RESEARCH PAPER

Contemporary Management of Pediatric Intractable Epilepsy: Integrating Medical and Surgical Strategies

Khaled Saad[1*], Usama M. El-Shokhaiby[2], Kawashty Ragab Mohamed[3], Abdelrahman N Abdelal[3], Abdulrahman A. Al-Atram[4], Mohamed M Bakr[5], Ahmed Beheiry[5], Wael Medhat Elkholy[5], Abd-Elmonem M Hassan[6], Anas Elgenidi[7], Eman S. Sawan[8]

[1]Department of Pediatrics, Assiut University, Assiut, Egypt.

Email: khaled.ali@med.au.edu.eg, ksaad8@yahoo.com (Corresponding Author)

[2]Department of Neurosurgery, Faculty of Medicine, Al Azhar University, Cairo, Egypt

[3]Department of Neurology, Faculty of Medicine, Al-Azhar University, Assiut, Egypt

[4]Department of Psychiatry, College of Medicine, Majmaah University, Al Majmaah, 11952, Saudi Arabia

[5]Neurosurgery Department, Damanhour Medical National Institute, Damanhour, Egypt

[6]Department of Pediatrics, Faculty of Medicine, Al-Azhar University, Assiut, Egypt

[7]Department of Neurology, Faculty of Medicine, Cairo University, Cairo, Egypt

[8]Pharmacy and Pharmacy Practice, Faculty of Pharmacy, Badr University, Cairo 11829, Egypt

ABSTRACT

Pediatric intractable epilepsy, defined as failure of two appropriately chosen and tolerated antiseizure medication (ASM) schedules to achieve sustained seizure freedom, remains one of the most consequential neurologic disorders of childhood because of its effects on cognition, behaviour, psychosocial development, academic attainment, and family quality of life. Over the past two decades, management has shifted from a predominantly pharmacologic model toward an integrated framework in which early referral to a comprehensive epilepsy center, precise localization of the epileptogenic zone, and individualized surgical or neuromodulatory treatment are considered central components of care rather than measures of last resort. Structural etiologies, particularly focal cortical dysplasia, hippocampal sclerosis, post-injury gliosis, and low-grade epilepsy-associated tumors (LEATs), comprise the most surgically remediable causes of pediatric drug-resistant epilepsy and illustrate the importance of linking lesion biology with network-level epileptogenicity. This scoping review maps current evidence on the medical and surgical management of pediatric intractable epilepsy, with particular attention to pre-surgical evaluation, lesion-directed and epilepsy-directed surgery, minimally invasive ablative approaches, and neuromodulation. The available evidence consistently supports early multidisciplinary evaluation, recognition of surgical candidacy soon after pharmacoresistance is established, and individualized treatment pathways that prioritize seizure freedom, developmental preservation, and functional safety.

Keywords: Pediatric epilepsy, drug-resistant epilepsy, epilepsy surgery, neuromodulation, low-grade epilepsy-associated tumors, stereoelectroencephalography

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Introduction

Epilepsy affects approximately 0.5–1% of the pediatric population, and 20–30% of children with epilepsy ultimately develop drug-resistant or intractable disease despite modern pharmacotherapy.[1] Revised: The International League Against Epilepsy (ILAE) defines drug-resistant epilepsy as failure of adequate trials of two tolerated, appropriately chosen, and appropriately used antiseizure medication (ASM) regimens (whether as monotherapy or in combination), to achieve sustained seizure freedom [1]. This definition is clinically important because it establishes a threshold beyond which the probability of achieving durable seizure control with serial medication trials alone becomes substantially

reduced. In contrast, the cumulative burden of uncontrolled seizures and medication toxicity continues to rise [2].

The morbidity associated with pediatric intractable epilepsy extends beyond seizure counts. Ongoing seizures and interictal epileptiform activity during critical windows of brain maturation are associated with adverse effects on language acquisition, executive function, attention, behaviour, school performance, social integration, and emotional wellbeing, and these sequelae may persist into adulthood even when seizure frequency later improves. Longitudinal neuropsychological studies and meta-analytic data indicate that successful epilepsy surgery can stabilize or improve cognitive trajectories (mean IQ change +3.2 points vs. −5.8 points in medically managed controls), whereas prolonged uncontrolled epilepsy is associated with continued developmental attrition [3, 4].

The etiologic spectrum of pediatric intractable epilepsy is broad and includes structural, genetic, metabolic, infectious, immune-mediated, and developmental causes. From a practical clinical perspective, structural epilepsies represent the most important surgically remediable subgroup and include focal cortical dysplasia, hippocampal sclerosis, developmental and post-injury lesions, hypothalamic hamartoma, and tumor-associated epilepsy. Within structural epilepsies, low-grade epilepsy-associated tumors such as ganglioglioma, dysembryoplastic neuroepithelial tumor (DNET), pleomorphic xanthoastrocytoma, angiocentric glioma, papillary glioneuronal tumor, and polymorphous low-grade neuroepithelial tumor of the young provide a particularly informative model because their management requires simultaneous consideration of lesion biology, epileptogenic cortex, network organization, and long-term developmental outcome [4,5]. Structural epilepsies account for approximately 60–70% of pediatric drug-resistant cases referred for surgical evaluation and represent the cohort with the highest likelihood of achieving Engel Class I outcomes following resective intervention (Table 1) [6,7].

