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Understanding childhood epilepsy: etiology, clinical manifestations, risk factors and management strategies

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Abstract:
Epilepsy is among the most common serious chronic neurological disorders of childhood and carries consequences that reach well beyond the seizures themselves. Children with epilepsy are at increased risk of learning difficulties, behavioural and psychiatric comorbidity, and social exclusion and, in the most severe forms, premature mortality. The past decade has seen substantial change in how paediatric epilepsy is understood. The International League against Epilepsy (ILAE) has revised its definition of epilepsy and its frameworks for classifying seizures, epilepsies and epilepsy syndromes, while advances in neuroimaging and genomic sequencing have shifted the emphasis from describing seizures to identifying the underlying cause. This article reviews the current understanding of childhood epilepsy, with particular attention to its etiology, the clinical manifestations of the major seizure types and age-related syndromes, the risk factors that predispose to onset and recurrence, and the strategies used for diagnosis and management. Management is considered across the full treatment spectrum, from first-line anti-seizure medication and emergency treatment of prolonged seizures to the ketogenic diet, neuromodulation, epilepsy surgery and precision therapies, together with the psychosocial care that determines long-term quality of life. Early and accurate syndromic and etiological diagnosis, rational treatment selection, timely referral of drug-resistant cases and attention to comorbidity are presented as the pillars of modern care. Persistent gaps, particularly in low-resource settings, are discussed.

Keywords:
childhood epilepsy; seizures; epilepsy syndromes; etiology; anti-seizure medication; ketogenic diet; epilepsy surgery; paediatric neurology.

1. Introduction:
Epilepsy is a disorder of the brain characterised by an enduring predisposition to generate epileptic seizures and by the neurobiological, cognitive, psychological and social consequences of this condition (Fisher et al., 2014). In childhood, the disorder has a particular significance because seizures occur in a brain that is still growing, forming connections and acquiring the skills on which later independence depends. Recurrent seizures, the underlying disease that causes them, and the medications used to treat them can all interfere with that process. For this reason, childhood epilepsy cannot be regarded as a smaller version of adult epilepsy. It differs in its causes, in the way seizures look, in the syndromes encountered, in the response to treatment and in the outcomes that matter most to families.

The incidence of epilepsy is highest in the first years of life, and a large proportion of lifetime cases begin before adulthood (Camfield and Camfield, 2015; Hauser et al., 1993). The global burden is considerable. Tens of millions of people live with active epilepsy worldwide, and the greatest burden falls on low- and middle-income countries where diagnosis is delayed and treatment gaps are wide (Beghi et al., 2019; Ngugi et al., 2010). In many communities, epilepsy is still surrounded by stigma, misconception and harmful traditional practices, which can lead families to delay seeking care or to withhold school and social participation from an affected child.

Paediatric epilepsy is also unusually heterogeneous. A child may have a single, brief and self-limited seizure disorder that remits spontaneously during adolescence, or a severe developmental and epileptic

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encephalopathy in which frequent seizures and profound neurodevelopmental impairment coexist from infancy. Between these extremes lies a wide range of presentations. The practical task for the clinician is to recognise which pattern a given child has, because prognosis, investigation and treatment all depend on it. A child with childhood absence epilepsy and a child with infantile epileptic spasms syndrome both have epilepsy, but the urgency of evaluation, the choice of drug and the expected outcome are entirely different.

The aim of this article is to provide an integrated overview of childhood epilepsy for clinicians, trainees and allied health professionals. After outlining definitions and classification, it summarises epidemiology, then considers etiology, clinical manifestations and risk factors in turn. It then reviews diagnostic evaluation and the management strategies currently available, followed by comorbidities, prognosis and future directions.

2. Definitions and classification:

2.1. Seizures and epilepsy:

An epileptic seizure is a transient occurrence of signs and symptoms caused by abnormal excessive or synchronous neuronal activity in the brain. Epilepsy is a disease of the brain defined by any of the following conditions: at least two unprovoked (or reflex) seizures occurring more than 24 hours apart; one unprovoked (or reflex) seizure with a probability of further seizures similar to the general recurrence risk after two unprovoked seizures, taken to be at least 60% over the next ten years; or the diagnosis of an epilepsy syndrome (Fisher et al., 2014). This practical definition allows treatment to begin after a first seizure when the risk of recurrence is high, for example when an epileptogenic structural lesion or a clearly epileptiform electroencephalogram (EEG) is present. The ILAE also recognises that epilepsy may be considered resolved in individuals who have remained seizure free for the last ten years, with no seizure medication for at least the last five years, or in those who had an age-dependent syndrome and have passed the applicable age (Fisher et al., 2014). The concept of resolution is particularly relevant in paediatrics, where many syndromes are self-limited.

It is important to separate epileptic seizures from provoked or acute symptomatic seizures, which occur in close temporal association with an acute insult such as meningitis, head trauma, hypoglycaemia or electrolyte disturbance, and from febrile seizures, which are age-related and do not by themselves constitute epilepsy. Each of these situations carries different implications for investigation and long-term treatment.

2.2. The ILAE framework for classification:

The ILAE classification of the epilepsies operates at three levels: seizure type, epilepsy type and epilepsy syndrome, with etiology and comorbidities considered at every level (Scheffer et al., 2017). The multilevel approach recognises that, in many children, the clinician will be able to establish only the first level at the initial consultation, and that the diagnosis is refined as further information accumulates from the history, EEG, imaging and genetic testing.

The operational classification of seizure types divides seizures according to onset into focal, generalised and unknown onset (Fisher et al., 2017). Focal seizures arise within networks limited to one hemisphere. Generalised seizures arise within, and rapidly engage, bilaterally distributed networks. Where onset is not observed or cannot be determined, the seizure is labelled as unknown onset, and this label can be revised later. Focal seizures are further described according to the level of awareness (aware or impaired awareness) and by whether the first prominent feature is motor or non-motor. A focal seizure that evolves to involve both hemispheres is described as a focal to bilateral tonic-clonic seizure. Generalised seizures are divided into motor types (such as tonic-clonic, tonic, clonic, myoclonic and epileptic spasms) and non-motor or absence types (Fisher et al., 2017).

