes of SE in the present developed world. Summarizing studies from 1990 up to 2008, the authors demonstrate the prognosis in relation to mortality and morbidity. Moreover, the authors analyze the frequency of the most common underlying causes of SE, even by respecting the geographic differences. Through this review they found that the outcome is strongly interrelated with the underlying cause [36].

4.1.1 Population vs. Hospital-Based Studies

There is a paucity of investigations to rate the incidence of various risk factors across the population. To combine results from studies investigating single risk factors however is impossible due to differing study designs and particularly as part of the studies are population and others hospital based. In 1994 an inquiry was conducted to identify the most common causes for SE in 1679 patients. Only in 19% was there no apparent reason (11% in children and 13% in aging people), while in 12% of the patients, febrile SE was the cause. Furthermore, toxic, acute metabolic, or anoxic reasons accounted for 14% and furthermore trauma, tumor, stroke, infection or perinatal complications each accounted for 7% to 10% [36].

4.1.2 Etiology in Specific Age Groups

Studies have shown that both incidence and risk factors differ in age groups at each end of the spectrum from those of the rest of the population. Children with the very first episode of SE episodes in a population-based study in London, UK showed the most frequent reason being a febrile illness in 32% followed by bacterial meningitis in 12%. While acute symptomatic SE in 17% was linked to metabolic disturbance or CNS infection. In the elderly, stroke is a substantial reason for SE, in particular when there were no seizures occurring in the past. Mortality and morbidity are higher in stroke-induced SE, in contrast to other causes particularly in the elderly [36].

4.1.3 Etiology in the Developing World

Even if there is no comparative data yet that attribute a higher frequency of SE to patients living in developing countries, studies from India, Africa and Trinidad might lead to believe that due to an increased rate of infection. A retrospective study on SE conducted in Senegal involving 697 patients over 11 years (of whom 48% of the children were younger than five years), could show that infections were the trigger for 67% of cases of SE. Other causes reported are poorly controlled epilepsy (10%) and cerebrovascular disease (8%) [36].

4.2 Specific Risk Factors

4.2.1 Race and Ethnicity

A particularly remarkable aspect becomes evident by focusing ones attention on race and ethnicity. The outcome of a study by DeLorenzo [29], which was later on replicated by Wu [38] states that in the black population the incidence of SE is three times higher than in the white population. Undoubtedly, that mirrors the importance of integrating ethnic backgrounds and socioeconomic factors in research studies [36].

4.2.2 Previous History of Epilepsy

Frequently encountered in patients with SE are cases with a past history of epilepsy. In these cases, CSE often occurs because antiepileptic drugs were reduced. Taken as a whole, 30% to 44% of the cases with SE have a history of epilepsy, whereas 60% of these cases have an acute symptomatic cause, particularly febrile illness. Lowenstein and Alldredge stated that in 154 adult patients treated for generalized SE, anticonvulsant drug withdrawal (n=39) and alcohol related (n=39) were leading among the four most frequent causes, followed by drug toxicity (n=14) and central nervous system infection (n=12) [36].

4.2.3 Alterations in Antiepileptic Drug Levels

According to Trinka, a low antiepileptic drug level (AED) is known to be the most common etiology in patients with a history of epilepsy. However, this group proved to have a low mortality rate of 4-8, (6%) and hence a good outcome [6], [29].

Furthermore, Neligan reports, that especially in patients with a history of epilepsy, noncompliance accounts for the most frequent cause, particularly in adults but not with children. In general, it is widely confirmed that low AED levels in course of anticonvulsant withdrawal, is a common cause in patients. In these cases, treatment with anticonvulsants responds well and therefore they have a good prognosis, even in a matter of refractory SE [36].

In children, the role of changing antiepileptic drug levels in inducing SE seems even more prominent. A hospital-based survey of 346 children with GCSE, with some of them (68%) having a history of epilepsy was conducted. Among the known causes noncompliance to antiepileptic drugs was found to be prevalent in about 28% (n=65), in those with epilepsy, cerebrovascular disease in 17% (n=40), systemic infection in 13% (n=31), alcohol abuse in 8% (n=18) and brain tumors in 5% (n=12) [36].

4.2.4 CNS Infections, Encephalitis

Especially in children, acute CNS infections and encephalitis are significant causes of SE, commonly accounting for about 1% to 12% in the developed world and are much more frequent than in adults. In hospital-based studies, CNS infections are linked with considerable morbidity and mortality. As for encephalitis, it is associated with a high rate of refractory cases. There is a significant increasing risk of an ensuing SE for those patients suffering from a refractory or non-refractory SE initiated by encephalitis [36].

4.2.5 Stroke

In a population-based survey, mortality was found to be 57% in patients with their first appearance of cerebrovascular-related SE. Summarizing the study of Neligan, stroke accounts for about 20% of the cases of SE and is especially predominant in the elderly. Patients suffering from stroke and SE have a worse outcome compared to solely stroke patients [36].

4.2.6 Alcohol and Drug Abuse

In several population and hospital-based studies, alcohol abuse was found to be a cause for SE with an occurence ranging from 8.1% to 25%. The mortality rate in alcohol-related SE was found to be up to 10%. Compared to drug-induced SE, alcohol-related SE seemingly has a somewhat better prognosis. These differences in outcome might be attributed to a generally poorer medical condition and higher drug toxicity in patients with illegal drug consumption [36].

4.2.7 Cerebral Tumor

Brain tumors are a seldom cause of SE, accounting for 2% to 5% of the cases of SE. Occurring rather chronic or subacute than acute, the paradoxical good prognosis of cerebral tumors-related SE might be because of their tendency to provoke partial SE, much more than GCSE, which is linked with a better outcome [36].

4.2.8 Trauma

Also acute trauma is not very common to provoke SE. Studies accounted trauma-related SE with 0% to 10% with a mortality of up to 25%. In a survey of 94 patients with moderate to grave traumatic brain injury (TBI), of whom in 21 (22%) seizures were determined by electroencephalography, the manifestation accounted for focal motor twitching or atypical myoclonus in 6 patients and in 2 it presented as nonconvulsive SE. All of the patients with SE died, but regardless of this outcome or that specific study, a clear statement concerning mortality and morbidity in general can't be made since large cohort studies on trauma-related SE weren't conducted as of yet [36].

4.2.9 Cerebral Anoxia

It is generally known that anoxia can cause deep coma after a cardiorespiratory arrest, for example. There are a number of authorities who interpret symptoms such as myoclonic jerking in coma to be a form of SE. Several studies were conducted to find out about the mortality rate and prognosis after cardiopulmonary resuscitation. Particularly, myoclonic SE in coma has a poor outcome with a mortality rate of 60-100%. Serious neurological deficits are important to mention as well as the findings that SE was found to be resistant to first-line therapy in many cases [36].

4.2.10 Metabolic Disorders

Another common cause is metabolic disorders. Hypoglycemia, hypocalcemia, hypomagnesemia, or electrolyte imbalances are common with prevalence ranging from 5-35% with a mortality rate of 10-35%. Along with this, in metabolic disturbance-related SE, the risk of mechanical ventilation is often increased, which independently leads to a poorer outcome [36].

4.2.11 Cryptogenetic Causes

Despite the progress in the last thirty years, the question concerning the etiology in many cases of SE remains unclear. In approximately 5% to 15% of patients, the etiology remains obscure and prognosis is variable. In these cases of cryptogenic or idiopathic-related SE, mortality rate is generally low but not in every case. In one-third of the patients, subsequent epilepsy will emerge, leading to a higher long-term mortality rate [36].