The contemporary management paradigm underscores a key principle: in children with epileptogenic lesions, seizure control should be regarded as a primary therapeutic goal rather than a secondary consequence of lesion treatment. This principle is especially relevant for LEATs and other cortically based lesions in which long-standing seizures may result in secondary epileptogenesis, perilesional cortical dysfunction, and expansion of the epileptic network beyond the radiographically visible lesion. Accordingly, the modern management of pediatric intractable epilepsy increasingly emphasizes integrated epilepsy-centered planning from the time of initial presentation, with coordination among pediatric neurologists, epileptologists, neurosurgeons, neuroradiologists, neuropsychologists, nuclear medicine specialists, rehabilitation teams, and, when relevant, neuro-oncology services [4, 5].

Another major shift in contemporary care is the abandonment of the older concept that epilepsy surgery should be reserved only for children who have exhausted all medical options over many years. Current evidence indicates that early pre-surgical referral is appropriate as soon as drug resistance is recognized, even in children who may ultimately prove not to be ideal candidates for resection, because the evaluation itself may identify alternative interventions such as laser ablation, disconnection, dietary therapy, or neuromodulation. In young children in particular, delay may permit preventable deterioration in developmental quotient, language acquisition, adaptive functioning, and caregiver quality of life [5-8]. Multicenter cohort data demonstrate that each year of delay in surgical evaluation after establishing pharmacoresistance is associated with a 4.2% reduction in the likelihood of postoperative seizure freedom and a measurable decline in developmental quotient scores [8,9].

The aim of this scoping review is to synthesize the contemporary literature on the medical and surgical management of pediatric intractable epilepsy, while using tumor-related epilepsy as a structural model that clarifies broader principles of epileptogenicity, localization, timing of intervention, and individualized treatment selection. Specific objectives are to summarize the current diagnostic framework, outline the role and limitations of pharmacologic treatment, review the indications and outcomes of resective and ablative surgery, assess the expanding role of neuromodulation, and identify future directions in molecular diagnostics, connectomics, and long-term surveillance.

Materials and Methods

This manuscript was structured as a scoping review in accordance with the PRISMA extension for scoping reviews (PRISMA-ScR) and updated Joanna Briggs Institute methodological guidance for scoping reviews [10]. A scoping review framework was selected because the objective was to map the breadth of current evidence

across diverse intervention types, including ASMs, ketogenic dietary therapies, pre-surgical evaluation, resective and ablative procedures, disconnection surgery, and neuromodulation, rather than to pool highly homogeneous outcome data suitable for a conventional meta-analysis. The review questions were organized around population, concept, and context, focusing on children and adolescents with drug-resistant epilepsy and the full spectrum of contemporary medical and surgical management strategies.

The evidence base incorporated into this review was derived from contemporary manuscripts and supplemented by recent key publications on pediatric epilepsy surgery, imaging, neuromodulation, and scoping review methodology. Eligible sources included guidelines, consensus statements, systematic reviews, meta-analyses, multicenter retrospective cohorts, prospective observational studies, and focused narrative reviews relevant to pediatric drug-resistant epilepsy and its management. Adult-only studies, isolated case reports, and articles not directly addressing treatment pathways or outcome assessment were given lower priority unless they provided essential mechanistic or methodological context.

Data were charted narratively with emphasis on definitions, etiologic categories, pre-surgical investigations, surgical selection criteria, procedural strategies, seizure outcomes, neurocognitive outcomes, complications, and emerging therapies. Because the literature encompassed multiple study designs and heterogeneous patient populations, the synthesis was intentionally descriptive and thematic, consistent with scoping review methodology. Particular attention was given to studies addressing lesion-related pediatric epilepsy, especially LEATs and other structural epilepsies, because these sources best illustrated the transition from lesion-centered management to network-informed epilepsy surgery and the role of combined medical, surgical, and neuromodulatory strategies.

Results and Discussion

Definitions and Etiologic Spectrum

Pediatric intractable epilepsy should be understood as a clinicobiological state rather than merely a pharmacologic endpoint. Once two appropriate ASM regimens have failed, the likelihood of seizure freedom with subsequent medication trials declines substantially. However, reductions in seizure burden and improvements in tolerability may still be achievable through rational polytherapy or syndrome-directed treatment. The major etiologic categories include structural, genetic, metabolic, infectious, immune, and unknown causes, but the highest rates of surgical cure are typically observed in focal structural epilepsies with a definable epileptogenic substrate [3, 7].

Structural epilepsies in childhood encompass a heterogeneous group of disorders, including focal cortical dysplasia, mesial temporal sclerosis, hemispheric developmental abnormalities, hypothalamic hamartoma, post-stroke and post-traumatic epilepsy, and epileptogenic tumors. Among tumor-related epilepsies, low-grade cortically based lesions are the most epileptogenic, particularly gangliogliomа and DNET, in which seizures frequently represent the presenting or dominant symptom for months to years before diagnosis. This prolonged prediagnostic interval is clinically important because it may allow maturation of an epileptic network extending beyond the lesion itself, thereby reducing the likelihood that simple lesionectomy alone will be sufficient in long-standing cases [5, 11].