The second level, epilepsy type, comprises focal epilepsy, generalised epilepsy, combined generalised and focal epilepsy, and unknown epilepsy. The third level, epilepsy syndrome, refers to a cluster of features that tend to occur together, including seizure types, EEG findings, imaging features, age of onset, triggers, comorbidities and prognosis. In 2022 the ILAE published position papers that defined and classified syndromes with onset in the neonatal and infant period and those with onset in childhood, and presented a methodology for syndrome classification (Zuberi et al., 2022; Specchio et al., 2022; Wirrell et al., 2022). These documents also introduced the term developmental and epileptic encephalopathy to describe conditions in which both the underlying etiology and the epileptic activity contribute to developmental impairment, replacing older and less precise labels.

2.3. Etiological categories:

The classification identifies six etiological groups: structural, genetic, infectious, metabolic, immune and unknown (Scheffer et al., 2017). These categories are not mutually exclusive. A child with tuberous sclerosis complex, for example, has a genetic etiology that expresses itself through structural brain lesions. Modern practice treats identification of the etiology as the central goal of the diagnostic evaluation, because it can alter treatment directly, inform prognosis and guide genetic counselling. The older terms idiopathic, symptomatic and cryptogenic, and the earlier categories of genetic, structural-metabolic and unknown, have been superseded, although they remain in widespread use in the older literature (Berg et al., 2010).

2.4. Drug-resistant epilepsy:

Drug-resistant epilepsy is defined as failure of adequate trials of two tolerated and appropriately chosen and used anti-seizure medication schedules, whether as monotherapies or in combination, to achieve sustained seizure freedom (Kwan et al., 2010). The definition has important practical value, since it identifies the point at which a child should be referred to a comprehensive epilepsy centre for evaluation for surgery, dietary therapy or other non-pharmacological treatments. Failure to recognise drug resistance early is one of the most common reasons why effective options are delayed in children.

3. Epidemiology:

3.1. Incidence and prevalence:

Reported estimates of epilepsy occurrence vary with the definition used, the age group, the method of case ascertainment and the setting. A systematic review and meta-analysis of international studies estimated the lifetime prevalence of epilepsy in the general population at around 7.6 per 1,000 and the incidence at roughly 61 per 100,000 person-years, with higher figures in low- and middle-income countries and in rural populations (Fiest et al., 2017). Studies focusing on children indicate that the incidence is highest in the first year of life and declines through childhood, before rising again in older adults (Hauser et al., 1993; Camfield and Camfield, 2015). Population-based data from Norway, using nationwide registry linkage, confirmed that epilepsy in childhood is common, affecting a little under 1% of children, and that the incidence was highest in infancy (Aaberg et al., 2017).

In resource-limited regions, the estimates are consistently higher. Contributing factors include a greater frequency of perinatal complications, central nervous system infections such as meningitis and cerebral malaria, neurocysticercosis, and head injury. A meta-analytic estimate of the burden of active and lifetime epilepsy found that the prevalence was considerably higher in many lower-income and rural settings than in high-income countries (Ngugi et al., 2010). The global burden analysis for 1990 to 2016 estimated that tens of millions of people have active epilepsy and that the disability burden is concentrated in younger age groups and in lower-resource regions (Beghi et al., 2019).

3.2. Age and sex patterns:

Onset is most common in infancy and early childhood. Many of the severe epilepsy syndromes begin in the first two years of life, whereas others have characteristic windows of onset in later childhood or adolescence, such as childhood absence epilepsy, which typically begins between four and ten years of age, and juvenile myoclonic epilepsy, which usually begins in adolescence (Specchio et al., 2022). Incidence tends to be slightly higher in boys than in girls in most cohorts, although specific syndromes show their own sex predominance, and some, including Rett syndrome and CDKL5 deficiency disorder, affect girls predominantly because of their X-linked inheritance (Ellis et al., 2020).

3.3. Mortality and burden:

Although most children with epilepsy do well, mortality is increased compared with the general population. In a long-term follow-up of a population-based cohort of children with epilepsy in Finland, mortality was elevated, and the excess was concentrated among those with remote symptomatic epilepsy, whereas children with idiopathic or cryptogenic epilepsy had mortality rates close to those of the general population (Sillanpää and Shinnar, 2010). Causes of death include the underlying neurological disease, status epilepticus, and accidents such as drowning and sudden unexpected death in epilepsy. These findings underline the heterogeneity of the condition and reinforce the importance of identifying children at high risk.

Beyond mortality, the burden of childhood epilepsy includes schooling and cognitive difficulties, behavioural and emotional disorders, parental stress, restrictions on activity and economic costs. A national profile of childhood epilepsy in the United States found that affected children had substantially higher rates of co-

occurring conditions, including learning disability, attention-deficit disorder, developmental delay, anxiety and depression, than children without epilepsy (Russ et al., 2012). These comorbidities are frequently as disabling as the seizures and are discussed in more detail below.

4. Etiology:

Identifying the cause of epilepsy in a child is among the most consequential steps in management. Advances in magnetic resonance imaging (MRI) and genetic sequencing have increased the proportion of children in whom a cause can be found, and the ILAE etiological categories provide a practical framework for the diagnostic search (Scheffer et al., 2017). The proportions attributed to each category vary with age, the setting and the investigations available, but in contemporary series a structural, genetic or other defined cause is identified in a substantial proportion of children, with the greatest yield in those with early-onset and severe epilepsy (Camfield and Camfield, 2015).

4.1. Structural etiologies:

Structural etiologies are abnormalities visible on neuroimaging that are concordant with the electroclinical assessment and are reasonably considered to be the cause of the seizures (Scheffer et al., 2017). They may be acquired or genetic in origin. In children, the main groups are as follows.

1. Malformations of cortical development, including focal cortical dysplasia, hemimegalencephaly, polymicrogyria, periventricular nodular heterotopia and lissencephaly. These are an important cause of early-onset and drug-resistant epilepsy and are among the most common pathologies found in children undergoing epilepsy surgery.
2. Perinatal brain injury, such as hypoxic-ischaemic encephalopathy, perinatal arterial ischaemic stroke, intraventricular haemorrhage and periventricular leukomalacia in preterm infants, which may lead to focal or multifocal epilepsy and to cerebral palsy.
3. Tumours and tumour-like lesions, particularly low-grade glioneuronal tumours such as dysembryoplastic neuroepithelial tumour and ganglioglioma, and hypothalamic hamartoma, which is classically associated with gelastic seizures.
4. Vascular lesions, including cavernous malformations, arteriovenous malformations and Sturge-Weber syndrome, and acquired childhood stroke.
5. Acquired injury from traumatic brain injury and from the sequelae of central nervous system infection, and hippocampal sclerosis, which is less frequent in young children than in adolescents and adults.