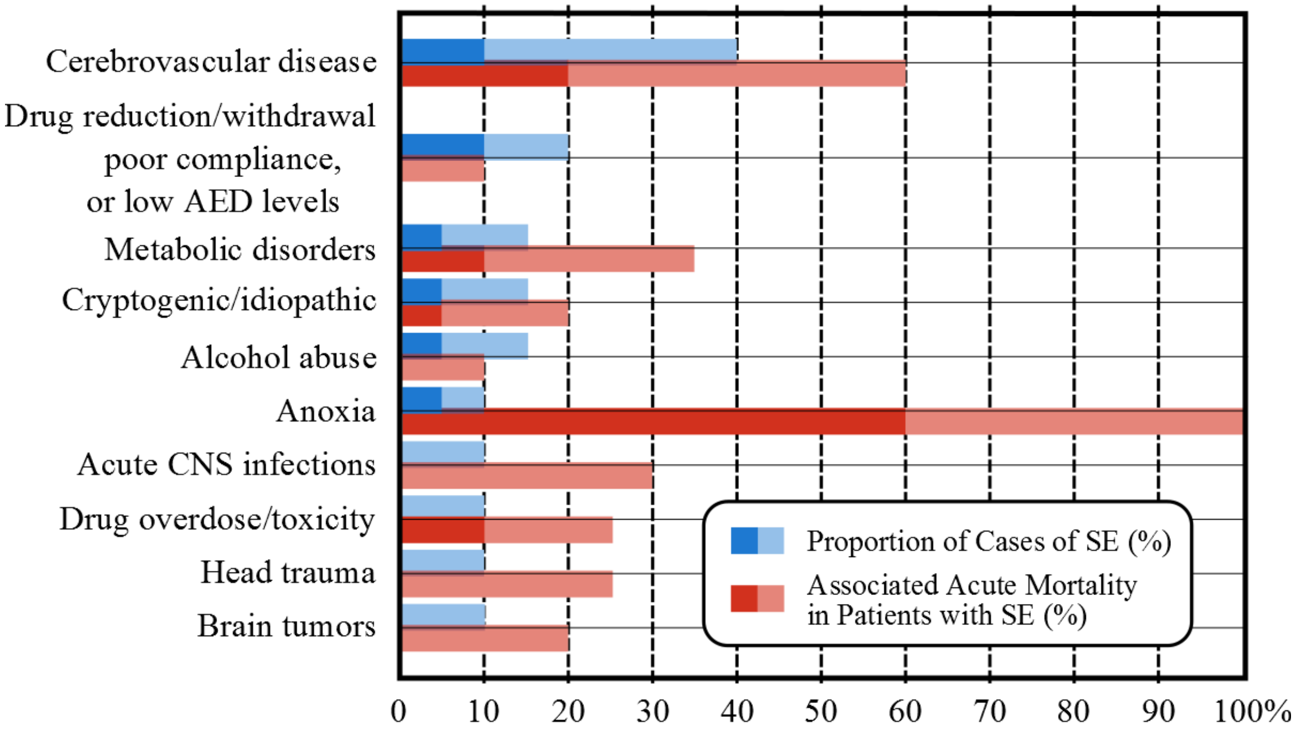

Figure 4.1.: Different etiologies of SE arranged according to the occurrence of SE. The blue bars indicate the occurrence of SE due to a particular cause. The red bars indicate the associated mortality. For instance, 10-40% of all patients suffering from cerebrovascular disease are affected by SE. Of all the affected patients, the mortality is 20-60%.

Abbr.: AED: antiepileptic drug; CNS: central nervous system; SE: status epilepticus;

This figure is based on data provided by Neligan [36].

5. Neurophysiology and Neuropathology of SE

In this chapter, neurophysiology and neuropathology of SE are described. The transformation of a single seizure into self-sustaining SE and the associated potential damages are discussed in the first section of this chapter. The important possibility of studying SE in murine models is also included. Furthermore, the outcome of the studies by Janigro [39] and Vezzani [40] are used to gain insight into the role of inflammation in SE. In the last section of this chapter, the influence to the brain due to duration and severity of seizures and a possible reduction of seizure time by proper medication is reviewed.

5.1 Neuropathological Changes in Cerebral Structures

A convulsion has many negative impacts, in particular because it affects the brain metabolism. Seizures that become self-sustaining tend to damage cerebral structures. Normally, a seizure should be stopped immediately, but sometimes ending of the seizure fails despite prolonged seizure activity. In the main part, it is induced by a dysfunctional mechanism. The interactions depicting epileptoform discharges are depicted in figure 5.1. The problem can stem either from a continuous, atypical excessive cell activity or from a lack of inhibition. But all in all the evident influence is still questionable [16], [41].

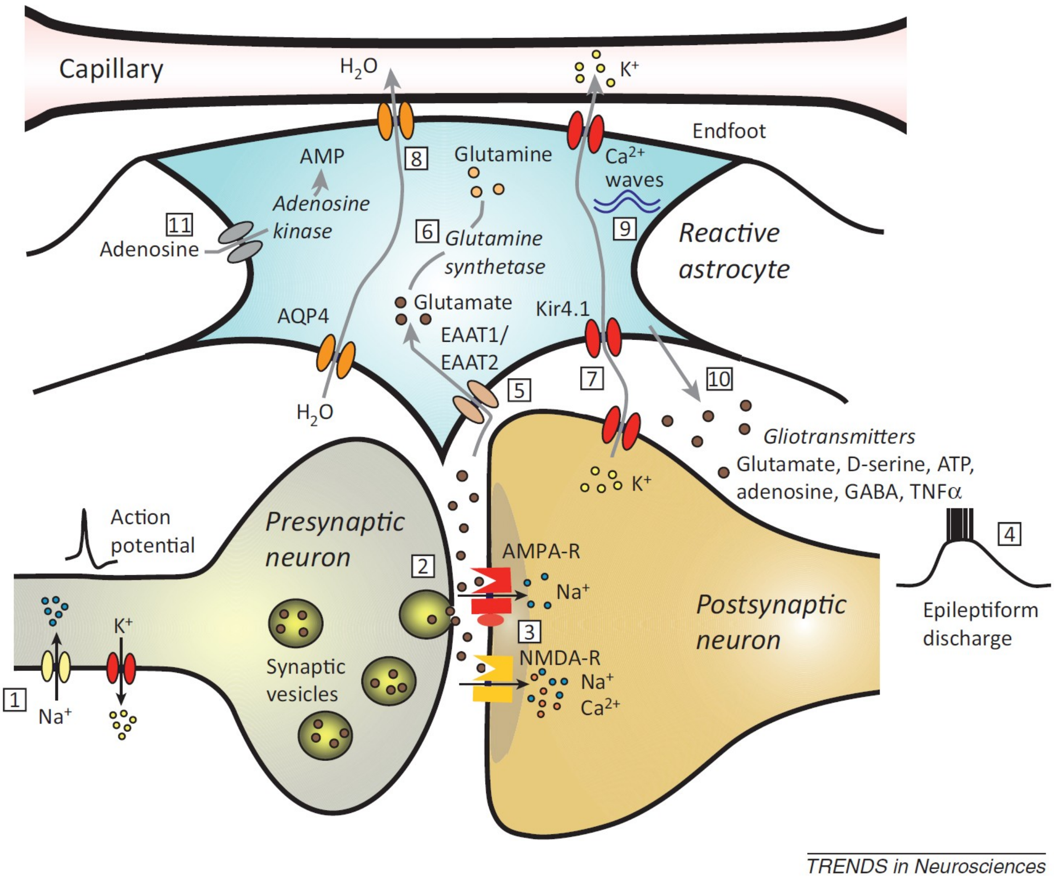

Figure 5.1.: Interactions between astrocytes and excitatory neurons. *"Voltage-gated Na+ and K+ channels (1) generate action potentials in the presynaptic neuron, leading to the exocytotic synaptic release of neurotransmitter glutamate (2). Glutamate activates AMPA and NMDA receptors (3) in the postsynaptic membrane, causing excitatory synaptic potentials generated by influx of Na+ and Ca2+. If sufficiently strong, synaptic excitation leads to epileptiform discharges (4). Glutamate is taken up into reactive astrocytes by the EAAT1 (GLAST) and EAAT2 (GLT-1) transporters (5) and is converted to glutamine by glutamine synthetase (6). Glutamine is a substrate for the production of GABA in inhibitory GABAergic neurons (not shown). Loss of glutamine synthetase in reactive astrocytes leads to a decrease in GABA production. K+ released from neurons by voltage-gated (outwardly rectifying) K+ channels enters astrocytes via inwardly rectifying K+ channels (Kir4.1) (7) and is distributed into capillaries. Aquaporin-4 (AQP4) concentrated at astrocytic endfoot processes regulates water balance (8). Ca2+ waves (9) stimulate the release of gliotransmitters (10) that can influence neuronal excitability. The inhibitory substance adenosine is taken up into astrocytes by the equilibrative nucleoside transporters ENT1 and ENT2 and concentrative nucleoside transporter CNT2. Excessive adenosine kinase in reactive astrocytes increases the removal of adenosine (11), enhancing hyperexcitability."* (Devinsky [42] 2013, *Trends in Neurosciences* **36**, p. 175). Image and label taken from Devinsky [42]. Copyright provided by Elsevier (No 3278910730993).

Nonetheless, recent studies could demonstrate cell loss in limbic structures in several animal models and hence gave an insight into the mechanism happening in SE. Furthermore these trials brought evidence that changes in the hippocampus region on histology level are rather the rule than the exception. However, it is yet unclear whether these findings in animal models can be transferred to human beings [16], [41].