Tumor-Related Epilepsy as a Model of Structural Drug-Resistant Epilepsy

LEATs are generally slow-growing, cortically based WHO grade 1 or 2 lesions with a marked association with chronic focal epilepsy in children and young adults. These tumors often exhibit dual pathology, most notably coexistence with focal cortical dysplasia or perilesional cortical abnormalities, which helps explain why postoperative seizure outcome is determined not only by the extent of lesion removal but also by whether the broader epileptogenic zone has been adequately defined and treated. Meta-analytic data indicate seizure freedom rates of 70–90% following gross total resection of gangliogliomа and DNET, with outcomes significantly correlated with the extent of resection of both lesion and associated epileptogenic cortex. However, outcomes are most favorable when surgery is performed early and when residual epileptogenic cortex is not left behind [5, 12, 13].

The biological basis of tumor-related epileptogenicity extends beyond mass effect or cortical irritation. Molecular alterations such as BRAF V600E mutations in gangliogliomа and activation of mTOR-related pathways in glioneuronal lesions may contribute directly to network hyperexcitability, while chronic inflammation, aberrant glial-neuronal signalling, and abnormal synaptic integration further sustain epileptogenesis. More recently, interest has expanded to IDH-associated epileptogenesis in diffuse gliomas, where the

oncometabolite D-2-hydroxyglutarate (D-2-HG) has been implicated in neuronal hyperexcitability via mTOR pathway activation and may partly explain seizure propensity in selected infiltrative tumors [12, 14].

Pre-Surgical Evaluation: General Principles (Table 2, Figure 1)

The goal of pre-surgical evaluation is to formulate a concordant hypothesis regarding the epileptogenic zone, seizure onset zone, symptomatogenic cortex, and eloquent functional regions that must be preserved. In children, this process is necessarily multidisciplinary and integrates semiology, scalp video-EEG, high-resolution structural imaging, functional and metabolic imaging, neuropsychology, and, when necessary, invasive monitoring. Concordance among these modalities is one of the strongest predictors of a favorable postoperative seizure outcome. It may permit direct progression to resection in selected patients with short epilepsy duration and a clearly localized non-eloquent lesion [15].

Long-term scalp video-EEG remains the first-line neurophysiologic investigation because it confirms epileptic events, characterizes seizure semiology, identifies interictal and ictal patterns, and provides an initial estimate of hemispheric and lobar localization. However, scalp EEG has intrinsic limitations in deep-seated, multifocal, rapidly propagating, or lesion-distorted epilepsies, and it may be insufficient for precise localization in mesial temporal, insular, or complex extratemporal networks. For this reason, scalp EEG findings must be interpreted in conjunction with structural and functional imaging rather than as an isolated determinant of operative candidacy [8, 17].

High-resolution epilepsy-protocol MRI remains the cornerstone of structural evaluation. Thin-slice T1-weighted, T2-weighted, FLAIR, and susceptibility-sensitive sequences improve detection of subtle focal cortical dysplasia, transmantle signs, hippocampal abnormalities, small glioneuronal tumors, and post-treatment cortical changes that may be occult on routine neuroimaging. Advanced MRI techniques such as diffusion tensor imaging, tractography, volumetric analysis, and, in selected centers, ultrahigh-field MRI further refine localization and clarify the relationship between the lesion, the epileptogenic cortex, and critical white matter pathways [18].

Functional imaging and ancillary localization studies often provide decisive information in children with MRI-negative or poorly localized epilepsy. FDG-PET identifies interictal hypometabolism that may colocalize with the epileptogenic region, while ictal or interictal SPECT with subtraction co-registration can highlight perfusion abnormalities when seizure recording is feasible. Magnetoencephalography can localize interictal spike clusters with high spatial resolution and is especially useful in planning electrode trajectories for stereo-EEG. In contrast, resting-state and task-based functional MRI, navigated transcranial magnetic stimulation, and diffusion-based language or motor tract mapping are valuable for estimating eloquent cortex in cooperative as well as developmentally limited children [18, 19].

Neuropsychological assessment is indispensable rather than adjunctive. It establishes a developmental and cognitive baseline, assists lateralization of language and memory function, identifies coexisting psychiatric and behavioral disorders, and helps distinguish deficits attributable to the lesion, seizure burden, medication effects, or broader neurodevelopmental conditions. In addition, preoperative neuropsychological findings are central to counselling regarding postoperative risks and to measuring the true benefit of intervention, which in pediatrics must include developmental progress, school functioning, behavioral stabilization, and family quality of life rather than seizure counts alone [20].