The yield of MRI depends on the quality of the study. Epilepsy-protocol MRI with thin-section sequences, performed on a high-field scanner and interpreted by a neuroradiologist experienced in paediatric epilepsy, detects subtle lesions such as focal cortical dysplasia that may be missed on routine imaging. In infants, the immature myelination can mask cortical abnormalities, and repeat imaging after myelination is complete is sometimes needed.

4.2. Genetic etiologies:

A genetic etiology is one in which epilepsy results directly from a known or presumed genetic variant in which seizures are a core symptom of the disorder (Scheffer et al., 2017). The expanding use of next-generation sequencing has transformed this area. Early work on the epilepsies concentrated on ion channel genes, which led to the concept of the channelopathies, and subsequent studies showed that genes encoding synaptic proteins, transcription factors, chromatin regulators and components of signalling pathways such as mechanistic target of rapamycin (mTOR) are also involved (Helbig et al., 2008).

In most common epilepsy syndromes, such as childhood absence epilepsy and genetic generalised epilepsies, inheritance is complex and polygenic, with many variants of small effect interacting with environmental influences. In contrast, in many severe early-onset epilepsies, a single de novo pathogenic variant is sufficient to cause disease. Well-known examples include SCN1A in Dravet syndrome, KCNQ2 and KCNQ3 in neonatal epilepsies, STXBP1 and SCN2A in early developmental and epileptic encephalopathies, CDKL5 in infantile spasms and early seizures with severe developmental impairment, and TSC1 and TSC2 in tuberous sclerosis complex (Ellis et al., 2020; Helbig et al., 2008). Copy number variants, such as deletions at 15q13.3 and 16p13.11, and chromosomal disorders, including Down syndrome, ring chromosome 20 and Angelman syndrome, are further genetic causes.

Genetic diagnosis has direct practical implications. Reported diagnostic yields for gene panels, exome sequencing and genome sequencing range widely, from around one in ten to around one in two children, depending on the population tested and the methods used, with the highest yield in those with early-onset epilepsy accompanied by developmental delay (Ellis et al., 2020). A confirmed diagnosis may support the use

of precision therapies, for example avoiding sodium channel blockers in SCN1A-related epilepsy and using mTOR inhibitors in tuberous sclerosis complex, may end a diagnostic odyssey, and allows accurate recurrence-risk counselling (Ellis et al., 2020).

4.3. Infectious etiologies:

An infectious etiology refers to epilepsy that results from a known infection, rather than seizures occurring in the context of acute infection (Scheffer et al., 2017). Worldwide, the most common infectious causes of epilepsy include neurocysticercosis, cerebral malaria, tuberculous meningitis, bacterial meningitis, viral encephalitis, congenital infections such as cytomegalovirus, toxoplasmosis and Zika virus infection, and HIV-related brain disease. Neurocysticercosis is the leading preventable cause of epilepsy in endemic areas and typically produces focal seizures in children living in regions with poor sanitation and pig-rearing. Children who have survived meningitis or encephalitis have a substantially greater risk of subsequent epilepsy than the general population, and the risk is greatest in the first years after the infection (Hesdorffer et al., 2011).

4.4. Metabolic etiologies:

Metabolic epilepsy results from a well-defined metabolic defect with biochemical changes in the body, such as porphyria, uraemia, aminoacidopathy or pyridoxine-dependent epilepsy (Scheffer et al., 2017). Although individually rare, metabolic disorders are of special importance because several are treatable. Examples include glucose transporter type 1 deficiency syndrome (treated with ketogenic diet), pyridoxine-dependent and pyridoxal phosphate-responsive epilepsies, biotinidase deficiency, creatine synthesis disorders, cerebral folate deficiency and certain mitochondrial disorders. The clinical features that raise suspicion include onset in the neonatal period or early infancy, seizures resistant to usual treatment, recurrent episodes of encephalopathy associated with fasting or intercurrent illness, developmental regression, and a family history of unexplained neonatal death or consanguinity. Early metabolic screening and, in selected cases, a time-limited trial of vitamin supplementation in neonatal and early-infantile seizures that are unresponsive to initial treatment can avoid irreversible injury.

4.5. Immune etiologies:

Immune epilepsy refers to epilepsy resulting directly from an immune disorder in which seizures are a core symptom of central nervous system inflammation (Scheffer et al., 2017). This group is increasingly recognised in children and includes anti-N-methyl-D-aspartate receptor encephalitis, anti-leucine-rich glioma-inactivated 1 and anti-contactin-associated protein-like 2 syndromes, anti-myelin oligodendrocyte glycoprotein disease, and Rasmussen encephalitis. Features that should raise suspicion include a subacute onset of seizures with behavioural change, movement disorder, memory or language decline or psychiatric features, and failure to respond to anti-seizure medication. Early immunotherapy, usually corticosteroids, intravenous immunoglobulin or plasma exchange, followed by second-line agents where necessary, can improve outcomes substantially.

4.6. Unknown etiology and perinatal factors:

Despite extensive investigation, the cause remains unknown in a considerable proportion of children, particularly those with focal epilepsy and normal MRI (Scheffer et al., 2017). Repeating the diagnostic evaluation periodically is worthwhile, since the pace of discovery in genetics and imaging means that a previously unexplained epilepsy may be explained later.

Perinatal factors straddle several categories. Preterm birth, low birth weight, neonatal encephalopathy, neonatal seizures, neonatal hypoglycaemia and severe neonatal infection are all associated with a greater risk of later epilepsy and cerebral palsy. In high-income countries, advances in neonatal care have reduced the burden of some perinatal causes, but in many low-resource settings, birth asphyxia and neonatal sepsis remain among the most important preventable causes of childhood epilepsy (Ngugi et al., 2010; Beghi et al., 2019).

5. Clinical Manifestations:

The clinical expression of epilepsy in children depends on the maturity of the brain, the seizure onset zone, the underlying cause and the epilepsy syndrome. Careful history, ideally including a witnessed account or home video recording of the event, remains the most important step in diagnosis.