If so, according to the above mentioned results, one can conclude that the brain faces a problem as soon as a seizure cannot be stopped. Based on an unforeseen enormous neuronal discharge malfunction of the cortical activity occurs. Besides the unnatural motor activity and radical change of the consciousness, body metabolism alters and the need of oxygen and glucose rises. The reply to increased metabolic demand is the start up of the sympathetic trunk which ensures an increased blood supply to the brain, but also causes tachycardia [13], [16].

After this phase, the brain enters a state in which normal regulatory mechanisms fail, demonstrating a breakdown of the preceded caused events. Cerebral and systemic blood pressure drop, but intracranial pressure raises. Due to a problem in the muscle activity, metabolic derangement of breathing occurs as the seizure cannot be stopped. As a result if no intervention is started, insufficient oxygen supply causing respiratory acidosis will occur [13], [16].

Apart from that, decompensation in muscles occurs by muscle hyperactivity and soon after primary respiratory acidosis is aggravated by a metabolic acidosis. The reason being that muscles need glucose to work properly, but glycogen storage does not last forever. Worst case, an organ failure, follows after the respiratory and metabolic breakdown [13], [16].

These pathological changes on the macroanatomic level are accompanied by a sophisticated patter of interactions on the cellular level majorly involving excitatory neurons and astrocytes which is depicted in figure 5.1.

5.2 Self-Sustaining Status Epilepticus

Chen and Colleagues stated in their review that there is no evidence based concepts on how seizures become self-perpetuating in human beings. However, analyzing investigations over the last decades about hardly stoppable seizures lasting longer than 30 minutes, one can assume that pathomechanisms that trigger self-sustaining seizures in animal models, might be similar to those in humans [20].

To avoid cerebral damage and epileptogenesis, it is important to understand the concept of transformation of a single seizure into a self-sustaining SE. Lothman, one of the researchers of SE, repeated electroconvulsive trials in animals. Lothman and his colleagues induced limbic seizures by hippocamal stimulation that generated brain damage and thereafter lead to chronic epilepsy. A similar result was shown by Vicedomini and Nadler who could prove that a series of ten after-discharges are enough to trigger a self-perpetuation SE [20].

The beginning of self-sustaining SE can indirectly be terminated either by drugs that are able to increase inhibition, or drugs that reduce excitation. These drugs mostly stop a self-perpetuating seizure by direct or indirect inhibition of glutamatergic neurotransmission. In barbiturates and GABAergic drugs, although never rendering completely ineffective, therapeutic response greatly reduces with time. As a consequence, they need to be administered in higher doses which quickly leads to toxic side effects such as cardiovascular depression [20].

Pharmacoresistence is also a defining characteristic of self-sustaining SE. Within 30 minutes in their investigation, Kapur and MacDonald could point out the decrease of benzodiazepine effect, whereas other investigations state that anticonvulsants (e.g. phenytoin) also undergo a steady reduction of their therapeutic effect. In contrast, NMDA blockers, even if administered late, don't lose their antiepileptic potential [20].

5.3 Murine Models of SE

In the laboratory there are many methods to induce a prolonged seizure. One of the common used techniques is the systemic injection where chemoconvulsants are utilized to trigger a prolonged seizure. To do this a convulsant substance is directly injected into rodents, resulting changes to the animals and in turn causes spontaneous relapsing seizures [24].

Glutamatergic agonist kainic acid as well as muscarinic agonist pilocarpine are the two main chemical substances used in the laboratory. However pilocarpine in combination with lithium is sometimes applied, as lithium induces a reduction of pilocarpine [24].

Because it is difficult to distinguish between the noxious effect of a convulsant substance and the alterations that emerge as a product of an induced seizure, electrical stimulation was applied. There is the assumption that the model of recurrent stimulation with electrical impulses resulting in a self-sustaining SE is most likely the direct effect of an induced seizure. For that reason electrical stimulation has been used in several studies, though it is known to cause better results in developed brains than in developing brains as high resistance to electrical stimulation often exists [24].

Since febrile SE occurs in 25% of adolescents, models were invented to reproduce this condition. For that, rodents, were heated with a constant air stream of 41.5°C which caused a seizure that also affected limbic structures [24].

5.4 The Role of Inflammation and Cytokines in Pathophysiology of Epilepsy

The review by Janigro reports about the role of inflammation in SE. Over the last centuries many different AEDs were developed but unfortunately alternative concepts needed to be found as AEDs do not work in all patients [39]. Apart from the well-explored neuronal mechanism of seizures, it is discussed that seizures could have their origin in an inappropriate inflammation response of the body as well as the alteration of the blood-brain barrier. At the moment, new pharmacological solutions are tested targeting the altered blood-brain barrier which may be the cause for seizures [39].

Over the last years, experiments in animal models were conducted to identify the role of inflammation processes in brain tissue. The question arose whether inflammatory cytokines contribute to etiopathogenesis of seizures and if so, if in the long run cytokines contribute to the manifestation of chronic epilepsy [40].

In epileptogenic tissue different inflammatory mediators are expressed from activated glia cells. Therefore it becomes essential to detect whether inflammation is a epiphenomenon of a seizure and as a consequence if inflammation is responsible for the pathology in resulting neuronal damage [40].

In experimental models, high levels of inflammatory mediators were reproduced in the involved epileptic brain regions. Also an inflammatory response was found in glia, after seizures were provoked by electrical stimulation or by chemoconvulsants. Generally an increase of inflammatory cytokines such as interleukin (IL)-1ß, IL-6, TNF-x appear in astrocytes and microglia, accompanied by a cascade of down-stream inflammatory events [40].

Furthermore, cytokine receptors play an important role in the pathophysiology. Patterns of cytokine receptor expression were investigated. IL-1R1 which is the mediator to IL-1ß is hardly detectable in normal brain tissue. However, less than 2 hours after a seizure IL-1R1 was found to have significantly increased in the hippocampal neurons. Similar findings were collected for the IL-6 receptor which is not detectable in normal brain tissue but after a seizure there was an increase in the forebrain of rats [40].

Other triggers for inflammation in the brain are brain insults such as stroke, infection, perinatal injury, febrile seizures, etc. (see figure 5.2). These injuries, even subclinical, at birth or sometime during life, set up the basis for a chronic inflammatory process in the CNS, which later on may contribute to the onset of epilepsy [40].

As inflammation might play a part in epilepsy, anti-inflammatory drugs such as steroids are taken into account, especially in seizures refractory to classic anticonvulsants. Investigations show a strong activation of the IL-1B/IL-1R1 system in the patients refractory to anticonvulsants [40].

Neuronal damage is described, particularly in the hippocampal formation and in forebrain structures affected by epileptic discharges. Both, cytokines and different inflammatory mediators lead to excitotoxis and apoptotic death of neuronal cells. Several studies show that once a seizure is established, an ongoing inflammation in the brain is likely [40].