Phase II Monitoring and Invasive Localization

When non-invasive data are discordant, when the suspected epileptogenic zone overlaps eloquent cortex, or when network architecture is complex, invasive monitoring becomes necessary. Current consensus guidelines recommend stereo-EEG as first-line invasive monitoring for deep-seated, multifocal, or MRI-negative epilepsies in children, given its superior spatial sampling of mesial temporal, insular, and cingulate structures with reduced morbidity compared to subdural grids [21,22]. Contemporary pediatric practice increasingly favors stereo-EEG because it permits three-dimensional sampling of superficial and deep structures with relatively limited cortical disruption, lower infection risk than prolonged grid implantation, and strong utility in mesial temporal, insular, cingulate, and multilobar epilepsies (Table 3). Depth electrodes also allow bedside functional mapping, including stimulation-based language and motor assessment, which is especially relevant when the lesion is adjacent to eloquent cortex [21]. Subdural grids and strips retain an important role, particularly when dense cortical surface coverage and fine-grained functional mapping are required in perisylvian, Rolandic, or opercular regions. Their

disadvantages include the need for craniotomy, increased risk of infection, cerebral edema, and cerebrospinal fluid-related complications, as well as technical difficulty in reoperations where adhesions and distorted anatomy may complicate placement. In selected cases, hybrid approaches combining subdural grids with depth electrodes can provide simultaneous surface and deep sampling. They may be especially useful in complex tumor-related epilepsy after prior surgery [22, 23].

Medical Management (Table 4)

Pharmacologic treatment remains foundational in pediatric epilepsy, but the role of ASMs in established intractable epilepsy is best understood as part of a broader therapeutic pathway rather than the sole endpoint of care. Initial ASM choice should be guided by seizure type, epilepsy syndrome, age, comorbidities, behavioural profile, and, in structural epilepsies, the likelihood that eventual surgery may be required. In focal epilepsies, levetiracetam and lacosamide are widely used because of broad-spectrum efficacy, ease of titration, and relatively favorable interaction profiles, although levetiracetam may aggravate irritability, aggression, mood lability, or hyperactivity in susceptible children [24]. Other agents, including oxcarbazepine, lamotrigine, topiramate, clobazam, brivaracetam, valproate, and, in carefully selected older adolescents, cenobamate, may be used according to seizure type and tolerability [24]. In pediatric patients with structural epilepsy, selection of ASMs with minimal enzyme-inducing properties is preferred when surgical intervention is anticipated, to avoid pharmacokinetic interactions with perioperative medications and potential confounding of postoperative seizure assessment [25,26].

In children with brain tumors or complex medical comorbidity, drug–drug interactions assume special importance because enzyme-inducing ASMs such as carbamazepine and phenytoin may interfere with corticosteroid metabolism, chemotherapy clearance, or targeted agents, while valproate may increase risks of hepatotoxicity or thrombocytopenia in medically fragile patients. The critical clinical point is that failure of two appropriate ASM schedules should trigger timely surgical referral, not indefinite serial medication substitution in the face of ongoing disabling seizures [27].

In syndrome-specific pediatric epilepsies, adjunctive medications such as cannabidiol and fenfluramine have expanded the therapeutic armamentarium, particularly in Dravet syndrome and Lennox-Gastaut syndrome, and have reinforced the importance of etiology-directed treatment. However, even when newer pharmacologic therapies reduce seizure burden, they do not obviate the need for pre-surgical assessment in focal structural epilepsies with a potentially resectable substrate. Thus, the contemporary medical line of management should be viewed as rational optimization of seizure control while the child undergoes diagnostic clarification and evaluation for curative or disease-modifying interventions [28].

Prophylactic ASM administration in children without a prior seizure history is generally discouraged outside selected perioperative or high-risk situations. This principle is well established in neuro-oncology. It is increasingly extrapolated to broader pediatric neurosurgical practice because routine prophylaxis has not shown consistent long-term benefit and exposes children to adverse drug effects without a clear seizure prevention advantage. After surgery, ASM reduction should be individualized according to pathology, completeness of resection, postoperative EEG, duration of preoperative epilepsy, and overall seizure trajectory; in many cases, stepwise reduction to monotherapy is a more realistic early goal than the abrupt pursuit of medication freedom.

Ketogenic and Dietary Therapies

Ketogenic dietary therapy, including the classic ketogenic diet, modified Atkins diet, and low-glycemic-index approaches, remains a valuable nonpharmacologic treatment line in pediatric intractable epilepsy, particularly in generalized epileptic encephalopathies, infantile epileptic spasms syndromes, GLUT1 deficiency, pyruvate dehydrogenase deficiency, and in focal epilepsies when surgery is not immediately feasible. These diets likely exert anticonvulsant effects through multiple mechanisms, including altered cerebral energetics, modulation of neurotransmitter balance, changes in mitochondrial function, and network-level effects on excitability. In practical terms, dietary therapy may function as an adjunct while pre-surgical work-up proceeds, as a palliative option in non-resectable epilepsies, or as part of multimodal long-term management when complete seizure freedom cannot be achieved surgically [29].

Timing of Surgery

The strongest and most consistent message across the pediatric epilepsy literature is that earlier surgical evaluation and earlier intervention, when appropriate, are associated with better outcomes. This is true not only for seizure freedom but also for preservation of

developmental potential, behavioral regulation, and long-term independence. In LEATs and other surgically remediable focal lesions, prolonged seizure duration is associated with a greater likelihood of secondary epileptogenesis, more diffuse cortical dysfunction, and diminished probability that a limited resection will suffice [30].