5.1. Seizure types:

Seizures are described according to the ILAE operational classification (Fisher et al., 2017). The principal types encountered in childhood are summarised in Table 1, and the most important are described below.

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Table. 1: Common seizure types in childhood

Seizure type	Key features	Typical age / setting
Focal aware	Preserved awareness; motor, sensory, autonomic or emotional onset	Any age; structural or genetic causes
Focal impaired awareness	Staring, automatisms, post-ictal confusion	Any age; common in temporal lobe epilepsy
Focal to bilateral tonic-clonic	Focal onset evolving to convulsion	Any age
Generalised tonic-clonic	Loss of consciousness, stiffening, rhythmic jerking	Any age; genetic generalised epilepsies
Absence	5–20 s behavioural arrest, no post-ictal state, 3-Hz spike-wave	Childhood absence epilepsy, 4–10 years
Myoclonic	Brief shock-like jerks	Juvenile myoclonic epilepsy; Dravet syndrome
Atonic / tonic	Drop attacks / sudden stiffening	Lennox-Gastaut syndrome
Epileptic spasms	Clusters of flexor/extensor spasms, often on waking	Infants, 3–12 months

Focal seizures with preserved awareness may present with isolated motor phenomena such as twitching of a limb or face, sensory symptoms, autonomic features such as pallor, sweating or epigastric rising sensation, or emotional and cognitive symptoms. Young children often cannot describe their experience, and these seizures may be recognised only by their observable signs. Focal impaired awareness seizures are characterised by a reduced ability to respond to the environment, commonly with staring, oral and manual automatisms, and a post-ictal period of confusion or drowsiness. Focal to bilateral tonic-clonic seizures begin with a focal onset, which may be subtle or missed, and then evolve to generalised convulsive activity.

Generalised tonic-clonic seizures involve sudden loss of consciousness, tonic stiffening, followed by rhythmic jerking and a post-ictal phase. Absence seizures are brief, lasting typically 5 to 20 seconds, with abrupt behavioural arrest and unresponsiveness, often with subtle eyelid flutter, and no post-ictal confusion; they may occur tens or hundreds of times per day and are frequently mistaken for daydreaming or inattention. Myoclonic seizures are sudden, brief, shock-like jerks, and atonic seizures produce sudden loss of muscle tone with drop attacks. Epileptic spasms are sudden flexion, extension or mixed flexion-extension movements of the proximal and truncal muscles, lasting about one to two seconds and typically occurring in clusters, especially on awakening.

5.2. Febrile seizures:

Febrile seizures are the most common seizure disorder of childhood, affecting a minority of children between about six months and five years of age. They are seizures associated with fever in the absence of central nervous system infection or an acute metabolic cause. Simple febrile seizures are generalised, last less than 15 minutes and do not recur within 24 hours, whereas complex febrile seizures are focal, prolonged or recurrent within the same illness. The American Academy of Pediatrics recommends that, for the child with a simple febrile seizure who is well-appearing, neuroimaging and EEG are not indicated, and lumbar puncture is not routinely required unless there are signs of meningitis or the child is incompletely immunised or has had prior antibiotic treatment (Subcommittee on Febrile Seizures, 2011). Febrile seizures are benign in most children and do not cause brain damage, but a small proportion later develop epilepsy, with higher risk in those with complex febrile seizures, pre-existing neurodevelopmental abnormality or a family history of epilepsy (Hesdorffer et al., 2011). Febrile seizures plus and Dravet syndrome form part of a genetic spectrum linked to SCN1A and other genes, and prolonged or repeated febrile seizures in the first year of life should raise suspicion of this condition.

5.3. Neonatal and infantile syndromes:

The ILAE has defined a series of syndromes with onset in the neonatal and infant period (Zuberi et al., 2022). Self-limited neonatal epilepsy and self-limited familial neonatal epilepsy are benign conditions linked to KCNQ2 and KCNQ3, in which seizures begin in the first week of life and usually remit within weeks to months, with normal development. Early infantile developmental and epileptic encephalopathy, which includes Ohtahara syndrome, presents with tonic spasms and burst-suppression patterns on EEG and carries a poor developmental prognosis.

Infantile epileptic spasms syndrome, previously known as West syndrome, usually begins between three and twelve months of age, with clusters of epileptic spasms, developmental stagnation or regression, and a disorganised high-amplitude EEG pattern called hypsarrhythmia (Zuberi et al., 2022). It is a neurological emergency, since the time to effective treatment influences the developmental outcome. Common etiologies include tuberous sclerosis complex, cortical malformations, hypoxic-ischaemic injury, genetic variants and metabolic disorders. Dravet syndrome typically begins in the first year of life in a previously normal infant with prolonged, often hemiclonic, fever-sensitive seizures; later, other seizure types including myoclonic, focal and atypical absence seizures emerge, development slows from the second year and ataxia and crouch gait may follow (Zuberi et al., 2022; Devinsky et al., 2017).

5.4. Childhood syndromes:

Childhood syndromes were described and classified by the ILAE Task Force in 2022 (Specchio et al., 2022). The most important are outlined below.

1. Childhood absence epilepsy typically starts between four and ten years of age in an otherwise normal child, with frequent typical absence seizures and generalised 3-Hz spike-and-wave discharges on EEG, often provoked by hyperventilation. Prognosis is good for many children, although a proportion later develop generalised tonic-clonic seizures (Glauser et al., 2010).
2. Self-limited epilepsy with centrotemporal spikes, formerly called benign rolandic epilepsy, is the most common focal epilepsy syndrome of childhood. It presents with brief hemifacial motor seizures, often with speech arrest and drooling, usually arising from sleep, and has characteristic centrotemporal spikes on EEG. Seizures remit by mid-adolescence, and treatment is frequently unnecessary when seizures are infrequent.
3. Self-limited epilepsy with autonomic seizures, previously called Panayiotopoulos syndrome, is characterised by nausea, vomiting, pallor and behavioural change, sometimes progressing to prolonged seizures and even autonomic status epilepticus, but with an overall favourable outcome.
4. Juvenile myoclonic epilepsy typically begins in adolescence with early-morning myoclonic jerks, generalised tonic-clonic seizures and sometimes absences, with sleep deprivation, alcohol and photic stimulation as common triggers. It usually requires lifelong treatment because relapse after drug withdrawal is common.
5. Lennox-Gastaut syndrome is a severe developmental and epileptic encephalopathy that typically begins between about two and six years of age, with multiple seizure types, notably tonic seizures during sleep and atonic or drop seizures, cognitive impairment and slow spike-and-wave discharges with paroxysmal fast activity on EEG. It is often drug-resistant and carries a substantial lifetime burden.
6. Developmental and epileptic encephalopathy with spike-and-wave activation in sleep, including the syndrome formerly called Landau-Kleffner syndrome, is characterised by a loss of acquired language or cognitive skills in association with markedly activated epileptiform discharges in non-rapid eye movement sleep.