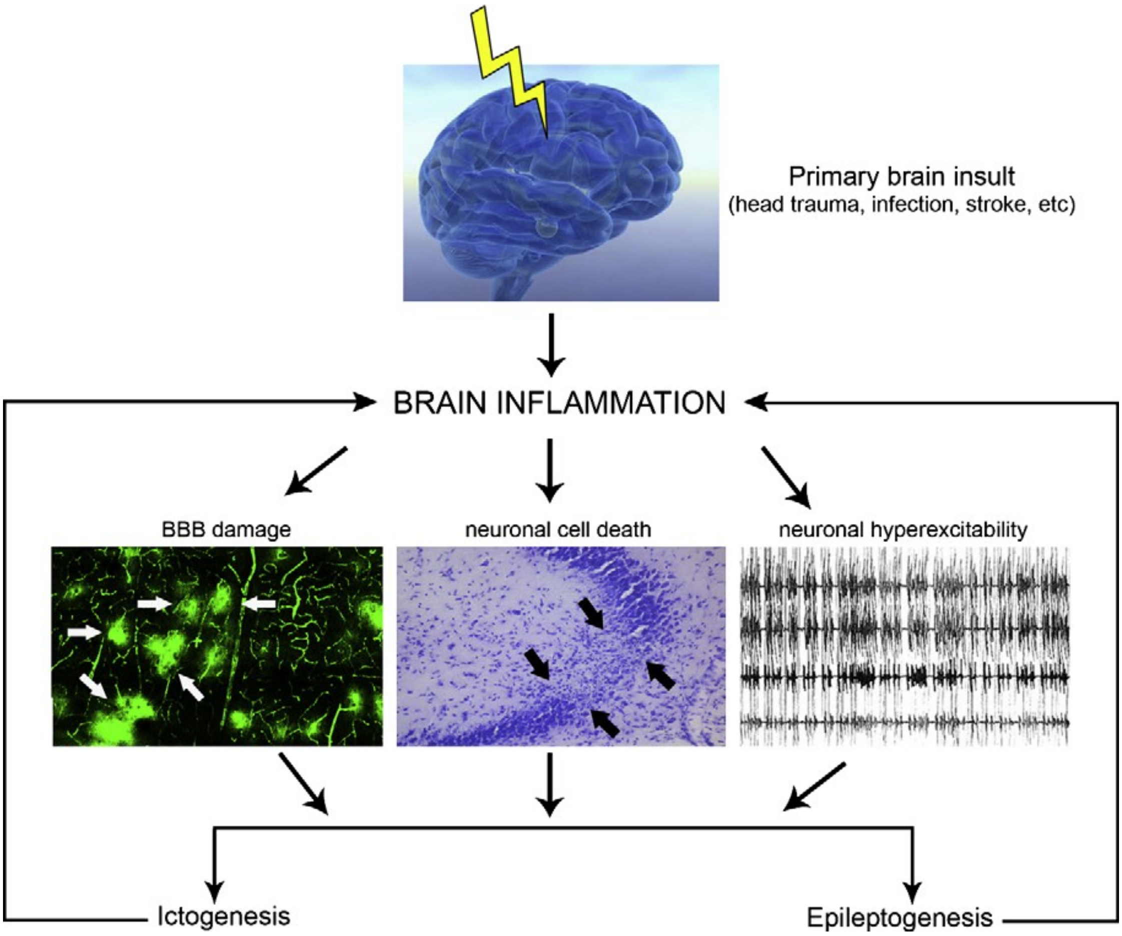

Figure 5.2.: Illustration of the brain inflammation process. *"BBB: blood brain barrier; Induction of brain inflammation in epileptogenic tissue. Various brain injuries, even subclinical, occurring at birth or during a lifetime may trigger brain inflammation chiefly involving the production of cytokines and related downstream inflammatory mediators. This event may lead to changes in brain parenchyma such as leakage of the BBB, neuronal hyperexcitability and cell damage that can contribute to lower the threshold for seizure induction and to trigger epileptogenesis, thus setting the basis for the onset of epilepsy. Activation of innate immune mechanisms during epileptogenesis can recruit inflammatory cells from the periphery thus perpetuating inflammation. The onset of seizure can in turn further promote inflammation via the production of proinflammatory cytokines and downstream inflammatory mediators."* (Vezzani 2008, Behavior, and Immunity 22, p. 797) [40]. Image and label taken from Vezzani [40]. Copyright provided by Elsevier (No 3391870311234).

5.5 Duration and Severity of Status Epilepticus

In the last 15 years SE models were used to discover how drugs work on SE. Investigations were also conducted to detect the consequences that can occur in the long run due to medication with AEDs. Especially notable is the difference in results dependent on when the drugs are administered [43].

The review by Löscher and Brandt stated that there is a much better outcome when drugs are initiated before or during the SE, rather than administered after a SE. They came to the conclusion that drugs can reduce the severity of SE as well as the duration. As a logical consequence this induces a positive outcome [43].

In their search for drugs, the authors analyzed a variety of experimental protocols. Testing the prophylactic effects of treatment with antiepileptic drugs used in clinical setting on rat models, they were trying to find drugs that work best, even if applied at a delayed time point after an insult. Notable was that the drugs used to terminate a SE may have an influence on the long-term consequences. In the experiment, the authors could prove that a combination of diazepam and phenobarbital were, compared to one drug alone, much more effective to end a pilocarbine induced SE [43].

Furthermore the authors examined that degeneration in the rats' brains was less serious when SE termination took place by diazepam plus phenobarbital, instead of diazepam on its own. Investigation are ongoing if the combination of phenobarbital and diazepam have a neuroprotective potential, or if these results are because of the more effective SE termination. At this point it is also important to mention that in 2008, Martin and Kapur reported the combination of diazepam and the NMDA antagonist as an effective option to end an SE [43].

6. Diagnosis

In this part of the thesis, the possibilities to diagnose SE with a special focus on EEG are discussed.

6.1 EEG Patterns in SE

Diagnosing SE can be challenging, especially in patients without any apparent manifestation of seizure activity, meaning no obvious clinical symptoms or radiographic findings. Therefore EEG often becomes the principal basis of the diagnosis [10], [44]. In the case of NCSE, EEG is the only tool for an accurate interpretation [45]. Although EEG is a forceful tool, the diversity of occurring patterns makes the interpretation difficult so expert knowledge is required. Nevertheless, different types of SE show comparable patterns. Referring to Kaplan, NCSE is present if at least one of the following EEG patterns is monitored [46]:

> *"1. Repetitive focal or generalized epileptiform activity (spikes, sharp waves, spike-and-wave, sharp-and-slow wave complexes) or rhythmic theta or delta activity at more than two per second*
>
> *2. The above EEG patterns at less than one per second, but with*

improvement in the clinical state following intravenous injection of a rapidly acting antiepileptic drug, such as a benzodiazepine.

3. A temporal evolution of epileptiform or rhythmic activity at more than one per second with change in location or frequency over time."

(Kaplan 2006, *Journal of Clinical Neurophysiology* **23**, p. 222)

The interpretation of EEG signals also plays an important role in the ongoing discussion about the different types of NCSE in comatose patients and indications for possible treatments [45].

Determination of convulsive forms of SE however is relatively obvious. In CSE EEG it is especially helpful to divide different forms of SE because there are forms that occur generalized from the very beginning, but also SE forms that appear with a partial onset [10], [44].

In convulsive forms of SE, EEG is nowadays mainly used to make a statement about the prognosis and the effectiveness of treatment, but it can also bring along evidence that SE has stopped. Studies conducted in intensive care units have shown that in 27-34% of the patients with coma/encephalopathy, electrographic seizures occur.

"In ambulatory patients the most common EEG patterns associated with NCSE are generalized spike-and-wave or generalized polyspike-and-wave discharges (absence of SE) or rhythmic or focal discharges (complex partial SE)." (Ng2012, *Journal of Paediatrics and Child Health* **49**, p. 2).

In comatose patients EEG interpretation can be challenging, particularly with the appearance of rhythmic or periodic patterns that can't easily be categorized [10]. Examples of EEG patterns in SE from the Department of Neurology in Graz are shown in figures 6.1, 6.2 and 6.3.