Data from pediatric epilepsy surgery cohorts and meta-analyses support this position. Children who undergo surgery at a younger age or after a shorter duration of uncontrolled seizures are more likely to achieve seizure freedom and to demonstrate postoperative stabilization or improvement in cognition than children exposed to years of uncontrolled epilepsy before referral. The implication for practice is clear: surgery should not be reserved for end-stage disease, particularly in lesional epilepsies where the probability of benefit is substantial, and the developmental cost of delay is high [31].

Resective Surgery

Resective surgery remains the treatment of choice for most children with focal structural intractable epilepsy in whom the epileptogenic zone can be removed safely. The central strategic distinction is between lesionectomy, which targets the radiographically visible lesion with limited surrounding tissue, and epilepsy-directed resection, which aims to remove the functional epileptogenic zone even when it extends beyond the lesion margin. For children with short-duration epilepsy, strong electroclinical-imaging concordance, and non-eloquent lesions, direct lesionectomy may be sufficient; in contrast, long-standing epilepsy, temporal lobe involvement, dual pathology, or atypical semiology more often require a broader epilepsy-centered operative strategy [31]. Systematic reviews of pediatric epilepsy surgery report Engel Class I outcomes in 65–85% of children undergoing resection for focal cortical dysplasia type II and low-grade epilepsy-associated tumors when gross total resection of the epileptogenic zone is achieved [5, 31, 32].

Postoperative seizure outcomes after pediatric epilepsy surgery are generally favorable, with the highest rates reported in well-selected lesional epilepsies, including LEATs and focal cortical dysplasia type II. Across large cohorts and systematic reviews, Engel class I outcomes are common after complete resection. However, the precise rates vary according to pathology, lobe, duration of epilepsy, prior surgery, and completeness of resection. Histopathology matters: low-grade glioneuronal tumors and focal cortical dysplasia often fare better than diffuse infiltrative lesions or multifocal epilepsies, reinforcing the need for pathology-specific counselling and operative planning [31, 32].

The tumor-related epilepsy literature provides especially clear evidence that gross total resection of both the lesion and associated epileptogenic cortex is one of the strongest predictors of seizure freedom. In ganglioglioma and DNET, lesionectomy alone may fail if mesial temporal structures, dysplastic cortex, or remote but connected epileptogenic regions have become incorporated into the seizure network. This is why children with long-standing epilepsy, temporal or insular tumors, or discordant non-invasive data should be evaluated for intracranial EEG rather than proceeding directly to limited lesionectomy on radiographic grounds alone [33].

Intraoperative Adjuncts and Functional Preservation

Intraoperative electrocorticography may help identify residual irritative cortex and guide extension of resection in selected children with LEATs, focal cortical dysplasia, or dual pathology. However, its predictive value is variable and must always be interpreted in the broader electroclinical context. Intraoperative neuromonitoring, including motor evoked potentials, somatosensory evoked potentials, continuous electromyography, and mapping strategies tailored to the child's age and lesion location, is essential when lesions are adjacent to eloquent regions. In cooperative older children, awake mapping has also been reported for selected tumors and epilepsy surgeries involving the language cortex, though its applicability remains limited compared with adult practice [34].

Ablative and Disconnective Procedures

Laser interstitial thermal therapy (LiTT) has emerged as an important minimally invasive option for selected pediatric epilepsies, particularly hypothalamic hamartoma, mesial temporal targets, and small deep or surgically challenging lesions. Its advantages include smaller incisions, reduced blood loss, shorter hospitalization, and feasibility in children with prior craniotomy or medical fragility. However, its limitations include restricted tissue sampling and reduced opportunity for extensive functional mapping. In hypothalamic hamartoma specifically, disconnection or ablation may produce major improvement in gelastic seizures and broader epileptic encephalopathy because the therapeutic objective is interruption of the epileptogenic network rather than simple lesion debulking [35]. For hypothalamic hamartoma, stereotactic

laser ablation or radiofrequency thermocoagulation targeting the hamartoma-hypothalamic interface achieves seizure freedom in 50–70% of cases, with superior outcomes when disconnection of afferent/efferent pathways is confirmed on post-procedural imaging [35, 36].

Other disconnective procedures retain an important role in carefully selected children. Corpus callosotomy is primarily a palliative operation for turning off generalized drop attacks and diffuse bilateral networks. In contrast, hemispherotomy remains one of the most effective interventions for catastrophic unilateral hemispheric epilepsies associated with hemimegalencephaly, perinatal stroke, Rasmussen encephalitis, or extensive unilateral malformation. Although these procedures are not curative in the same sense as focal lesion resection, they can substantially reduce seizure burden, injury risk, and medication load. They may facilitate developmental progress in children with otherwise devastating epileptic encephalopathy [37]. Table 5 summarizes surgical approaches in pediatric intractable epilepsy.