5.5. Status epilepticus:

Status epilepticus is a seizure that is prolonged or that recurs without recovery of consciousness between episodes. Operationally, a convulsive seizure lasting more than five minutes is unlikely to stop spontaneously and should be treated as status epilepticus (Shinnar et al., 2001). Children, particularly those under the age of three, are at greater risk of status epilepticus than adults, and febrile status epilepticus is a common presentation. Complications include hypoxia, acidosis, hypoglycaemia, raised intracranial pressure, rhabdomyolysis and, with prolonged episodes, neuronal injury. Rapid treatment reduces both seizure duration and the risk of progression to refractory status epilepticus, which is why standardised treatment protocols are recommended.

5.6. Paroxysmal non-epileptic events:

Misdiagnosis is common in paediatric epilepsy, and a substantial proportion of children referred with suspected epilepsy turn out to have other conditions. Important mimics include syncope and reflex anoxic seizures, breath-holding spells, parasomnias, benign sleep myoclonus of infancy, tics, gastro-oesophageal reflux with Sandifer syndrome, shuddering attacks, daydreaming, migraine variants, and psychogenic non-epileptic events. Features that favour a non-epileptic cause include clear situational triggers, events provoked by emotion or posture, retained awareness during bilateral motor activity, prolonged duration with fluctuating intensity, and a lack of post-ictal change. Video recording by parents is extremely helpful, and video-EEG monitoring may be needed to confirm the diagnosis in uncertain cases.

6. Risk factors:

Risk factors for childhood epilepsy can be considered in three groups: those that predispose a child to developing epilepsy, those that predict recurrence after a first seizure, and those that predict drug resistance and poor outcome. Many are modifiable at the population level, and their recognition forms the basis of prevention.

6.1. Risk factors for the development of epilepsy:

1. Prenatal and perinatal factors. Preterm birth, low birth weight, intrauterine growth restriction, perinatal asphyxia, neonatal seizures, neonatal intracranial haemorrhage, congenital brain malformations and maternal infection during pregnancy all increase the risk of subsequent epilepsy (Camfield and Camfield, 2015; Ngugi et al., 2010).
2. Family history and genetic predisposition. A family history of epilepsy increases the risk in first-degree relatives, particularly in the genetic generalised epilepsies, although the absolute risk to most offspring and siblings remains modest. In monogenic disorders, the recurrence risk depends on the mode of inheritance and on the possibility of parental mosaicism (Helbig et al., 2008; Ellis et al., 2020).
3. Central nervous system infection. Bacterial meningitis, viral encephalitis, cerebral malaria and neurocysticercosis markedly increase the risk of both acute symptomatic seizures and later unprovoked seizures. A population-based study showed that central nervous system infection and severe head injury were associated with a several-fold higher risk of developing epilepsy that remained elevated for years after the insult (Hesdorffer et al., 2011).
4. Traumatic brain injury. The risk increases with the severity of injury, and is greatest after penetrating injury, intracranial haemorrhage, depressed skull fracture and prolonged loss of consciousness (Hesdorffer et al., 2011). Preventive measures such as helmets, seat belts and child restraint systems reduce this risk.
5. Neurodevelopmental disorders. Cerebral palsy, intellectual disability and autism spectrum disorder are associated with a higher risk of epilepsy; the relationship is probably bidirectional and shared mechanisms are likely (Russ et al., 2012).
6. Neurocutaneous syndromes and structural brain abnormalities. Tuberous sclerosis complex, Sturge-Weber syndrome and neurofibromatosis are strongly associated with seizures, as are cortical malformations and brain tumours.
7. Febrile seizures. Complex febrile seizures, an abnormal neurological status before the seizure, and a family history of epilepsy raise the risk of later epilepsy (Hesdorffer et al., 2011).
8. Socioeconomic and environmental factors. In low-resource settings, poor perinatal care, inadequate access to immunisation, malnutrition, poor sanitation and limited access to health services contribute to the burden (Ngugi et al., 2010; Beghi et al., 2019).

6.2. Risk factors for recurrence after a first seizure:

After a first unprovoked seizure, a substantial proportion of children will have a second, with most recurrences occurring within the first two years. A quantitative review of the literature reported recurrence risks of roughly 30% to 50% overall, with the risk depending on etiology, EEG findings and seizure type (Berg and Shinnar, 1991). A remote symptomatic cause, such as a prior neurological insult, and an abnormal EEG, particularly with epileptiform discharges, carry the highest risk, whereas children with a normal EEG and no known cause have the lowest risk. Seizure occurring during sleep, a prior history of febrile seizures and Todd paralysis have been associated with a higher risk of recurrence in several studies. The American Academy of Neurology practice parameter on the child with a first unprovoked seizure supports a careful and individualised approach, noting that treatment with anti-seizure medication reduces the risk of recurrence but does not alter long-term prognosis (Hirtz et al., 2003).

6.3. Risk factors for drug resistance and poor outcome:

Children who are likely to develop drug-resistant epilepsy are often identifiable early. Established predictors include an identified structural or genetic etiology, onset in infancy, multiple seizure types, a high seizure frequency before treatment, developmental delay or abnormal neurological examination at baseline, abnormal MRI and failure to respond to the first appropriate anti-seizure medication (Kwan et al., 2010; Moshé et al., 2015). Recognition of these features should prompt early consideration of surgical evaluation and other non-pharmacological treatments. Another important concept is that of modifiable contributors to poor control, which include poor adherence, inappropriate drug choice, subtherapeutic dosing, aggravating drug interactions

and unaddressed triggers such as sleep deprivation. Nonadherence is particularly common in adolescence and may be mistaken for drug resistance.