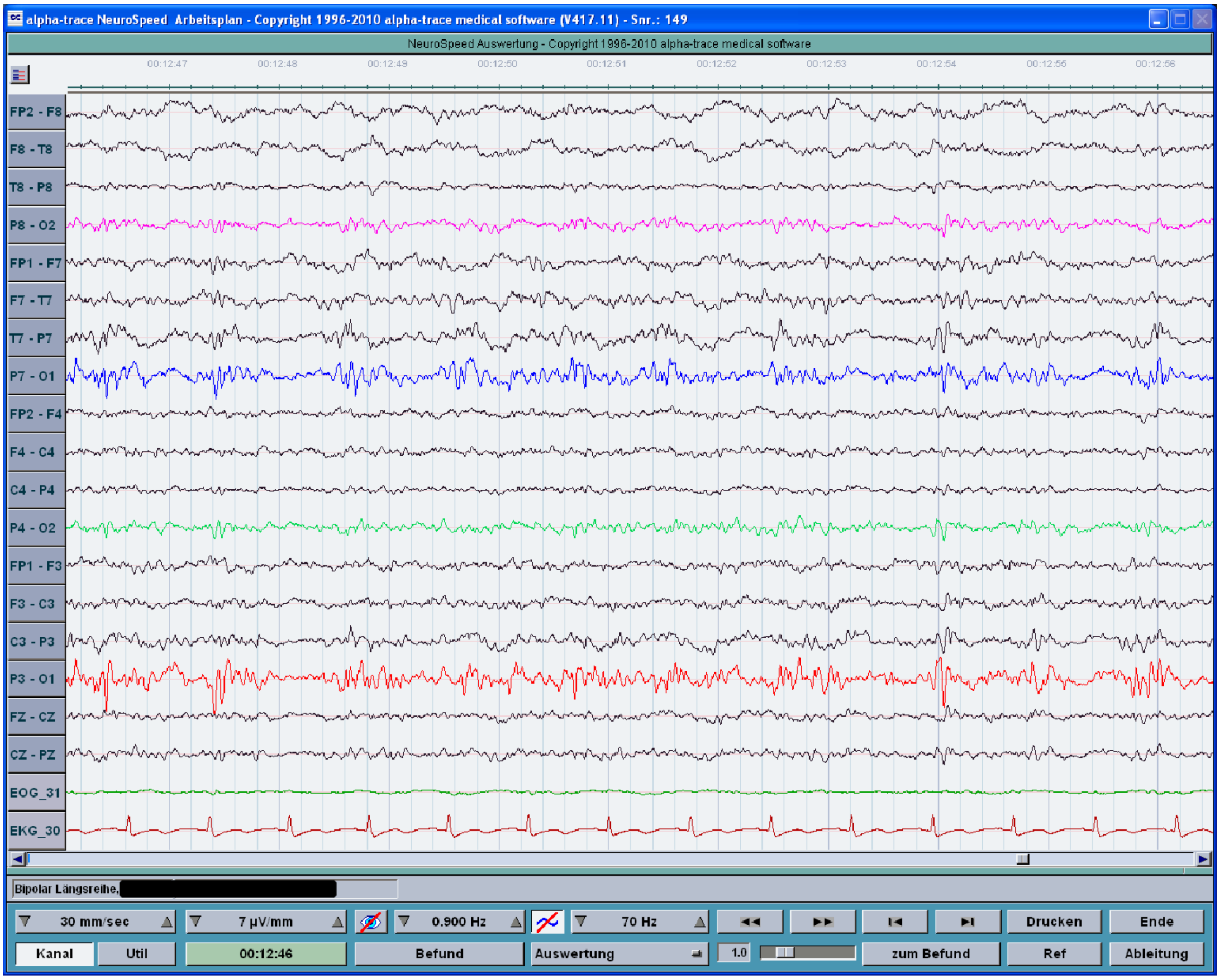

Figure 6.1.: The ictal EEG reveals subtle continuous spiking over the left parieto-occipital region corresponding to focal status epilepticus. The clinical presentation was as subtle as muscle twitching of the thumb. The data were acquired at 200 Hz, high-pass-filtered above 0.9 Hz, low-pass filtered below 70 Hz, and notch-filtered. The EEG image is depicted on 30 mm/sec time scale and 7 µV/mm voltage scale. Recorded in the Department of Neurology in Graz.

Figure 6.2.: This EEG example depicts a more obvious continuous spike-wave activity over the left hemisphere. This patient was awake, confused and showed a repetitive clonic jerking oft the right hand. The data were acquired at 200 Hz, high-pass-filtered above 0.9 Hz, low-pass filtered below 50 Hz, and notch-filtered. The EEG image is depicted on 30 mm/sec time scale and 7 µV/mm voltage scale. Recorded in the Department of Neurology in Graz.

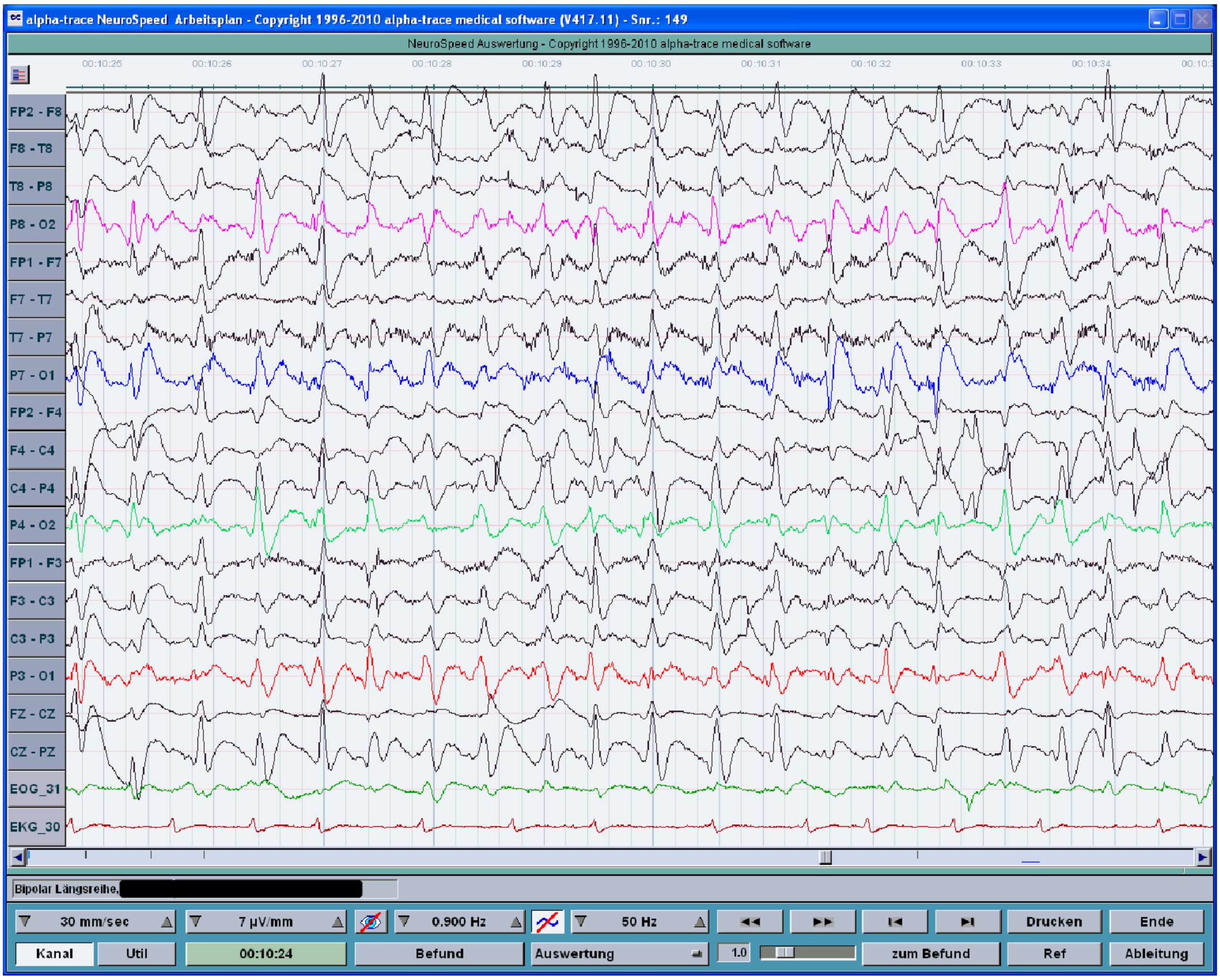

Figure 6.3.: This EEG figure is characterized by generalised continuous spike-wave discharges, as shown on this longitudinal bipolar montage. The data were acquired at 200 Hz, high-pass-filtered above 0.9 Hz, low-pass filtered below 50 Hz, and notch-filtered. The EEG image is depicted on 30 mm/sec time scale and 7 µV/mm voltage scale. Recorded in the Department of Neurology in Graz.

6.2 Clinical Features of GCSE

There are some patients who exhibit prodomi, while other patients with established epilepsy may suffer from behavioral changes, withdrawal and irritability even hours before GCSE emerge. Whereas in other cases, a crescendo of serial seizures is first presented, followed by imperfect recovery, which later on is followed by GCSE [41], [47].

Usually patients with GCSE are unresponsive and present clinically significant seizures, such as tonic, clonic, or tonic-clonic movement of extremities. As time goes on, the diagnosis becomes demanding as clinical features are often subtle. In some patients, GCSE manifests itself merely by a small-amplitude of muscle twitching of the hands, feet or face. Whereas electroencephalography becomes mandatory when there is no recognizable motor activity. This is typical for myoclonic SE occurring after extended anoxia or short and sudden movements. These may be triggered by mechanical stimulation of the body, such as through ventilation or from routine nursing care procedures. Particularly in patients with a past history of GCSE, preventive medication can be quite successful [41], [47].

7. Treatment Options of SE

In the following part, treatment options for SE are reviewed. This starts with a section dealing with Pre-hospital treatment and pointing out the importance of time. Guidelines for the management of CSE and the management for seizures and SE in infancy are also given. Different treatment options are discussed, with a focus on new attempts in the treatment of SE with steroids.

7.1. Pre-hospital Treatment

A number of studies prove that treatment before hospitalization is highly advisable. The review by Chen and colleagues state that rectal diazepam is recommended in patients with frequent seizures. It is reliable and potent in children as well as in adults, especially before they enter hospital. The benefit of rectal diazepam is primarily the therapeutic effect over more than 8 hours, plus the peak of the serum drug concentrations within 3-30 minutes [20].

One randomized double-blind prospective study illustrates treatments of continuous seizures (>5 min) before the patients arrive at the emergency department. It was shown that the seizures were terminated more commonly when treated with intravenous lorazepam (59.1%) or diazepam (42.6%) than treated with placebo (21.1%). Respiratory or circulatory system complications appeared in 10.3% - 10.6% versus 22.5% in patients treated with placebo. As this pilot study was accomplished by qualified paramedics, intravenous therapy might be harmful in a pre-hospital environment where a physician is not immediately present [48].