Neuromodulation (Table 6)

Neuromodulation has become an increasingly important line of therapy for children who are not candidates for curative resection, who have multifocal or bilateral epileptogenic networks, or who continue to have disabling seizures after prior surgery [38]. Pooled evidence from systematic reviews supports the effectiveness of vagus nerve stimulation (VNS) in pediatric drug-resistant epilepsy, with a median seizure reduction of 45–55% and ancillary improvements in alertness, behavior, sleep architecture, and caregiver-perceived quality of life, even when complete seizure freedom remains uncommon [39,40]. Its principal advantages include relative technical simplicity, broad applicability across focal and generalized epilepsies, preservation of future surgical options, and a favorable safety profile with low rates of hardware-related complications [41,42]. Vagus nerve stimulation (VNS) remains the most established pediatric modality and provides meaningful seizure reduction in a substantial proportion of patients, often with ancillary improvements in alertness, behaviour, sleep, or caregiver-perceived quality of life, even when complete seizure freedom is uncommon. Its principal advantages are relative technical simplicity, broad applicability across focal and generalized epilepsies, and preservation of future surgical options [43].

Responsive neurostimulation (RNS) and deep-brain stimulation (DBS) are increasingly utilized in carefully selected adolescents with focal or network-level drug-resistant epilepsy. Contemporary multicenter series and systematic reviews report responder rates (≥50% seizure reduction) of 60–75% for RNS and 50–70% for DBS at 2-year follow-up in appropriately selected pediatric cohorts[44,45,46]. Responsive neurostimulation offers closed-loop detection and stimulation of seizure onset patterns and is conceptually attractive for patients with one or two well-characterized foci that cannot be safely resected, while thalamic deep brain stimulation, particularly centromedian or anterior nucleus targeting, may be useful in diffuse or generalized epileptic networks such as Lennox-Gastaut syndrome [47,48]. A crucial practical issue in tumor-related epilepsy is MRI compatibility and radiographic artifact, because postoperative oncologic surveillance may remain essential for years after implantation; current-generation devices offer conditional compatibility at 1.5T with protocol-specific considerations for artifact mitigation [49,50].

While Level I evidence supports VNS in pediatric drug-resistant epilepsy, the evidence base for RNS and DBS comprises primarily Class III–IV data from retrospective multicenter series and prospective registries [51,52]. Nonetheless, contemporary systematic reviews indicate growing utilization and encouraging medium-term seizure reduction in appropriately selected patients, with no signal of increased serious adverse events compared with historical controls [45,53]. The pediatric evidence base for RNS and DBS remains less mature than for VNS or resective surgery. However, contemporary reviews indicate growing utilization and encouraging medium-term seizure reduction in appropriately selected patients. These modalities should not be viewed as competing with pre-surgical evaluation; rather, they are often the result of an advanced pre-surgical work-up that demonstrates resection would be unsafe or insufficient. In this sense, neuromodulation is best understood as a network-targeted surgical therapy, not as a substitute for comprehensive localization. Emerging data suggest that RNS electrocorticographic recordings may further refine epileptogenic zone mapping and guide subsequent resective interventions in select cases[38,54].

Cognitive Outcomes, Quality of Life, and Survivorship

Seizure outcome alone is an incomplete measure of success in pediatric intractable epilepsy. Postoperative

cognition, language development, school participation, mood, behaviour, adaptive functioning, and family burden are equally important and may, in fact, drive the long-term benefit of successful intervention [55]. Longitudinal neuropsychological studies demonstrate that seizure freedom following pediatric epilepsy surgery correlates with stabilization of IQ trajectories (mean change +3.2 points vs. −5.8 points in medically managed controls) and improved adaptive behavior scores at 5-year follow-up [4, 56].

Studies of pediatric epilepsy surgery show that seizure freedom is associated with improved neuropsychological trajectory. In contrast, even partial seizure reduction may permit rational de-escalation of sedating polytherapy, leading to measurable improvements in attention, behavioral regulation, and daytime functional capacity, as documented by standardized neuropsychological and quality-of-life instruments [57,58].

Late-onset epilepsy or recurrent epilepsy after an initial period of remission represents an increasingly recognized survivorship issue in children with structural lesions and prior neuro-oncologic treatment[59]. Population-based cohort data indicate that late-onset seizures are approximately 12-fold more common in childhood central nervous system tumor survivors compared with sibling controls, with cranial radiation therapy and younger age at diagnosis identified as independent risk factors [60,61].

In tumor survivors, seizures may emerge years after apparently successful treatment because of residual epileptogenic cortex, radiation-related injury, perilesional gliosis, evolving network reorganization, or recurrent tumor. These children require renewed multimodal evaluation rather than empiric medication escalation alone, because a second operation, ablation, or neuromodulation may still provide meaningful benefit [62,63].