6.4. Precipitating factors:

Seizures in children with established epilepsy may be provoked by fever and intercurrent illness, sleep deprivation, missed medication doses, photic stimulation in photosensitive epilepsy, hyperventilation in absence epilepsy, excessive alcohol or recreational drug use in adolescents, hormonal changes in some adolescent girls, and certain drugs that lower the seizure threshold. Education of families and adolescents about these factors is an effective and inexpensive part of management.

7. Diagnostic evaluation:

7.1. History and examination:

The diagnosis of epilepsy is primarily clinical. A detailed description of the event from a witness, including the circumstances before the event, the sequence of observable features, the duration, the level of responsiveness, any post-ictal state and the child's developmental and medical background, is the most valuable single source of information. Questions on prenatal and birth history, developmental milestones, past central nervous system infection, head injury, family history of epilepsy, febrile seizures or consanguinity, medication exposure and school performance are essential. Examination should include growth parameters, head circumference, neurocutaneous stigmata such as hypopigmented macules, café-au-lait spots and facial angiofibromas, dysmorphic features, neurological signs and a developmental assessment.

7.2. Electroencephalography:

EEG is the principal investigation for epilepsy and is useful for confirming the diagnosis, classifying the seizure and epilepsy type, identifying a syndrome and estimating the risk of recurrence. A routine interictal EEG, ideally including photic stimulation, hyperventilation and sleep, has a limited sensitivity, and a normal tracing does not exclude epilepsy, while epileptiform discharges may also occasionally be found in children who never have seizures. Sleep-deprived EEG and prolonged recordings increase the yield. Video-EEG monitoring allows correlation of clinical events with electrical activity, which is invaluable for diagnosing uncertain events, characterising seizure types and localising the seizure onset zone in surgical candidates. The EEG is also essential in infants with suspected epileptic spasms, where hypsarrhythmia, and in children with sleep-activated discharges, may be seen (Zuberi et al., 2022). Current practice parameters recommend an EEG as part of the evaluation of a child with a first unprovoked seizure (Hirtz et al., 2003).

7.3. Neuroimaging:

MRI is the preferred neuroimaging technique in children with epilepsy, particularly in those with focal seizures, a focal neurological deficit, and epilepsy onset in infancy, drug resistance or an epilepsy syndrome that is not self-limited. Imaging is generally not required in children with a clear diagnosis of an idiopathic generalised epilepsy such as childhood absence epilepsy, or in typical self-limited focal epilepsy syndromes. Computed tomography is reserved for emergency situations in which MRI is not immediately available and an acute structural cause such as haemorrhage must be excluded. In children being evaluated for surgery, advanced techniques including positron emission tomography, ictal single-photon emission computed tomography, magnetoencephalography and functional MRI contribute to localisation and to planning.

7.4. Laboratory, metabolic and genetic testing:

The laboratory evaluation should be guided by the clinical picture. Glucose, electrolytes, calcium and magnesium are relevant in acute presentations, particularly in infants. In neonates and infants with seizures that are unexplained or that fail to respond to treatment, a metabolic evaluation, including blood gas, lactate, ammonia, amino acids, urine organic acids and, where relevant, cerebrospinal fluid glucose and neurotransmitters, should be considered. Lumbar puncture is indicated where central nervous system infection or autoimmune encephalitis is suspected.

Genetic testing is now a first-tier investigation in many children with epilepsy of unknown cause, especially those with onset in infancy, developmental delay, multiple seizure types, and features of a syndrome or a family history. Chromosomal microarray, targeted gene panels, exome sequencing and genome sequencing are available, with choice depending on the clinical question and resources (Ellis et al., 2020). Pre- and post-test counselling is important, as results may be uncertain, may reveal incidental findings and have implications for relatives.

8. Management strategies:

The goals of management are complete seizure freedom, where possible, without adverse effects from treatment, and optimal development, participation and quality of life. Treatment should be tailored to the seizure type and syndrome, the etiology, the age and sex of the child, the comorbidities and the preferences of the family. It should be delivered by a multidisciplinary team and be accompanied by education and psychosocial support.

8.1. Initiating treatment:

Treatment is not automatically started after a first unprovoked seizure. In a child with a normal examination and EEG and no identifiable cause, the risk of recurrence is moderate, and the decision to treat is made after a discussion of the risks and benefits with the family; medication reduces early recurrence but does not improve long-term remission rates (Hirtz et al., 2003; Berg and Shinnar, 1991). Treatment is generally started after a second unprovoked seizure, or after a first seizure if the risk of recurrence is high, for example in the presence of a structural lesion or a clear epilepsy syndrome (Fisher et al., 2014). Monotherapy is the preferred initial strategy, with the drug chosen according to syndrome and seizure type, started at a low dose and titrated to effect.

8.2. Anti-seizure medication:

Anti-seizure medications (ASMs) remain the cornerstone of treatment. Approximately two-thirds of children with epilepsy become seizure free with appropriate drug treatment, and about half of those who do not respond to the first drug may respond to a second (Kwan et al., 2010; Moshé et al., 2015). An updated ILAE evidence review of initial monotherapy graded the efficacy of drugs for different seizure types and syndromes and emphasised the paucity of high-quality paediatric trials, with the strongest evidence for ethosuximide in childhood absence epilepsy (Glauser et al., 2013). The landmark randomised trial in childhood absence epilepsy found that ethosuximide and valproic acid were more effective than lamotrigine, with freedom from treatment failure at 16 weeks in 53%, 58% and 29% of children, respectively, while attentional dysfunction was more frequent with valproic acid (Glauser et al., 2010). Ethosuximide is therefore regarded as the first choice in absence epilepsy without generalised tonic-clonic seizures.

Table 2 summarises commonly used drugs by syndrome. Drug selection must consider adverse effects, which in children include somnolence, behavioural change, cognitive effects, weight change, rash, hepatotoxicity and teratogenic risk in girls approaching reproductive age. Valproate, in particular, carries a well-recognised risk of fetal malformation and neurodevelopmental impairment, and its use in girls and women of childbearing potential should be restricted to situations where alternatives are ineffective or unsuitable and where a pregnancy prevention programme is in place. Carbamazepine and some other sodium channel blockers may aggravate absence and myoclonic seizures and should be avoided in the genetic generalised epilepsies and in Dravet syndrome. Vigabatrin is first-line for epileptic spasms in tuberous sclerosis complex but requires monitoring for visual field defects.