Usually the i.v. treatment is prefered by the patients since the rectal route is socially not accepted and uncommon in adults. Chen also states that further investigation should be taken to examine alternative routes of application such as intramuscular application. Clinical trials in this field have shown encouraging results exploring the nasal and buccal route although a lot more effort should be made to find new solutions in pre-hospital treatment. To summarize and in spite of all these results, intravenous lorazepam or rectal diazepam initiated before hospitalization have proven to be highly beneficial [20].

7.2. Therapeutic Principles: Time is Brain

Further clinical trials are needed to confirm the efficacy even of the best treatment for SE. Intravenous anticonvulsants initiated without delay seem to be the key to success. The therapeutic interventions and the diagnostic methods should run simultaneously and in order to avoid complications, seizures must be stopped rapidly [19], [20].

As time lapses, clinical data shows rapid cessation in the effect of benzodiazepines, mainly due to the loss of synaptic $GABA_A$ receptors. If one treatment fails, there should not be a delay in initiation of the subsequent treatments, even if current treatment algorithms are not established [20].

In order to prevent neuronal damage, rapid seizure cessation, prevention of hyperthermia, sustained stable cardiorespiratory condition, oxygenation and glucose supply to the brain, are essential. Diagnostic evaluation is crucial but should not decelerate treatment and therefore electroencephalogram should not be conducted before treatment initiation. Also the laboratory studies should not delay treatment and SE protocols ready for implementation are highly recommended. These arrangements can help to avoid delays in SE treatment [20].

7.3. First-line Treatment in Children and in Adults

In children and adults, the same medications are used to prevent seizures. Still it is controversial if children react in the same way as adults do and unfortunately, there is no clear data available yet. Nevertheless, when choosing the best treatment option, it is advisable to consider distinct pharmacokinetic mechanisms [9]. Published instructions for SE-treatment in adults are freely accessible and one is depicted in figure 7.1. However, practiced guidelines for the management of CSE and the management of seizures and SE in infancy are not openly available. Thus they vary greatly from centre to centre. One exemplary paediatric guideline is shown in figure 7.2.

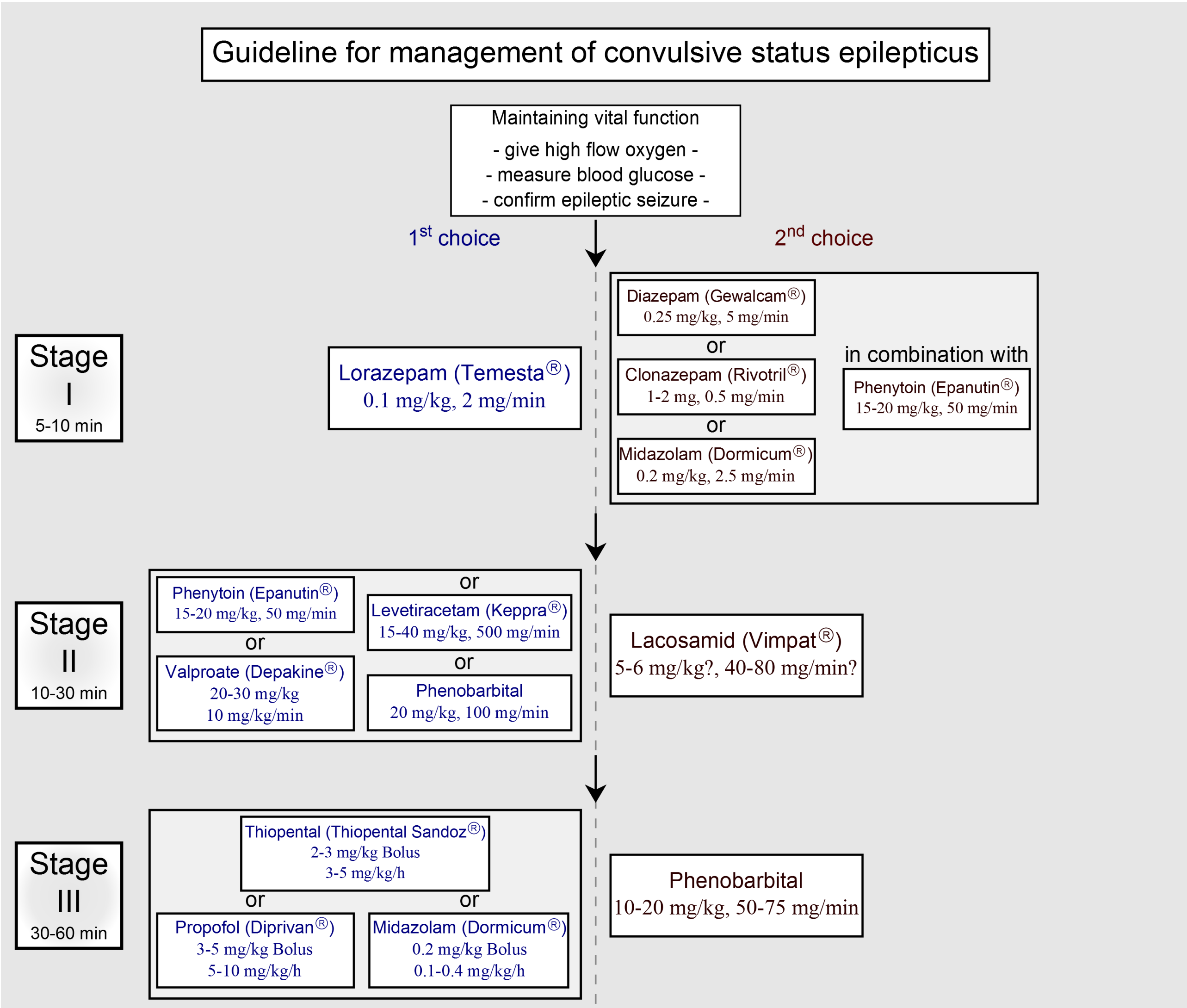

Figure 7.1.: Staged approach to the treatment of convulsive status epilepticus. This figure is based on data provided by Trinka [6] and LKH Graz [49].