Future Directions

Contemporary literature increasingly supports a transition from purely lesion-centered to network-informed epilepsy care. Connectome-based analyses, resting-state functional MRI, higher-field structural imaging, and advanced tractography may help define the broader epileptogenic network, explain postoperative failure in apparently complete resections, and identify optimal targets for resection or stimulation [64, 65]. Parallel advances in molecular neuropathology, including recognition of BRAF-, FGFR-, mTOR-, and IDH-related epileptogenic mechanisms, raise the possibility of more precise integration of targeted oncologic therapy and seizure management in selected lesions[66]. Mechanistic studies indicate that the oncometabolite D-2-hydroxyglutarate in IDH-mutant gliomas may promote neuronal hyperexcitability via mTOR pathway activation, providing a rationale for combined molecular and electrophysiological therapeutic strategies [14,67].

One of the most promising developments is the intersection of molecular therapy and epilepsy control. Mechanistic understanding of mTOR activation, BRAF-associated signaling, and IDH-related metabolic disruption may eventually inform targeted antiepileptogenic strategies, particularly in lesion-associated epilepsies where oncologic and epileptic mechanisms overlap [67]. The exploratory seizure findings from modern targeted glioma therapy further suggest that future pediatric management may increasingly combine lesion resection, network-based surgery, and biologically directed treatment rather than relying on any single modality.

Clinical Implications

The contemporary management of pediatric intractable epilepsy requires a deliberate shift in mindset. Once drug resistance is established, the central clinical question is no longer which additional medication to try next, but whether the child has a surgically remediable epilepsy or would benefit from another nonpharmacologic strategy [1, 2]. Structural epilepsies, particularly those associated with LEATs and focal cortical dysplasia, should be assessed early because delay risks expansion of the epileptogenic network and cumulative developmental injury [8, 30]. Multicenter cohort data demonstrate that each year of delay in surgical evaluation after establishing pharmacoresistance is associated with a measurable reduction in the likelihood of postoperative seizure freedom and adverse effects on developmental quotient scores [8,31]. The most effective care model is therefore multidisciplinary, time-sensitive and individualized, integrating optimized pharmacotherapy, dietary treatment when appropriate, advanced localization, resection or ablation when feasible and neuromodulation for non-resectable or persistent epilepsy.

In summary, the available evidence supports a treatment paradigm in which seizure freedom is treated as a primary therapeutic endpoint and neurodevelopmental preservation as a coequal objective, with outcome assessment incorporating standardized neuropsychological, adaptive functioning, and quality-

of-life metrics alongside Engel classification [20,55,58]. For many children with focal structural epilepsy, surgery is not a last resort but the most effective disease-modifying therapy available. The enduring challenge is not whether effective interventions exist, but whether children are referred early enough, evaluated comprehensively enough, and managed within systems capable of integrating neurology, neurosurgery, neuropsychology, imaging, rehabilitation, and, when indicated, neuro-oncology into a unified epilepsy care pathway.

Conclusion

Pediatric intractable epilepsy represents a complex, heterogeneous disorder requiring a paradigm shift in management from purely pharmacologic approaches to integrated, multidisciplinary care. The evidence overwhelmingly supports early surgical evaluation following failure of two appropriately chosen ASMs, as delay risks irreversible cognitive decline and expansion of epileptogenic networks. Structural epilepsies, particularly LEATs and focal cortical dysplasia, demonstrate excellent surgical outcomes when managed with comprehensive pre-surgical evaluation, precise localization using advanced neuroimaging and invasive monitoring when indicated, and tailored resective or neuromodulatory interventions. The contemporary standard of care recognizes seizure freedom as a primary therapeutic goal rather than a secondary benefit, with neurodevelopmental preservation as an equally important objective. Future directions include network-based surgical planning, molecularly targeted therapies, and minimally invasive ablative techniques. The challenge facing the medical community is ensuring timely referral, comprehensive evaluation, and access to multidisciplinary epilepsy care centers capable of delivering the full spectrum of evidence-based interventions to optimize long-term outcomes for children with intractable epilepsy.

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Tables

Table 1: Etiologic Categories of Pediatric Intractable Epilepsy and Surgical Candidacy

Etiology	Frequency in Pediatrics	Surgical Candidacy	Expected Seizure Freedom Rate
Focal cortical dysplasia	20-30%	High	60-80%
Low-grade epilepsy-associated tumors	10-15%	High	70-90%
Hippocampal sclerosis	10-15%	High	60-75%
Hypothalamic hamartoma	2-5%	Moderate-High	50-70%
Vascular malformations	5-10%	Moderate	60-80%
Tuberous Sclerosis Complex	5-10%	Variable	40-60%
Genetic epilepsies	15-20%	Low	<20%
Metabolic disorders	5-10%	Low	<10%
Unknown	10-15%	Variable	30-50%

Table 2: Pre-Surgical Evaluation Modalities in Pediatric Intractable Epilepsy

Modality	Primary Purpose	Key Advantages	Limitations
Scalp video-EEG	Confirm epilepsy, characterize semiology and initial localization	Gold standard, non-invasive, captures ictal events	Limited spatial resolution, poor for deep foci
High-resolution MRI (3T+)	Detect structural lesions	Excellent anatomical detail, detects FCD, tumors	May be negative in 20-30% cases
FDG-PET	Identify the hypometabolic zone	Useful in MRI-negative cases	Interictal only, radiation exposure
Ictal/Interictal SPECT	Localize seizure onset zone	High sensitivity when ictal capture is achieved	Requires seizure during scan, radiation
MEG	Localize interictal spikes	Excellent spatial-temporal resolution	Expensive, limited availability
fMRI (task/resting-state)	Map eloquent cortex	Non-invasive, no radiation	Requires cooperation; sedation affects results
DTI/Tractography	Map white matter tracts	Preserves critical pathways	Indirect measure, tract displacement
Neuropsychological testing	Cognitive baseline, lateralization	Essential for outcome assessment	Time-consuming, age-dependent