Table. 2: Commonly used anti-seizure medications by syndrome

Syndrome / seizure type	Commonly used first-line options	Cautions
Childhood absence epilepsy	Ethosuximide; valproate (if tonic-clonic seizures also present); lamotrigine	Valproate: teratogenicity, attention effects; avoid carbamazepine
Focal epilepsy	Carbamazepine, oxcarbazepine, lamotrigine, levetiracetam	Rash (carbamazepine, lamotrigine); behavioural effects (levetiracetam)
Juvenile myoclonic epilepsy	Valproate (not in girls of childbearing potential), levetiracetam, lamotrigine	Avoid sodium channel blockers; lamotrigine may worsen myoclonus
Infantile epileptic spasms	ACTH, oral corticosteroids, vigabatrin	Hypertension, infection (steroids); visual field loss (vigabatrin)
Dravet syndrome	Valproate, clobazam, stiripentol, cannabidiol, fenfluramine	Avoid sodium channel blockers
Lennox-Gastaut syndrome	Valproate, lamotrigine, rufinamide, clobazam, cannabidiol	Polytherapy interactions; sedation
Prolonged seizure	Benzodiazepine (midazolam, lorazepam, diazepam)	Respiratory depression; give within 5 minutes

Practical principles for prescribing include starting low and increasing slowly, using the lowest effective dose, checking adherence before declaring failure, avoiding unnecessary polytherapy, monitoring for adverse effects and, when changing drugs, cross-titrating carefully. Routine drug level monitoring is not necessary for most children but is useful when adherence or toxicity is in question, in the setting of drug interactions, or in changing physiology such as pregnancy. After a prolonged seizure-free period, usually two years, withdrawal can be considered, and the risk of relapse depends on etiology and syndrome, being lowest in self-limited syndromes and highest in juvenile myoclonic epilepsy and in those with structural lesions. Withdrawal should be gradual over several months.

8.3. Emergency management of prolonged seizures:

Prolonged seizures are medical emergencies, and the longer they last, the more difficult they are to stop. Because convulsive seizures lasting more than five minutes seldom stop spontaneously (Shinnar et al., 2001), treatment should begin promptly. Principles include securing the airway, breathing and circulation, giving oxygen, checking blood glucose and giving a benzodiazepine as first-line treatment. Options include intravenous lorazepam or diazepam, intramuscular midazolam, and buccal, intranasal or rectal preparations when intravenous access is not available; the latter are particularly valuable in the community, and families of children at risk of prolonged seizures should be given a rescue plan and trained in its use. If seizures persist after adequate benzodiazepine dosing, a second-line anti-seizure drug such as levetiracetam, phenytoin or fosphenytoin, or valproate is given, and refractory status epilepticus is managed in an intensive care setting with anaesthetic agents. Underlying causes, including infection, metabolic disturbance and toxins, must be sought and treated at the same time.

8.4. Dietary therapies:

The ketogenic diet is a high-fat, adequate-protein, low-carbohydrate diet that mimics the metabolic state of fasting. A randomised controlled trial in children aged 2 to 16 years with drug-resistant epilepsy found that after three months, 38% of children on the ketogenic diet had more than a 50% reduction in seizures compared with 6% of controls (Neal et al., 2008). The diet is the treatment of choice in glucose transporter type 1 deficiency syndrome and pyruvate dehydrogenase deficiency, and is widely used in infantile spasms, Dravet syndrome, Lennox-Gastaut syndrome and other drug-resistant epilepsies. Less restrictive alternatives, such as the modified Atkins diet and the low glycaemic index treatment, are better tolerated by older children and adolescents. Adverse effects include constipation, vomiting, hypoglycaemia in the early stage, hyperlipidaemia, kidney stones, growth faltering and bone health concerns, so the diet must be supervised by a specialist team including a dietitian.

8.5. Newer and precision therapies:

Cannabidiol has been shown to reduce seizure frequency in children with Dravet syndrome and Lennox-Gastaut syndrome. In a randomised controlled trial in Dravet syndrome, the median frequency of convulsive seizures fell by 38.9% with cannabidiol at 20 mg/kg/day compared with 13.3% with placebo, and adverse effects included somnolence, diarrhoea, and decreased appetite and raised transaminases, particularly with concomitant valproate (Devinsky et al., 2017). Other drugs, including fenfluramine, stiripentol, clobazam, cenobamate and everolimus for tuberous sclerosis complex, have also expanded the options for specific syndromes. Beyond these, the identification of specific genetic causes has opened the way to precision approaches, such as sodium channel blockers for gain-of-function SCN2A and SCN8A variants, the avoidance of the same drugs in loss-of-function variants, and emerging antisense oligonucleotide and gene therapy strategies in conditions such as Dravet syndrome (Ellis et al., 2020; Moshé et al., 2015). Hormonal therapy with adrenocorticotropic hormone or oral corticosteroids, and vigabatrin, are first-line treatments for infantile epileptic spasms, and early initiation is associated with better developmental outcomes.

8.6. Epilepsy surgery:

Surgery is the most effective treatment for selected children with drug-resistant focal epilepsy. A randomised controlled trial of children and adolescents with drug-resistant epilepsy in India showed that 77% of those who underwent surgery were seizure free at 12 months compared with 7% of those continuing medical therapy, with a corresponding improvement in quality of life and behaviour (Dwivedi et al., 2017). Surgical options include lesionectomy, lobar and multilobar resection, hemispherectomy or functional hemispherotomy for unilateral hemispheric disease, corpus callosotomy as a palliative option for drop attacks, and laser interstitial thermal therapy for selected lesions. Early referral is advocated for any child who meets the definition of drug resistance, and for particular conditions with a well-known surgical profile such as focal cortical dysplasia,

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Scienxt Journal of Pharmaceutical Sciences

tumours, hemispheric syndromes and Sturge-Weber syndrome (Kwan et al., 2010; Dwivedi et al., 2017). Cognitive and developmental outcomes may be better when surgery is performed earlier, as continuing seizures can impair development.

8.7. Neuromodulation:

Vagus nerve stimulation, which involves an implanted pulse generator delivering intermittent stimulation to the left vagus nerve, is an adjunctive option for children with drug-resistant epilepsy who are not candidates for resective surgery, and is associated with a reduction in seizure frequency in a proportion of patients, along with potential benefits for mood and alertness. Responsive neurostimulation and deep brain stimulation are used mainly in adolescents and adults and are being evaluated in younger patients. These therapies are palliative and seldom lead to seizure freedom, but they can improve quality of life.