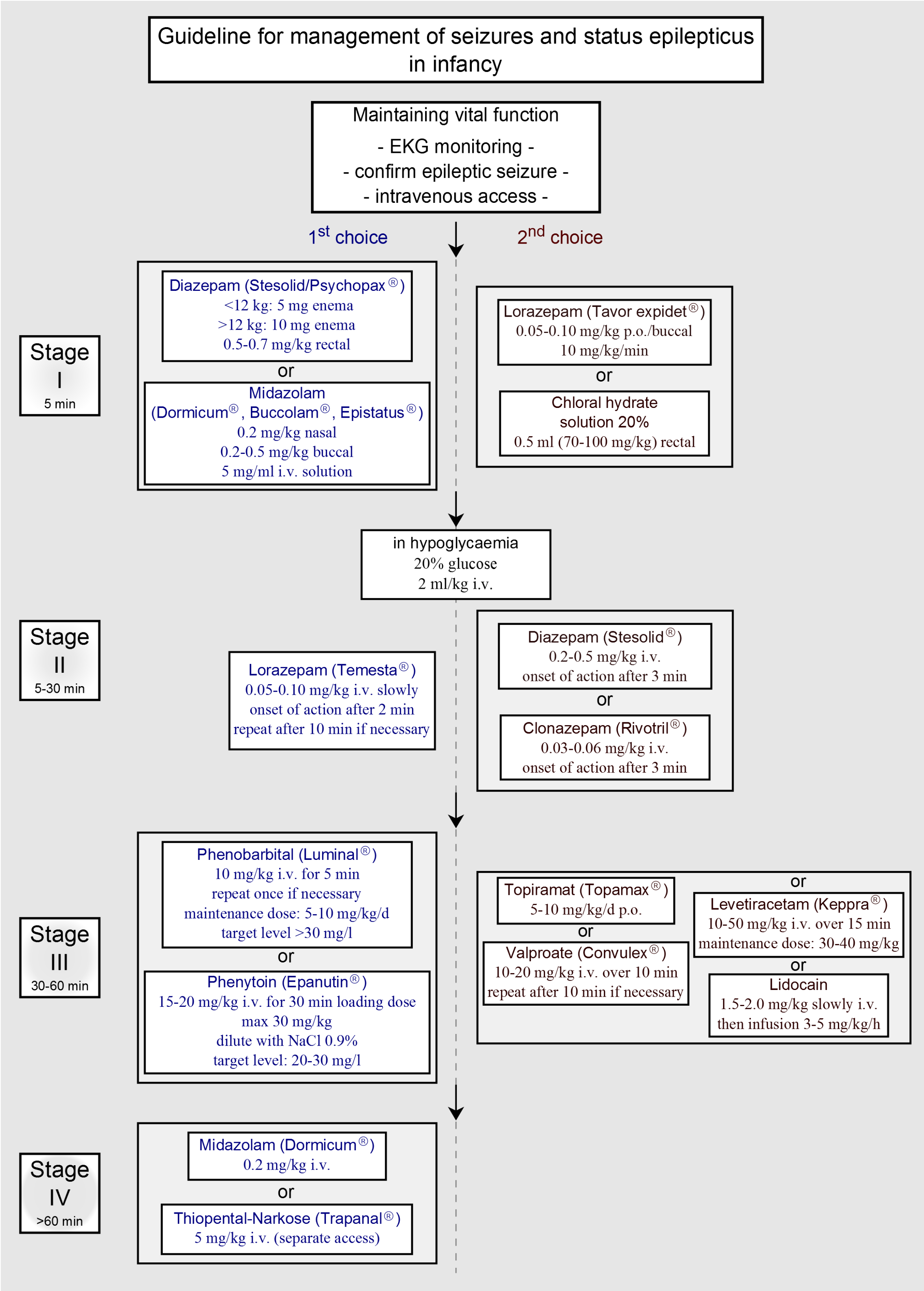

Figure 7.2.: Guideline for treatment of SE in children. This figure is based on data provided by OA Dr. Edda Haberlandt, Universitätsklinik für Kinder- und Jugendheilkunde, Medizinische Universität Innsbruck [50].

Caution should be paid particularly in children younger than 2 years, especially those who suffer from metabolic disorders or mitochondrial dysfunction. In this group, liver failure may result after valproic acid administration and in the group of children with metabolic disorders, diazepam continuous infusion is an alternative. [9].

In children as well as in adults, the first-line medication for CSE is usually the application of benzodiazepine. The access can be intravenous, rectal or buccal, depending on the setting. Benzodiazepines have distinguished themselves by their fast effect and moreover are available almost everywhere in the world. The mechanism of action is the binding of the active agent on $GABA_A$ receptors and can cause a restraint on neuronal level in further consequences. Several studies have shown that initial benzodiazepine administration results in 70-86% SE termination [11].

Whereas in the article of Martland on Management of SE, the authors state that if two doses of benzodiazepines are applied in an out-of-hospital situation, the risk for the need for pediatric intensive care unit (PICU) rises due to a respiratory depression. Despite this disadvantage, it is still important that emergency medication is administered without delay. But as infusions can't be done everywhere, diazepam as a rectal gel was established as the first choice over the last century in the UK. However as rectal diazepam is neither easy to apply in a convulsing child, nor is it approved in society, it was finally replaced by buccal midazolam which became the first choice over the past years [11], [13].

Buccal midazolam has the advantage that it is relatively safe and due to that, it became the current preferred first-line medication in out-of-hospital situations. Nonetheless, as soon as intravenous access is established, lorazepam should be injected as it has a prolonged effect compared to diazepam [11], [13]. The review by Wait states that approximately 30% of children taking antiepileptic medication are at risk of breakthrough seizures because their drugs are not controlled well. As most prolonged acute seizures happen in community settings, far away from medical facilities, immediate seizure control rarely gets induced. Particularly, if in schools there is no healthcare plan how to manage a prolonged acute convulsive seizures, treatment will inevitably be delayed [51].

7.4. Choice of Treatment in Different Forms of SE

General anesthetics are usually applied in RSE. Benzodiazepine can control seizures rapidly and antiepileptic drugs are in general, sufficient in early resistant forms. In three trials, benzodiazepines were found to be the only evidence proven medication. In general, aggressiveness of treatments is determined by the type of SE. With regard to long-term consequences of GCSE this form should be treated aggressively, however treatment can be more conservative in NCSE as pathophysiological processes in NCSE are not linked to the same brain injuries as in GCSE. Specialists tend to treat SE episodes such as absence or myoclonic SE with valproic acid or benzodiazepines. Debates are still ongoing if focal complex SE should be admitted to the intensive care unit for induction of coma as a range of complications can occur. Ileus, neuropathy and pneumonia due to mechanical ventilation are just a few named complications, therefore the risk of treatment should be balanced against the benefit of better seizure control [19].

7.5. Choice of Anesthetic Agents in RSE and Occurring Problems

For coma induction to control RSE, there are three $GABA_A$ receptor modulators available as initial treatment [19] (see figure 7.3).

	Loading dose	Comments
Midazolam	0,2 mg/kg	Increasing doses needed with time
Propofol	2 mg/kg	Attention to PRIS*, especially in young children; combine with benzodiazepines
Barbiturates:		
Pentobarbital	1-2 mg/kg	Both need loading with repetitive boluses
Thiopental	5 mg/kg	and have long wash-out times
		PIRS = propofol infusion syndrome

Figure 7.3.: Anaesthetic agents for RSE. Modified according to Rossetti [19].

Midazolam is a drug usually used as a first-line treatment. However, in order to sustain the pharmacological effect in RSE, there is a need to increase the dose. Compared to barbiturates, midazolam seldom causes an entire suppression of the cerebral activity. In general, combined combination with propofol is used. So far, no particular complications with midazolam use have been described, even so, having flumazenile available as a potent antidote is an additional advantage. The only problem that can emerge using this combination is the so called propofol infusion syndrome (PRIS). This syndrome occurs when an oil emulsion of propofol is injected, thus triggering cardiocirculatory failure with lactic acidosis but also hypertriglyceridaemia and rhabdomyolysis. As PRIS occurs primarily in young children and in patients with brain trauma, propofol should be used with caution especially in relation to young patients. In general accurate monitoring of serum lactate is obligatory in order to avoid complications. In order to further cut down the risk of PRIS, concomitant use of benzodiazepines to decrease the required dose of propofol should be considered [19].

The oldest medications used in RSE are anesthetic barbiturates like thiopental with its metabolite pentobarbital. These barbiturates show, apart from $GABA_A$ modulation in vitro, NMDA-antagonist action, which may be useful in relation to pathophysiological happenings in RSE. A disadvantage of barbiturates is the long half-life that can lead to an accumulation in adipose tissue, especially in elderly with cardiovascular problems [19].

7.6. Treatment of Super-refractory Status Epilepticus

Super-refractory status epilepticus is considered as a phase of refractory SE in which initial anesthetic therapy is ineffective. Hence, SE continues or reappears despite 24 hours or more of anesthetic therapy. Mostly, this form frequently occurs in two clinical situations. In patients after a serious brain injury while in some patients, SE occurs entirely unexpectedly with no obvious reason or previous medical history of epilepsy. As there are neither randomized or controlled studies concerning super-refractory SE therapy, approaches have to rely primarily on case reports [21].

The basis for treatment in super-refractory SE is the use of general anesthesia coupled with mechanic ventilation. Anesthesia needs to be continued over 24 hours and can then gradually be reversed. In case that seizures reemerge, anesthesia needs to be reintroduced [21]. Still it is not known whether anesthetics are useful in terms of if they have an antiepileptic effect. The main purpose of anesthesia is primarily to assert stable clinical parameters and to prevent complications [21].

Propofol is usually the easiest to make use of out of the conventional anesthetics with pentobarbital, thiopental or midazolam. Pharmacokinetic properties are seen as superior in comparison to pentobarbital/thiopental. The only potential disadvantage is the possible risk of PRIS, particularly in children when administered together with steroids or catecholamines. But in general, all of these mentioned conventional anesthesia's involve the risk of hypotension and cardiac depression [21].

There are also alternative anesthetics such as ketamine which brings along two benefits in contrast to conventional anesthetics. Neither this substance causes cardiac depression nor it induces hypotension and might potentially be neuroprotective. Other anesthetics, such as etomidate or isoflurane were only tested in small series [21].

Antiepileptic drugs have been administered many times but still it is not known if any drug operates better than the other, though this is likely. Generally it is recommended to maintain a combination of two or three AEDs in a large dose but without switching substances repeatedly. Magnesium is often applied in SE even though there is no proof for a deficiency. Over the past years, application of immunologically active agents became popular, even if there is no evidence for an immunologic cause for SE [21].

7.7. New Attempts in the Treatment of SE

At the moment, benzodiazepine is used for the first-line treatment in SE. The most prominent problem with tranquilizer use is that in one third of the patients, benzodiazepine fails to end the seizures. Usually the mode of action of benzodiazepine is the binding on $GABA_A$ receptors. However, as time is progressing in SE, these receptors get internalized and become inactivated. Due to this, it is believed that treatment with benzodiazepine eventually becomes inefficient so several animal trials were conducted to find new solutions for the treatment of refractory SE\ [52].