EEG, electroencephalography; MRI, magnetic resonance imaging; FDG-PET, fluorodeoxyglucose-positron emission tomography; SPECT, single-photon emission computed tomography; MEG, magnetoencephalography; fMRI, functional MRI; DTI, diffusion tensor imaging.

Table 3: Comparison of Stereo-EEG and Subdural Grids in Pediatric Intractable Epilepsy

Feature	Stereo-EEG (sEEG)	Subdural Grids
Access to deep structures	Excellent (mesial temporal, insula, cingulate)	Limited to the superficial cortex
Suitability in post-surgical anatomy	More feasible; can be placed via scarred tissue	Often very difficult due to dural adhesions
Infection risk	Lower (1-2%)	Higher (5-10%), especially with prolonged monitoring
Coverage of the cortical surface	Limited, targeted sampling	Excellent for broad surface coverage
Functional mapping capability	Bedside stimulation for eloquent cortex	Gold standard for detailed cortical mapping
Preferred use case	Deep lesions, multifocal epilepsy, post-craniectomy	First-time surgeries near the eloquent surface cortex
Hospital stay	7-14 days	10-21 days
Anesthesia requirement	General anesthesia for implantation	General anesthesia for craniotomy

Table 4: Antiseizure Medications Commonly Used in Pediatric Intractable Epilepsy

Medication	Mechanism	Pediatric Dose Range	Key Adverse Effects	Drug Interactions
Levetiracetam	SV2A modulation	20-60 mg/kg/day	Behavioral changes, irritability	Minimal
Lacosamide	Sodium channel	4-12 mg/kg/day	Dizziness, PR prolongation	Minimal
Oxcarbazepine	Sodium channel	20-50 mg/kg/day	Hyponatremia, rash	Moderate
Lamotrigine	Sodium channel	5-15 mg/kg/day	Stevens-Johnson syndrome	Significant
Valproate	Multiple mechanisms	20-60 mg/kg/day	Hepatotoxicity, weight gain, thrombocytopenia	Significant
Topiramate	Multiple mechanisms	5-10 mg/kg/day	Cognitive slowing, weight loss, acidosis	Moderate
Clobazam	GABA-A modulation	0.5-2 mg/kg/day	Sedation, tolerance	Moderate
Brivaracetam	SV2A modulation	2-10 mg/kg/day	Somnolence, behavioral effects	Minimal

SV2A, synaptic vesicle protein 2A; GABA, gamma-aminobutyric acid.

Table 5: Surgical Approaches in Pediatric Intractable Epilepsy

Procedure	Indication	Seizure Freedom Rate	Key Advantages	Key Risks
Lesionectomy	Well-defined non-eloquent lesions	60-80%	Preserves normal tissue	Might overlook the epileptogenic zone
Epilepsy-directed resection	Long-standing epilepsy, dual pathology	70-90%	Addresses the entire EZ	More tissue removal
Laser interstitial thermal therapy	Deep lesions, hypothalamic hamartoma	50-70%	Minimally invasive	No tissue sampling
Stereo-EEG guided resection	Complex networks, deep foci	60-80%	Precise localization	Invasive monitoring required
Corpus callosotomy	Drop attacks, generalized epilepsy	10-20% (complete freedom)	Palliative care reduces injuries	Disconnection syndrome
Hemispherectomy	Unilateral hemispheric epilepsy	60-80%	Curative for catastrophic cases	Hemiparesis, visual field defect
Multiple subpial transections	Eloquent cortex involvement	40-60%	Preserves function	Variable outcomes

Table 6: Neuromodulation Therapies in Pediatric Intractable Epilepsy

Modality	Mechanism	Indications	Seizure Reduction	MRI Compatibility
Vagus Nerve Stimulation (VNS)	Intermittent vagal stimulation	Focal/generalized epilepsy	45-55% median reduction	Conditional (1.5T)
Responsive Neurostimulation (RNS)	Closed-loop detection/stimulation	1-2 focal onsets	60-75% median reduction	Conditional (1.5T)
Deep Brain Stimulation (DBS) - ANT	Anterior thalamic nucleus stimulation	Multifocal, generalized	50-70% median reduction	Conditional
Deep Brain Stimulation (DBS) - CM	Centromedian thalamic stimulation	Lennox-Gastaut, generalized	50-60% median reduction	Conditional

VNS, vagus nerve stimulation; RNS, responsive neurostimulation; DBS, deep brain stimulation; ANT, anterior nucleus of thalamus; CM, centromedian nucleus of thalamus.

Figure 1: Integrated Management Algorithm for Pediatric Intractable Epilepsy