8.8. Psychosocial care, education and safety:

Medical treatment of seizures is only part of care. Children and their families need clear information on the nature of epilepsy, the purpose and risks of medication, seizure first aid, triggers and safety. First aid for convulsive seizures involves staying calm, noting the time, protecting the child from injury, placing the child on their side after the convulsion, not putting anything in the mouth and calling for emergency help if a seizure lasts more than five minutes. Safety advice should include supervised bathing and swimming, caution with heights and cycling, and for adolescents, guidance on driving, alcohol, contraception and sleep. Schools should be informed, and teachers trained to recognise seizures and administer rescue medication. Screening for depression, anxiety, attention problems and learning difficulties should be routine, and referral to psychology, educational support and social services made where needed. Transition planning for adolescents moving to adult services is also important and is often neglected.

9. Comorbidities and prognosis:

9.1. Comorbidities:

Comorbidity is the rule rather than the exception in childhood epilepsy. In a national profile of children in the United States, those with epilepsy were considerably more likely than their peers to have developmental delay, learning disability, attention-deficit/hyperactivity disorder, autism spectrum disorder, anxiety, depression, speech and language problems and chronic health conditions (Russ et al., 2012). The ILAE classification explicitly places comorbidities at every level of diagnosis, since they often determine quality of life and call for specific intervention (Scheffer et al., 2017). The causes are multiple and include shared underlying pathology, the effects of recurrent seizures and interictal discharges on developing brain networks, adverse effects of medication and the psychosocial impact of the condition.

Cognitive and educational difficulties are common even in children with otherwise uncomplicated epilepsy. Attention, processing speed, memory and executive function may all be affected, and educational attainment tends to be below that of siblings. Neuropsychological assessment at diagnosis and at transition points can identify difficulties early, and school plans can be adapted accordingly. Mood and anxiety disorders are frequent, are often under-recognised, and may be exacerbated by some ASMs, such as levetiracetam, perampanel and topiramate, while others, including lamotrigine and valproate, may have mood-stabilising properties. Sleep disorders, headaches, motor difficulties and obesity are also overrepresented.

9.2. Prognosis:

Outcome in childhood epilepsy is diverse and depends largely on the underlying etiology and syndrome. Long-term population-based follow-up has shown that a majority of children eventually enter remission, many of whom remain off medication, while a smaller proportion have intractable seizures that continue into adulthood (Sillanpää and Shinnar, 2010). Self-limited syndromes, such as childhood absence epilepsy and self-limited epilepsy with centrotemporal spikes, have an excellent prognosis in most cases, whereas developmental and epileptic encephalopathies, structural epilepsies with extensive lesions and some genetic syndromes carry a guarded outlook, with persistent seizures and neurodevelopmental disability. Mortality is increased in those with symptomatic epilepsy (Sillanpää and Shinnar, 2010).

Sudden unexpected death in epilepsy is rare in children but accounts for an important share of deaths in those with uncontrolled generalised tonic-clonic seizures. Attention to seizure control, adherence, nocturnal supervision in selected high-risk children and counselling are the main preventive strategies. It is important that clinicians discuss this risk sensitively with families, balancing honesty with reassurance.

10. Challenges and future directions:

Several challenges remain. First, there is a persistent treatment gap in low- and middle-income countries, where a large proportion of children with epilepsy receive no treatment. The causes include shortage of trained health workers, unavailability of low-cost ASMs, stigma, and reliance on traditional healers. Strategies such as task-sharing with trained primary-care workers, ensuring consistent supply of inexpensive first-line drugs such as phenobarbital, carbamazepine and valproate, community education to counter stigma and prevention of perinatal and infectious causes can narrow this gap (Beghi et al., 2019; Ngugi et al., 2010).

Second, delays in diagnosis and referral remain frequent even in well-resourced settings. Wider use of structured referral criteria, telemedicine, home video recording and rapid access to genetic testing could shorten the time to a precise diagnosis. Third, the evidence base for many ASMs in children remains thin, and many drugs are extrapolated from adult trials. More paediatric-specific, syndrome-specific trials, including trials using core outcome sets that capture development and quality of life as well as seizure counts, are needed (Glauser et al., 2013).

Fourth, precision medicine offers the prospect of therapies directed at the molecular cause of epilepsy. Antisense oligonucleotides, gene replacement, gene regulation and small molecules targeting specific channels or pathways are in development or early clinical trials, and genomic diagnosis in infancy is likely to be increasingly used to guide treatment from the outset (Ellis et al., 2020; Moshé et al., 2015). Fifth, advances in wearable seizure detection, artificial intelligence-assisted EEG and MRI interpretation, and minimally invasive surgical techniques promise to improve monitoring and expand surgical candidacy. Finally, a more holistic approach is needed, in which cognitive, behavioural and social outcomes are considered as important as seizure freedom and in which children and families are partners in decision-making.

11. Conclusion

Childhood epilepsy is a diverse group of disorders, from benign self-limited conditions to devastating developmental and epileptic encephalopathies. The ILAE framework provides a shared language for describing seizures, epilepsy types and syndromes, and places the identification of etiology and comorbidity at the heart of diagnosis (Scheffer et al., 2017; Specchio et al., 2022). The causes are increasingly well understood, with structural, genetic, infectious, metabolic and immune mechanisms each demanding specific investigation, and with many risk factors, particularly perinatal injury and central nervous system infection, preventable through public health measures.

Management has advanced from empirical drug treatment to a multimodal approach combining carefully selected ASMs, emergency protocols, dietary therapy, surgery, neuromodulation and, increasingly, precision therapies. Evidence from randomised trials supports ethosuximide in absence epilepsy, the ketogenic diet and cannabidiol in selected drug-resistant epilepsies, and surgery for suitable children with focal disease (Glauser et al., 2010; Neal et al., 2008; Devinsky et al., 2017; Dwivedi et al., 2017). Timely recognition of drug resistance and early referral to specialist centres are essential. Equally, attention to cognitive, behavioural and psychosocial needs, school support, safety education and transition to adult services is indispensable. The central message for clinicians is that a child with epilepsy should be assessed not only for seizures but as a whole child, whose development, family and future deserve the same attention as the electroencephalogram.

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