7.7.1. Steroids

Allopregnanolone

Rogawski depicts in the article on neuroactive steroids for the treatment of status epilepticus, the results of animal seizure models administered with neuroactive steroids, such as allopregnanolone. The most important benefit of allopregnanolone is the potentization of synaptic $GABA_A$ receptors, but also an enhancing of extrasynaptic $GABA_A$ receptors, which mediate tonic inhibition. In seizure models, during a continuous seizure, extrasynaptic $GABA_A$ receptors are neither internalized nor desensitized. Rogawski was able to demonstrate in animal studies that even when benzodiazepine fails, parenteral allopregnanolone is effective in inhibiting ongoing behavioral and electrographic seizures. Thus he concludes allopregnanolone might be a potential option for the treatment of refractory SE in patients [52].

Stiripentol

Another allosteric modulator of the $GABA_A$ receptor is Stiripentol. In the article of Grosenbaugh, the authors described the anticonvulsant effects of Stiripentol. In a rodent model, this drug was able to stop a seizure in an established SE where therapy with benzodiazepine already failed. As the potential of Stiripentol was found to be age-dependent, the substance was found to work greater in juvenile rodents than in adult rodents and so might provide an efficient treatment in children. Grosenbaugh recommends to administer Stiripentol either alone or as an additional therapy to benzodiazepine in resistant SE [53].

8. Current Advances, Problems and Future Prospects

Recent advances in the understanding and treatment of SE, as well as new or still open questions were discussed in a Colloquium in Salzburg in 2013 and are reviewed in the following section. In addition, the succeeding section discusses lately published results from the RAMPART (Rapid Anticonvulsant Medication Prior to Arrival Trial) study.

8.1. Salzburg Colloquium illustrating current problems

In April 2013, the 4th Colloquium was held in Salzburg, to outline the latest facts about SE and discuss advances, to implement clinical knowledge in the near future. There is better understanding about the basic science, especially on molecular level. There are discoveries made of trafficking of GABA and glutamate receptors, new approaches for a potential possibility of future gene therapy and a better insight into inflammatory processes and autoimmunity. Many fascinating progresses have been made but despite improved neuromonitoring, prognosis of super-refractory status nor the high incidence of SE are satisfactory [54].

The main problem is that in about 30% of patients with SE, initial treatment is not prescribed in time, which results in a high mortality rate of 20% and a substantially high morbidity rate among survivors. In new-onset SE in approximately 30% of the patients, the cause still cannot be identified. Clinical trials on a high level, particularly in refractory SE are difficult to accomplish resulting in a low number of academic trials [54]. In addition the pharmaceutical industry is not interested in this small niche, leading to a lack of sponsored randomized controlled trials, besides the low number of academic trials

Another big problem constitutes the availability of medication for SE around the world. Often treatment is not marketed or even licensed due to the lack of interest of the economic system. Furthermore many medications for refractory SE are at disposal but not evaluated sufficiently. Thus resulting in a lack of optimum treatment options for the patients, both in refractory and super-refractory SE [54].

8.2. Results of the RAMPART study

In 2013, Silbergleit published their results from the Rapid Anticonvulsant Medication Prior to Arrival Trial, the RAMPART study. This study investigated the best routes of administration in SE. Comparing non-intravenous administration of benzodiazepines to intravenous administration, it is already known that early treatment of prolonged seizures with benzodiazepines in pre-hospital settings have shown an improved outcome compared to delayed treatment in several studies [55].

Traditionally in pre-hospital settings intravenous diazepam is used, although there is evidence that intravenous lorazepam has the better effect. But for emergency medical services (EMS) lorazepam is unpractical due to its short shelf life without refrigeration [55].

More recently in some EMS systems, midazolam was adopted for intramuscular or transmucosal administration because of its rapid absorption. Although to date, no randomized controlled trial has proved the efficiency and safety of intramuscular midazolam [55].

A new direction was tested by a large number of EMS, paramedics and receiving hospitals across the United States. Due to this, in the RAMPART study, intramuscular (IM) midazolam was compared to intravenous (IV) lorazepam with the hypothesis that in a pre-hospital treatment, midazolam (IM) would not be inferior to lorazepam (IV) [55].

After the double-blind randomized clinical trial midazolam (IM) versus lorazepam (IV) in pre-hospital treatment conducted by paramedics, the hypothesis proved to be right. As a matter of fact, intramuscular midazolam turned out to be the better option for pre-hospital treatment compared to lorazepam (IV). The latter administered intravenously used to be favored due to its rapid onset of action, but disadvantages such as the short shelf life without refrigeration and the challenge to get IV access in a convulsing patient advocate for midazolam (IM). Midazolam intramuscular could prove a faster and more reliable application and so led to a superior outcome particularly to decreased rates of hospital and ICU admissions [55].

A few EMS systems using midazolam in pre-hospital setting decided for alternative routes. Midazolam administered either buccal, nasal or rectal are less invasive and the onset of action after administration is potentially similar fast. In the context of SE, nasal administration might lead sometimes to the problem that during a seizure a patient might blow or spit out medication initiated [55].

RAMPART can report a well-defined proposal for pre-hospital treatment of seizures, but still there are many questions to be answered. One of the most pressing issues is that as many as 26.5% of patients in this study remained refractory despite treatment with benzodiazepine. Future clinical trials should focus on second-line anticonvulsant, as well as on additional agents for pre-hospital treatment [55].

9. Conclusion

This thesis is the result of a literature research with the aim to give an overview of the recent status of research on SE with a special focus on the age of the patient and thus the occurrent differences in etiology, the disease itself, diagnosis, and its treatment methods. In the first chapter, historical as well as renewed definitions of SE were presented. The state-of-the-art definition was published by Lowenstein [8]:

> *"Generalized, convulsive status epilepticus in adults and older children (>5 years old) refers to a 5min of (a) continuous seizures* ***or*** *(b) two or more discrete seizures between which there is incomplete recovery of consciousness."* (Lowenstein et al. [8] 1999, *Epilepsia* **40**, p. 120)

In chapter 2 a classification scheme presented the clinical forms of SE in general and also different forms affecting children and the elder population. However, the underlying concepts are mainly based on findings during the last centuries. Hence, 2011 a study by Berg [28] pointed out the importance of including recent advances in epilepsy research, e.g. due to improved imaging techniques or completely new fields of research, e.g. genetics.

The many different etiologies for SE were presented and illustrated in figure 3 with their related mortalities. Although only one underlying factor (cerebrovascular disease) causes SE with a probability of more than 20%, the associated mortality rates are all >=10%, in the majority of cases even >=25%. Population-based studies by DeLorenzo [29] and Neligan [35] showed mean mortality rates, of SE to be 3% in children, 14-26% in adults and 38% in the elderly.

Studies investigating the neurophysiology and neuropathology of SE were presented, these tried to answer the question of why a seizure can become self-sustaining, e.g. by an investigation of murine models. Studies by Vezzani [40] revealed that inflammation is an epiphenomenon of a seizure and may cause neuronal damage. Additionally, it was shown that once a seizure is established, an ongoing inflammation in the brain is likely to occur.

In chapter 6 the diagnosis of SE was summarized, concluding that a thorough analysis and expertise knowledge of specific EEG patterns is often indispensable, especially in the case of diagnosing NCSE.

Treatment options of SE were presented in chapter 7. Main findings were the *Guideline for Management of CSE*, schematically presented in figure 7.1 (partly based on data provided by the LKH Graz [49]), and the *Guideline for Management of seizures and SE in infancy*, schematically presented in figure 7.2 (based on data provided by the Medical University of Innsbruck [50]). However, these guidelines are only based on the literature research for this thesis. Therefore, further (clinical) trials are necessary to prove their superiority to other treatment procedures. Summarized, all research yields time is brain, i.e. the earlier treatment is started the better the outcome. In the last chapter, recent advancements in the field of SE research were discussed by reviewing results of the Salzburg Colloquium [54] and the RAMPART study [55]. Both conclude that treatment (different options, availability of medication) of SE is still far away from the optimum for patients and has to be improved, but research on SE is often neglected by the pharmaceutic industry due to negligible interest of academia and pharmaceutical industry in the rather small niche of SE.

In summary this thesis suggests that despite recent advances in clarifying stringent definitions and classifications for SE, in elucidating potential patho-mechanisms and risk factors for SE and in developing new treatment options, the treatment of many patients with SE and particularly RSE and SRSE remains suboptimal.

Particularly astonishing was to find out that there are neither national nor international guidelines for the treatment of SE in children and that there is a paucity regarding high level comparative studies of available treatment options both in children and adults.

There is great need for research and development to improve patient care in SE and I hope that this work can contribute to heighten the awareness for this.

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